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- (54) Benævnelse: **HIDTIL UKENDTE FORBINDELSER SOM HISTONDEACETYLASE-6-INHIBITORER OG FARMACEUTISKE SAMMENSÆTNINGER, DER OMFATTER DISSE**
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WO-A1-03/076422
WO-A1-2003/076400
WO-A1-2005/040101
WO-A2-03/011851
WO-A2-2012/106343
L. YU ET. AL.: "Pharmacophore Identification of Hydroxamate HDAC1 Inhibitors", CHINESE JOURNAL OF

Fortsættes ...

CHEMISTRY, vol. 27, no. 3, 2 April 2009 (2009-04-02), pages 557-564, XP002765019,
SMIL, D. V. ET AL.: 'Novel HDAC6 isoform selective chiral small molecule histone deacetylase inhibitors'
BIOORGANIC & MEDICINAL CHEMISTRY LETTERS vol. 19, 2009, pages 688 - 692, XP025925795

DESCRIPTION

Technical Field

[0001] The present invention relates to novel compounds having histone deacetylase 6 (HDAC6) inhibitory activity, stereoisomers thereof, pharmaceutically acceptable salts thereof, pharmaceutical compositions comprising the same, and methods for preparing the novel compounds, and the novel compounds, stereoisomers thereof or pharmaceutically acceptable salts thereof for use in preventing or treating disease.

Background Art

[0002] Post-translational modifications such as acetylation are very crucial regulatory modules at the heart of biological processes in the cells and are tightly regulated by a multitude of enzymes. Histones are the chief protein components of chromatin and act as spools around which DNA strands. Also, the balance of histone acetylation and deacetylation is a critical role in the regulation of gene expression.

[0003] Histone deacetylases (HDACs) are enzymes that remove acetyl groups from lysine residues on histone proteins of chromatin, and are known to be associated with gene silencing and induce cell cycle arrest, angiogenic inhibition, immune regulation, cell death, etc. (Hassig et al., Curr. Opin. Chem. Biol. 1997, 1, 300-308). In addition, it was reported that the inhibition of enzymatic function of HDACs induces the apoptosis of cancer cells *in vivo* by reducing the activity of cancer cell survival-associated factors and activating cancer cell apoptosis-associated factors (Warrell et al, J. Natl. Cancer Inst. 1998, 90, 1621-1625).

[0004] In humans, 18 HDACs have been identified and are subdivided into four classes based on their homology to yeast HDACs. Among them, 11 HDACs use zinc as a cofactor and can be divided into three groups: Class I (HDAC1, 2, 3 and 8), Class II (IIa: HDAC4, 5, 7 and 9; IIb: HDAC6 and 10), Class IV (HDAC 11). Additionally, 7 HDACs of Class III (SIRT 1-7) require NAD⁺ instead of zinc as a cofactor (Bolden et al., Nat. Rev. Drug Discov. 2006, 5(9), 769-784).

[0005] Various HDAC inhibitors are in preclinical or clinical development, but to date, only non-selective HDAC inhibitors have been identified as anticancer agents, and only vorinostat (SAHA) and romidepsin (FK228) have been approved for the treatment of cutaneous T-cell lymphoma. However, non-selective HDAC inhibitors are known to cause side effects such as fatigue and nausea, generally at high doses (Piekarz et al., Pharmaceuticals 2010, 3, 2751-2767). Such side effects have been reported to be due to the inhibition of class I HDACs. Due to such side effects, the use of non-selective HDAC inhibitors in the development of drugs other than anticancer drugs has been limited (Witt et al., Cancer Letters, 2009, 277, 8-21).

[0006] Meanwhile, it was reported that the selective inhibition of class II HDACs would not show toxicity shown in the inhibition of class I HDACs. Also, when selective HDAC inhibitors are developed, side effects such as toxicity, which are caused by the non-selective HDAC inhibition, can be overcome. Thus, selective HDAC inhibitors have potential to be developed as therapeutic agents effective for the treatment of various diseases (Matthias et al., Mol. Cell. Biol. 2008, 28, 1688-1701).

[0007] It is known that HDAC6, a member of Class IIb HDACs, is present mainly in the cytoplasm and is involved in the deacetylation of a number of non-histone substrates (HSP90, cortactin, etc.), including tubulin, (Yao et al., Mol. Cell 2005, 18, 601-607). HDAC6 has two catalytic domains, and the zinc finger domain of C-terminal can bind to ubiquitinated proteins. It is known that HDAC6 has a number of non-histone proteins as substrates, and thus plays an important role in various diseases, including cancer, inflammatory diseases, autoimmune diseases, neurological diseases and neurodegenerative disorders (Santo et al., Blood 2012 119: 2579-258; Vishwakarma et al., International Immunopharmacology 2013, 16, 72-78; Hu et al., J. Neurol. Sci. 2011, 304, 1-8).

[0008] Accordingly, there is a need for the development of selective HDAC 6 inhibitors for treatment of cancer, inflammatory diseases, autoimmune diseases, neurological diseases and neurodegenerative disorders, which cause no side effects, unlike non-selective inhibitors.

[0009] WO 03/076422 describes sulfonyl derivatives as novel inhibitors of histone deacetylase.

[0010] WO 2003/011851 describes aromatic dicarboxylic acid derivatives with HDAC inhibitor activity.

[0011] Yu et al. Chinese Journal of Chemistry, 2009, 27, 557-564, describes pharmacophore identification hydroxamate acids as HDAC1 inhibitors.

Disclosure of Invention

Technical Problem

[0012] It is an object of the present invention to provide novel compounds having selective HDAC6 inhibitory activity, stereoisomers thereof, or pharmaceutically acceptable salts thereof.

[0013] Another object of the present invention is to provide pharmaceutical compositions containing novel compounds having selective HDAC6 inhibitory activity, stereoisomers thereof, or pharmaceutically acceptable salts thereof.

[0014] Still another object of the present invention is to provide methods for preparing the

novel compounds.

[0015] Still another object of the present invention is to provide pharmaceutical compositions for use in prevention or treatment of HDAC6 activity-associated diseases, including cancer, inflammatory diseases, autoimmune diseases, neurological diseases and neurodegenerative disorders, which contain the above compound.

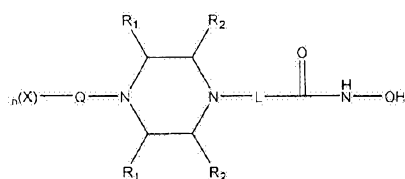
[0016] Still another object of the present invention is to provide the use of the compounds for the preparation of therapeutic medicaments against HDAC6 activity-associated diseases.

Solution to Problem

[0017] The present inventors have discovered novel dimethylpiperazine derivative compounds, particularly dimethylpiperazine hydroxamic acid derivative compounds, which have histone deacetylase 6 (HDAC6) inhibitory activity, and have found that these compounds can be used for the inhibition or treatment of histone deacetylase 6 (HDAC6) activity-associated diseases, thereby completing the present invention.

Novel HDAC6 inhibitors

[0018] To achieve the above objects, the present invention provides compounds represented by the following formula I, stereoisomers thereof, or pharmaceutically acceptable salts thereof:
Formula I



wherein

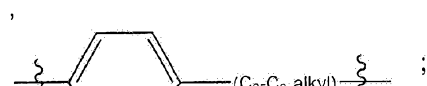
* R₁ is hydrogen or -CH₃,

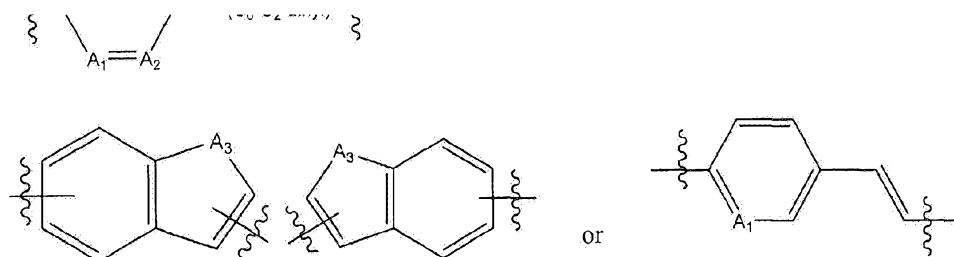
* R₂ is hydrogen or -CH₃, provided that R₂ is -CH₃ when R₁ is hydrogen, and R₂ is hydrogen when R₁ is -CH₃

* L is -(C₄-C₅ alkyl)-; -(C₁-C₃ alkyl)-L₁; -C(=O)-L₁- or -S(=O)₂-L₁-,

wherein -(C₄-C₅ alkyl)- and -(C₁-C₃ alkyl)- may be unsubstituted or substituted with - CH₃,

L₁ is -(C₃-C₆)cycloalkyl-;



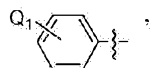


A_1 and A_2 are each independently -N- or -CR₃-, provided that both A_1 and A_2 cannot be -N-,

R_3 is hydrogen; -F, -Cl, -Br, -I or -OH, and

A_3 is -NH- or -O-,

* Q is selected from the group consisting of -(C₁-C₆)alkyl-, -(C₂-C₆)alkenyl-, -C(=O)-; -C(=S)-; -S(=O)₂- or



wherein -(C₁-C₆)alkyl- and -(C₂-C₆)alkenyl- may be unsubstituted or each independently substituted 1 to 3 -CH₃ groups or halogen atoms,

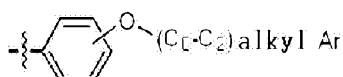
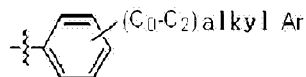
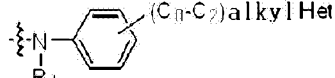
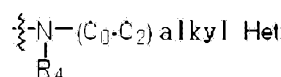
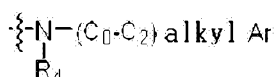
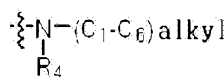
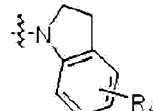
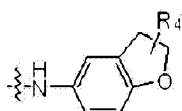
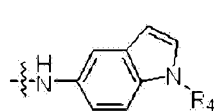
Q_1 is hydrogen; -F, -Cl, -Br or I,

* n is an integer of 0, 1 or 2, provided that n is 0 when Q is



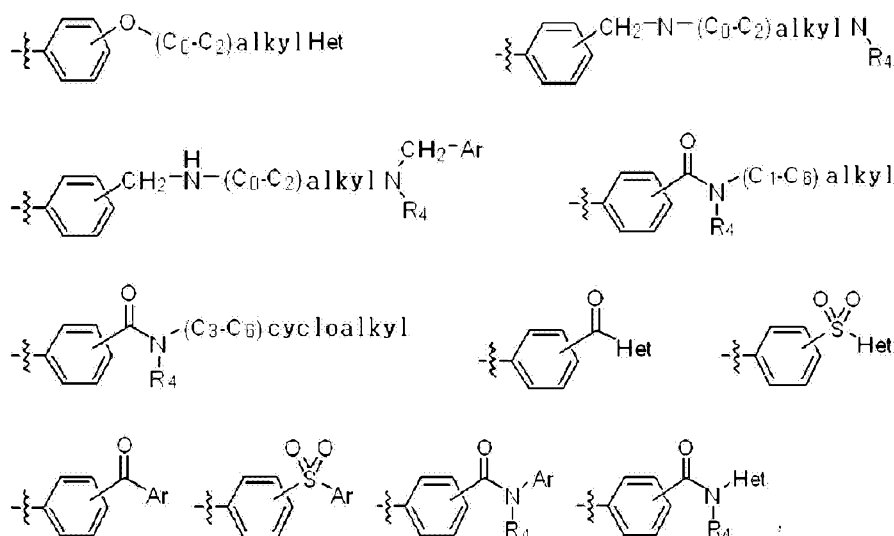
n is 1 when Q is -C(=O)-; -C(=S)- or -S(=O)₂-, and n is 1 or 2 when Q is -(C₁-C₆)alkyl- or -(C₂-C₆)alkenyl-, and

* X may be selected from the group consisting of -C₁-C₆alkyl; -C₃-C₆cycloalkyl; -C₂-C₆alkenyl; -C₃-C₆cycloalkenyl; -(C₀-C₂alkyl)Ar; -OAr; -(C₀-C₂alkyl)Het; naphthyl and following groups:



H

R_4



wherein R_4 is H or $\text{-C}_1\text{-C}_4$ alkyl,

$\text{-C}_0\text{-C}_2$ alkyl, $\text{-C}_2\text{-C}_6$ alkenyl and $\text{-C}_1\text{-C}_6$ alkyl may be unsubstituted or substituted with 1 to 2 -CH_3 groups; 1 to 3 -F groups, or a combination thereof,

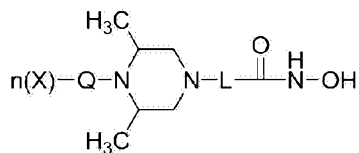
Ar is a C_6 monocyclic aromatic compound, which may be unsubstituted or substituted with one or more halogen atoms; -OH ; -NH_2 ; $\text{-C}_1\text{-C}_6$ alkyl; $\text{-O(C}_1\text{-C}_6\text{)alkyl}$; $\text{-C}_3\text{-C}_6$ cycloalkenyl; $\text{-NH(C}_1\text{-C}_6\text{)alkyl}$; $\text{-N(C}_1\text{-C}_3\text{alkyl)}_2$; $\text{-CH}_2\text{N(C}_1\text{-C}_3\text{alkyl)}_2$; $\text{-S(=O)}_2\text{-(C}_1\text{-C}_3\text{ alkyl)}$ or phenyl groups, wherein $\text{-C}_1\text{-C}_3$ alkyl; $\text{-C}_1\text{-C}_6$ alkyl and $\text{-C}_3\text{-C}_6$ cycloalkenyl may be each independently substituted with 1 to 5 -F or -CH_3 groups, and

Het is a 4- to 6-membered heteroaromatic or non-aromatic ring compound containing 1 to 3 elements selected from the group consisting of N, O and S while having 0 to 3 double bonds, and may be unsubstituted or substituted with one or more halogen atoms; $\text{-C}_1\text{-C}_6$ alkyl; $\text{-C(=O)(C}_1\text{-C}_3\text{ alkyl)}$; $\text{-S(=O)}_2\text{(C}_1\text{-C}_3\text{ alkyl)}$ or benzyl groups, wherein $\text{-C}_1\text{-C}_3$ alkyl and $\text{-C}_1\text{-C}_6$ alkyl may be each independently substituted with -OH ; 1 to 5 -F or -CH_3 groups.

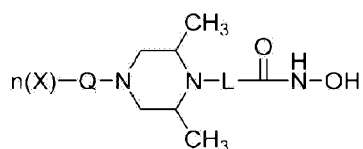
[0019] As used herein, " C_0 alkyl" means that there is no carbon and therefore represents a bond. For example, " $\text{-(C}_0\text{ alkyl)Ar}$ " means -Ar .

[0020] The compounds represented by formula I according to the present invention may be compounds represented by the following formula II or formula III:

Formula II



Formula III

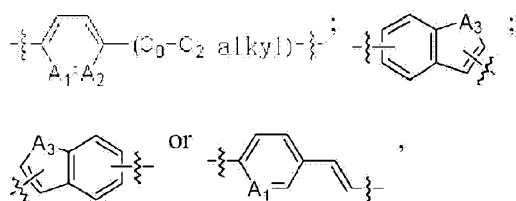


wherein

* L is $-(C_5 \text{ alkyl})-$; $-(C_1-C_2 \text{ alkyl})-L_1-$; $-C(=O)-L_1-$ or $-S(=O)_2-L_1-$,

wherein $-(C_5 \text{ alkyl})-$ and $-(C_1-C_2 \text{ alkyl})-$ are straight-chain and may be unsubstituted or substituted with $-CH_3$,

L_1 is $-(C_3-C_6 \text{ cycloalkyl})-$;

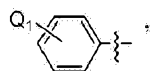


A_1 and A_2 are each independently $-N-$ or $-CR_3-$, provided that both A_1 and A_2 cannot be $-N-$,

R_3 is hydrogen; $-F$ or $-OH$, and

A_3 is $-NH-$ or $-O-$,

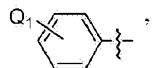
* Q is selected from the group consisting of $-(C_1-C_3 \text{ alkyl})-$; $-C(=O)-$; $-C(=S)-$; $-S(=O)_2-$ or



wherein $-(C_1-C_3 \text{ alkyl})-$ may be unsubstituted or substituted with 1 to 3 $-CH_3$ groups or halogen atoms,

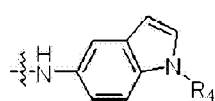
Q_1 is hydrogen; $-F$ or $-Cl$,

* n is an integer of 0 or 1, provided that n is 0 when Q is

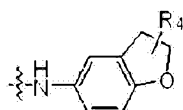


and n is 1 when Q is $-C(=O)-$, $-C(=S)-$, $-S(=O)_2-$ or $-(C_1-C_3 \text{ alkyl})-$, and

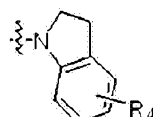
* X may be selected from the group consisting of $-C_1-C_6 \text{ alkyl}$; $-C_3-C_6 \text{ cycloalkyl}$; $-C_2-C_6 \text{ alkenyl}$; $-C_3-C_6 \text{ cycloalkenyl}$; $-(C_0-C_2 \text{ alkyl})Ar$; $-OAr$; $-(C_0-C_2 \text{ alkyl})Het$; naphthyl; and following groups:



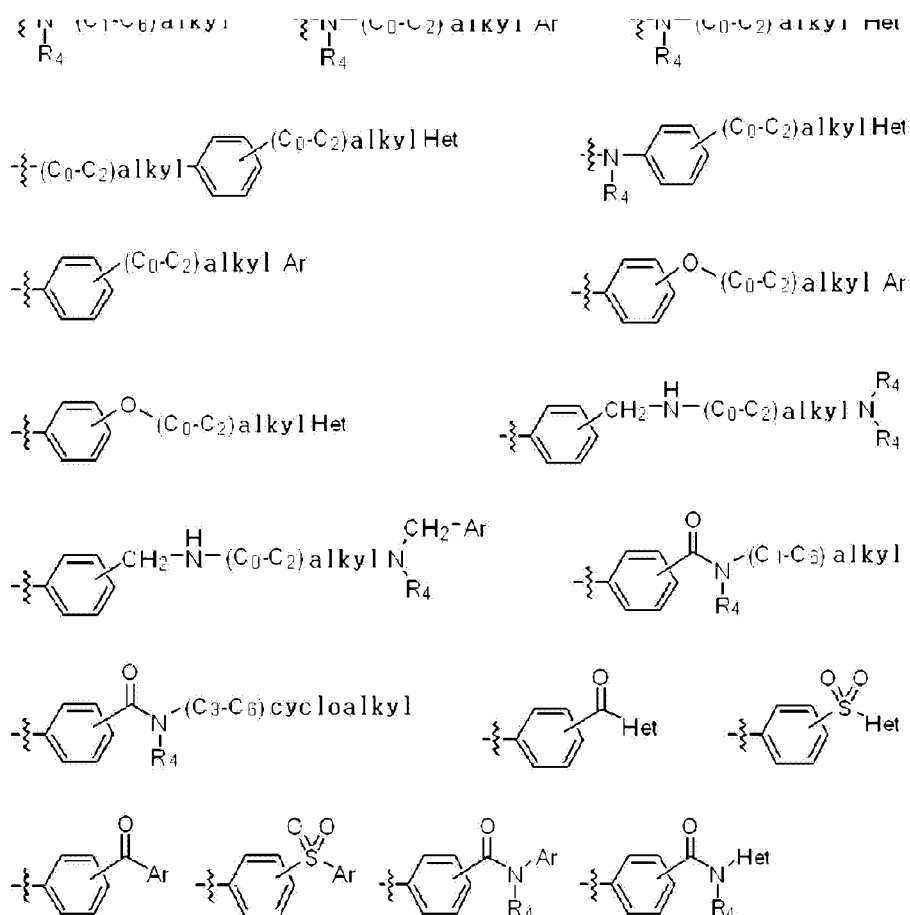
$-\{N-(C_1-C_6 \text{ alkyl})\}$



$-\{N-(C_1-C_6 \text{ alkyl})-O\}$



$-\{N-(C_1-C_6 \text{ alkyl})\}$



wherein R_4 is H or $-\text{C}_1\text{-C}_4$ alkyl,

$-\text{C}_0\text{-C}_2$ alkyl; $-\text{C}_2\text{-C}_6$ alkenyl and $-\text{C}_1\text{-C}_6$ alkyl may be unsubstituted or substituted with 1 or 2 $-\text{CH}_3$ groups or 1 to 3 F groups,

Ar is a C_6 monocyclic aromatic compound, which may be unsubstituted or substituted with one or more halogen atoms; $-\text{OH}$; $-\text{NH}_2$; $-\text{C}_1\text{-C}_6$ alkyl; $-\text{O}(\text{C}_1\text{-C}_6)\text{alkyl}$; $-\text{C}_3\text{-C}_6$ cycloalkenyl; $-\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$; $-\text{N}(\text{C}_1\text{-C}_3 \text{ alkyl})_2$; $-\text{CH}_2\text{N}(\text{C}_1\text{-C}_3 \text{ alkyl})_2$; $-\text{S}(=\text{O})\text{T}(\text{C}_1\text{-C}_3 \text{ alkyl})$ or phenyl groups, wherein $-\text{C}_1\text{-C}_3$ alkyl; $-\text{C}_1\text{-C}_6$ alkyl and $-\text{C}_3\text{-C}_6$ cycloalkenyl may be each independently substituted with 1 to 5 $-\text{F}$ or $-\text{CH}_3$ groups, and

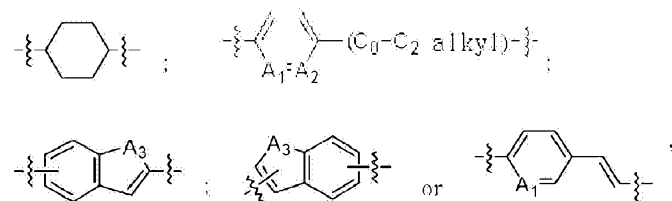
Het is a 4- to 6-membered heteroaromatic or non-aromatic ring compound containing 1 to 3 elements selected from the group consisting of N; O and S while having 0 to 3 double bonds, and may be unsubstituted or substituted with one or more halogen atoms; $-\text{C}_1\text{-C}_6$ alkyl; $-\text{C}(=\text{O})(\text{C}_1\text{-C}_3 \text{ alkyl})$; $-\text{S}(=\text{O})_2(\text{C}_1\text{-C}_3 \text{ alkyl})$ or benzyl groups, wherein $-\text{C}_1\text{-C}_3$ alkyl and $-\text{C}_1\text{-C}_6$ alkyl may be each independently substituted with $-\text{OH}$; or 1 to 5 $-\text{F}$ or $-\text{CH}_3$ groups.

[0021] In a preferred embodiment of the present invention, L, Q and X in formulas I, II and III may be defined as follows:

* L is $-\text{CH}_2-\text{L}_1-$,

wherein

L_1 is



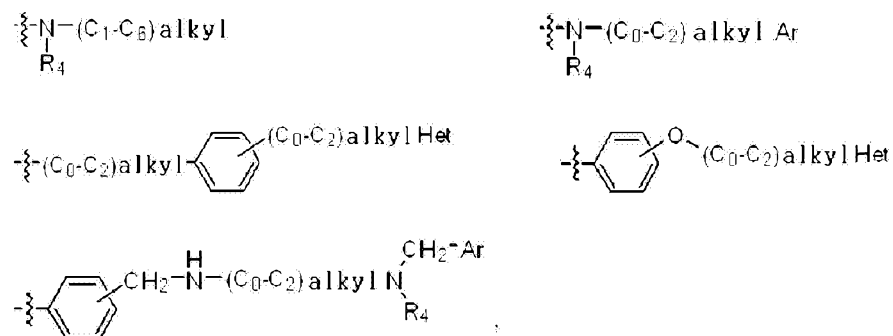
A_1 and A_2 are each independently $-\text{N}-$ or $-\text{CR}_3-$, provided that both A_1 and A_2 cannot be $-\text{N}-$,

R_3 is hydrogen; $-\text{F}$ or $-\text{OH}$, and

A_3 is $-\text{NH}-$ or $-\text{O}-$,

* Q is $-\text{CH}_2-$, $-\text{C}(=\text{O})-$ or $-\text{S}(=\text{O})_2-$, and

* X may be selected from the group consisting of $-\text{C}_1-\text{C}_6$ alkyl; $-(\text{C}_0-\text{C}_2 \text{ alkyl})\text{Ar}$; $-(\text{C}_0-\text{C}_2 \text{ alkyl})\text{Het}$; $-\text{OAr}$; or following groups:

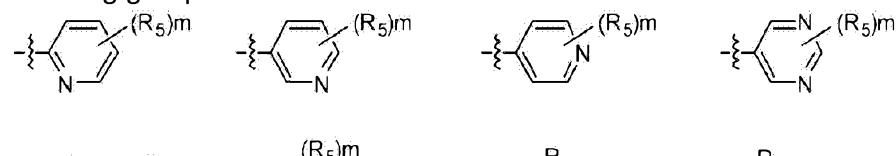


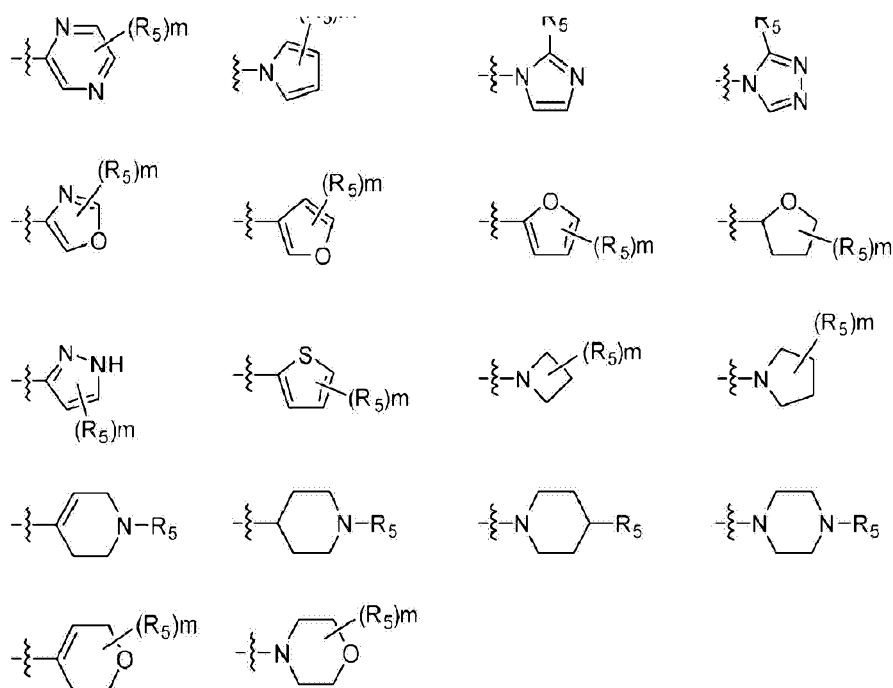
wherein R_4 is H or $-\text{C}_1-\text{C}_4$ alkyl,

$-\text{C}_0-\text{C}_2$ alkyl and $-\text{C}_1-\text{C}_6$ alkyl may be unsubstituted or substituted with 1 or 2 $-\text{CH}_3$ groups and/or 1 to 3 $-\text{F}$ groups, and

Ar and Het is each independently as defined in formula I to formula III.

[0022] In an embodiment of the present invention, the heterocyclic compound (Het) mentioned as X or a substituent in formula I to formula III above may have a structure selected from the following group:





wherein

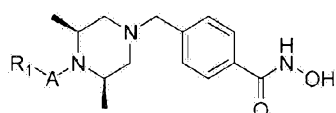
R_5 are each independently hydrogen; -F; -Cl; -C₁-C₆ alkyl; -C(=O)(C₁-C₃ alkyl); -S(=O)₂(C₁-C₃ alkyl) or benzyl, wherein -C₁-C₃ alkyl and -C₁-C₆ alkyl may be each independently substituted with -OH; 1 to 5 -F or -CH₃ groups,

m is an integer of 0, 1, 2 or 3, and

Het is unsubstituted when m is 0, and Het may be substituted with independent R_5 when m is 1, 2 or 3.

The compounds represented by formula I according to the present invention may be compounds represented by the following formula I-1:

Formula I-1



wherein

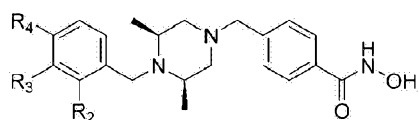
A is -C(=O)-; -CH₂-; -NH(C=O)-; -C(=S)- or -S(=O)₂-, and

R_1 is a straight or branched chain C₁-C₄ alkyl; a straight or branched chain C₁-C₄ alkenyl; a C₃-C₅ cycloalkyl; -OC₆C₅; -(C₀-C₂ alkyl)CF₃; phenyl (which may be unsubstituted or substituted with C₁-C₃ alkyl; pyrrole; -OCH₃; -CF₃; -F; -Cl or -OH); pyridyl; furanyl; thiophenyl; benzyl (which may be unsubstituted or substituted with one or more C₁-C₃ alkyl; pyrrole; -OCH₃; -CF₃; -F; -Cl or OH groups); phenethyl; naphthyl; oxazolyl; pyrimidinyl; pyrazolyl or pyrazinyl.

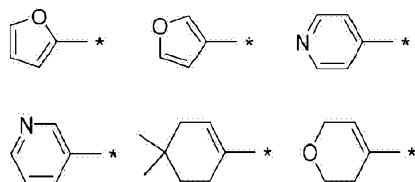
[0023] The compounds represented by formula I-1 are preferably compounds 82, 83, 84, 98, 99, 100, 120, 121, 122, 123, 125, 126, 127, 128, 145, 146, 147, 148, 149, 159, 160, 161, 177, 184, 188, 204, 211, 212, 213, 214, 222, 223, 224, 225, 232, 255, 265, 266, 267, 270, 272, 275, 290, 291, 292, 293, 294, 295, 296, 297, 354, 355, 403, 404 and 405 as disclosed herein.

[0024] The compounds represented by formula I may be compounds represented by the following formula I-2:

Formula I-2



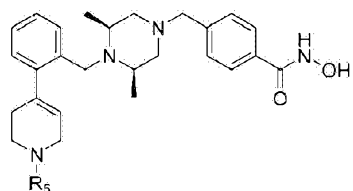
wherein R₂, R₃ or R₄ may be each independently hydrogen or any one selected from the following group:



[0025] The compounds represented by formula I-2 are preferably compounds 309, 327, 328, 329, 330, 331, 332, 342, 343, 344, 345, 346 and 347 as disclosed herein.

[0026] The compounds represented by formula I according to the present invention may be compounds represented by the following formula I-3:

Formula I-3

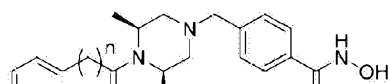


wherein R₅ may be selected from the group consisting of a straight or branched chain C₁-C₄ alkyl; -COCH₃; -CH₂CF₃ and -SO₂CH₃.

[0027] The compounds represented by formula 1-3 are preferably compounds 481, 482, 483, 484 and 485 as disclosed herein.

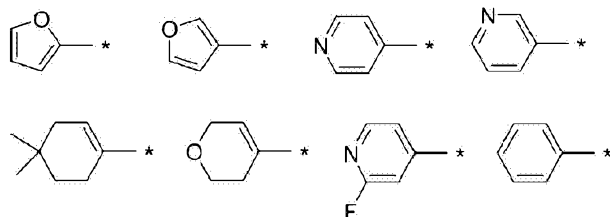
[0028] The compounds represented by formula I according to the present invention may be compounds represented by formula I-4:

Formula I-4





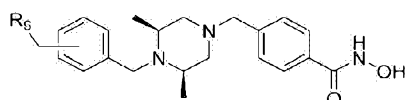
wherein n is an integer of 0, 1 or 2, and R_6 , R_7 or R_8 may be each independently hydrogen or any one selected from the group consisting of the following group:



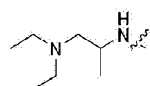
[0029] The compounds represented by formula I-4 are preferably compounds 234, 242, 243, 244, 245, 246, 247, 283, 284, 285, 286, 288, 326 and 340 as disclosed herein.

[0030] The compounds represented by formula I according to the present invention may be compounds represented by formula I-5:

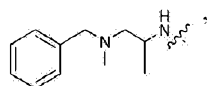
Formula I-5



wherein R_9 may be selected from among morpholine; piperidine; pyrrolidine; azetidine; piperazine; $-C_1$ - C_2 primary or secondary alkylamine;



or

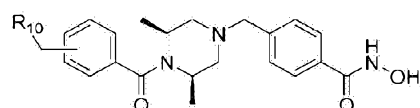


wherein pyrrolidine may be unsubstituted or substituted with one or more $-F$ or $-Cl$ groups, azetidine may be unsubstituted or substituted with one or more $-F$ or $-Cl$ groups, and piperazine may be unsubstituted or substituted with one or more straight or branched chain C_1 - C_5 alkyl; benzyl; $-COCH_3$; $-CH_2CF_3$ or $-SO_2CH_3$ groups.

[0031] The compounds represented by formula I-5 are preferably compounds 356, 376, 382, 383, 384, 385, 411, 412, 413, 426, 427, 428, 429, 430, 431, 452, 453, 454, 455, 456, 457, 466, 467, 468 and 486 as disclosed herein.

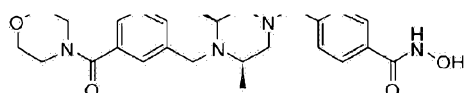
[0032] The compounds represented by formula I according to the present invention may be compounds represented by the following formula I-6_A or formula I-6_B:

Formula I-6_A

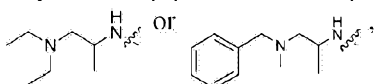


Formula I-6_B





wherein R_{10} may be selected from among pyrrolidine; piperidine; C_1 - C_2 primary or secondary alkylamine; piperazine; morpholine;

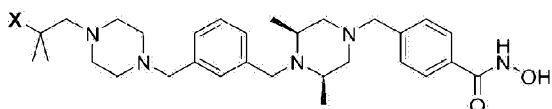


wherein pyrrolidine may be unsubstituted or substituted with one or more -F or -Cl groups, and piperazine may be unsubstituted or substituted with one or more straight or branched chain C_1 - C_5 alkyl; -COCH₃; -CH₂CF₃ or -SO₂CH₃ groups.

[0033] The compounds represented by formula I-6_A are preferably compounds 423, 424, 425, 432, 433, 434, 435, 439, 440, 441, 442, 443, 444, 458, 459, 460, 461, 462 and 463 as disclosed herein. Furthermore, the compounds represented by formula I-6_B are preferably compound 446 as disclosed herein.

[0034] The compounds represented by formula I according to the present invention may be compounds represented by the following formula I-7:

Formula I-7

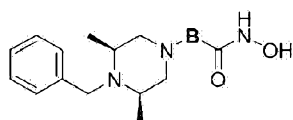


wherein X may be selected from -OH; -F; -Cl or -Br.

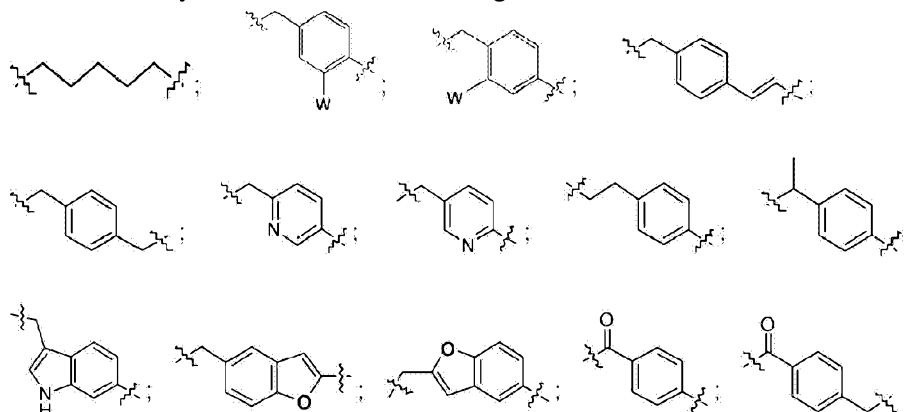
[0035] The compounds represented by formula I-7 are preferably compounds 386 and 387 as disclosed herein.

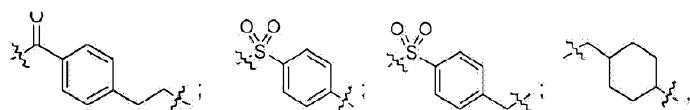
[0036] The compounds represented by formula I according to the present invention may be compounds represented by the following formula I-8:

Formula I-8



wherein B may be selected from among



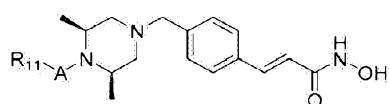


wherein w is hydrogen or may be substituted with -F; -Cl or -OH.

[0037] The compounds represented by formula 1-8 are preferably compounds 154, 171, 172, 173, 194, 218, 219, 520, 571, 574, 652, 812, 813, 814, 818, 820, 822, 823 and 824 as disclosed herein.

[0038] The compounds represented by formula I according to the present invention may be compounds represented by the following formula I-9:

Formula I-9

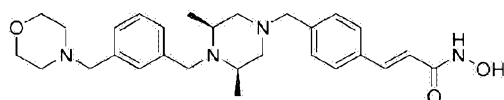


wherein A is -C(=O)-; -CH₂-; -NH(C=O)-; -C(=S)- or -S(=O)₂-, and R₁₁ may be selected from among furanyl; benzyl; pyrrole-substituted phenyl or pyrrole-substituted aniliny.

[0039] The compounds represented by formula I-9 are preferably compounds 321, 322 and 323 as disclosed herein.

[0040] The compounds represented by formula I according to the present invention may be compounds represented by the following formula I-10:

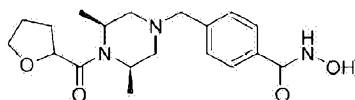
Formula I-10



[0041] The compounds represented by formula I-10 are preferably compound 472 as disclosed herein.

[0042] The compounds represented by formula I according to the present invention may be compounds represented by the following formula I-11:

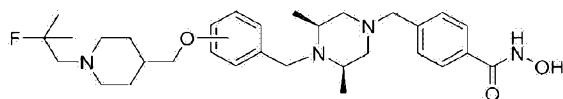
Formula I-11



[0043] The compounds represented by formula I-11 are preferably compound 402 as disclosed herein.

[0044] The compounds represented by formula I according to the present invention may be compounds represented by the following formula I-12:

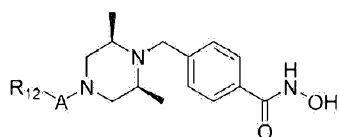
Formula I-12



[0045] The compounds represented by formula I-12 are preferably compounds 380 and 388 as disclosed herein.

[0046] The compounds represented by formula I according to the present invention may be compounds represented by the following formula I-13:

Formula I-13

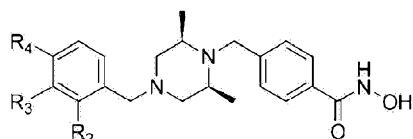


wherein A is -C(=O)-; -CH₂-; -CH(CH₃)-; -NH(C=O)-; -NCH₃(C=O)-; -C(=S)- or -S(=O)₂-, and R₁₂ may be selected from among straight or branched C₁-C₄ alkyl; phenyl (which may be unsubstituted or substituted with one or more straight or branched chain C₁-C₃ alkyl; -F; -Cl; CF₃; -OCH₃; -C₁-C₂ primary or secondary alkylamine; -SO₂CH₃; thiophenyl; pyrrole; pyrazole; furanyl; triazolyl or imidazolyl); pyridinyl; thiophenyl; furanyl; benzyl (which may be unsubstituted or substituted with -F, -Cl or -OCH₃); indole (which may be unsubstituted or substituted with one or more straight or branched chain C₁-C₃ alkyl groups), dihydrobenzofuranyl; phenylamine (which may be unsubstituted or substituted with straight or branched chain C₁-C₃ alkyl); indoline or naphthyl.

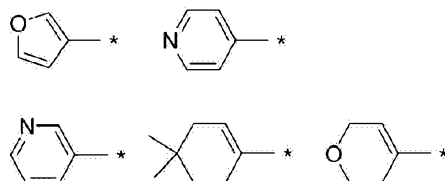
[0047] The compounds represented by formula I-13 are preferably compounds 80, 81, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 118, 162, 163, 164, 165, 166, 167, 168, 183, 185, 186, 187, 189, 196, 197, 215, 220, 230, 231, 233, 256, 268, 271, 273, 274, 298, 299, 300, 301, 302, 303, 304 and 305 as disclosed herein.

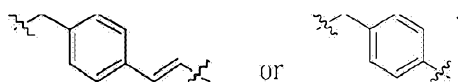
[0048] The compounds represented by formula I according to the present invention may be compounds represented by the following formula I-14:

Formula I-14



wherein R₂, R₃ and R₄ may be each independently hydrogen or any one selected from the following group:



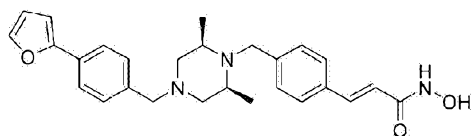


Also, R_{13} may be selected from among pyrrolidine and $-C_1-C_2$ primary or secondary alkylamine.

[0055] The compounds represented by formula I-17 are preferably compounds 475, 476, 478, 479, 480 and 487 as disclosed herein.

[0056] The compounds represented by formula I according to the present invention may be compounds represented by the following formula I-18:

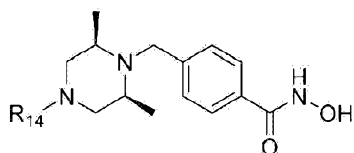
Formula I-18



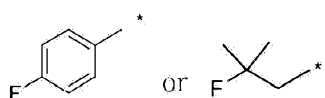
[0057] The compounds represented by formula I-18 are preferably compound 477 as disclosed herein.

[0058] The compounds represented by formula I according to the present invention may be compounds represented by the following formula I-19:

Formula I-19



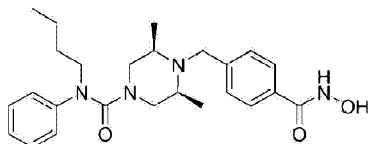
wherein R_{14} may be selected from among



[0059] The compounds represented by formula I-19 are preferably compounds 119 and 193 as disclosed herein.

[0060] The compounds represented by formula I according to the present invention may be compounds represented by the following formula I-20:

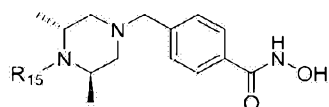
Formula I-20



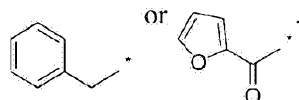
[0061] The compounds represented by formula 1-20 are preferably compound 198 as disclosed herein.

[0062] The compounds represented by formula I according to the present invention may be compounds represented by the following formula I-21:

Formula I-21



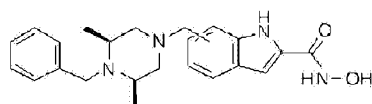
wherein R_{15} may be selected from among



[0063] The compounds represented by formula I-21 are preferably compounds 248 and 249 as disclosed herein.

[0064] The compounds represented by formula I according to the present invention may be compounds represented by the following formula I-22:

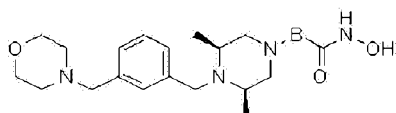
Formula I-22



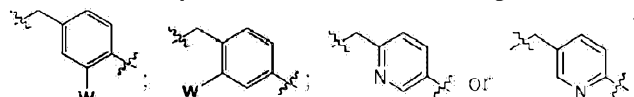
[0065] The compounds represented by formula I-22 are preferably compounds 569 and 573 as disclosed herein.

[0066] The compounds represented by formula I according to the present invention may be compounds represented by the following formula I-23:

Formula I-23



wherein B may be selected from among



wherein w is hydrogen; -F; -Cl or -OH.

[0067] The compounds represented by formula I-23 are preferably compounds 609, 653 and 696 as disclosed herein.

[0068] The compounds represented by formula I, formula II, formula III and formulas I-1 to I-23 are shown in Table 1 below.

Table 1: Names of dimethylpiperazine derivative compounds

No.	Name of Compound
080	4-(((2S,6R)-4-benzoyl-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
081	4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
082	4-(((3R,5S)-4-acetyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
083	4-(((3R,5S)-4-benzoyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
084	4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
098	(2S,6R)-4-(4-(hydroxycarbamoyl)benzyl)-N-isopropyl-2,6-dimethylpiperazine-1-carboxamide
099	(2S,6R)-N-(3-chlorophenyl)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylpiperazine-1-carboxamide
100	4-(((3R,5S)-3,5-dimethyl-4-(phenylsulfonyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
103	(3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-N-isopropyl-3,5-dimethylpiperazine-1-carboxamide
104	(3R,5S)-N-(3-chlorophenyl)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethylpiperazine-1-carboxamide
105	4-(((2S,6R)-2,6-dimethyl-4-(phenylsulfonyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
106	4-(((2S,6R)-4-(4-chlorobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
107	4-(((2S,6R)-4-(3-chlorobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
108	4-(((2S,6R)-4-(2-chlorobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
109	4-(((2S,6R)-4-((4-chlorophenyl)sulfonyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
110	4-(((2S,6R)-4-((2-chlorophenyl)sulfonyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
111	4-(((2S,6R)-2,6-dimethyl-4-picolinoylpiperazin-1-yl)methyl)-N-hydroxybenzamide
112	4-(((2S,6R)-2,6-dimethyl-4-nicotinoylpiperazin-1-yl)methyl)-N-hydroxybenzamide
113	4-(((2S,6R)-2,6-dimethyl-4-(pyridin-3-ylsulfonyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
114	4-(((2S,6R)-2,6-dimethyl-4-(thiophene-2-carbonyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

No.	Name of Compound
115	4-(((2S,6R)-4-(furan-2-carbonyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
118	4-(((2S,6R)-4-(2-chlorobenzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
119	4-(((2R,6S)-4-(4-fluorophenyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
120	4-(((3R,5S)-4-(2-chlorobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
121	4-(((3R,5S)-4-(3-chlorobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
122	4-(((3R,5S)-4-(4-chlorobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
123	1-(((3R,5S)-3,5-dimethyl-1-picolinoypiperazin-1-yl)methyl)-N-hydroxybenzamide
125	4-(((3R,5S)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
126	4-(((3R,5S)-3,5-dimethyl-4-(thiophene-2-carbonyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
127	4-(((3R,5S)-4-(2-chlorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
128	4-(((3R,5S)-4-(3-chlorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
145	4-(((3R,5S)-4-(furan-2-ylmethyl)-3,5-dimethylpiperaziri-1-yl)methyl)-N-hydroxybenzamide
146	4-(((3R,5S)-3,5-dimethyl-4-(2-phenylacetyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
147	4-(((3R,5S)-4-ethyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
148	4-(((3R,5S)-3,5-dimethyl-4-propylpiperazin-1-yl)methyl)-N-hydroxybenzamide
149	4-(((3R,5S)-3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
154	6-((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)-N-hydroxyhexanamide
159	(2S,6R)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-phenylpiperazine-1-carboxamide
160	(2S,6R)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-(o-tolyl)piperazine-1-carboxamide
161	(2S,6R)-N-benzyl-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylpiperazine-1-carboxamide

No.	Name of Compound
162	(3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-N-phenylpiperazine-1-carboxamide
163	(3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-N-(2-methoxyphenyl)-3,5-dimethylpiperazine-1-carboxamide
164	(3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-N-(3-methoxyphenyl)-3,5-dimethylpiperazine-1-carboxamide
165	(3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-N-(4-methoxyphenyl)-3,5-dimethylpiperazine-1-carboxamide
166	(3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-N-(o-tolyl)piperazine-1-carboxamide
167	(3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-N-(m-tolyl)piperazine-1-carboxamide
168	(3R,5S)-N-benzyl-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethylpiperazine-1-carboxamide
171	4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-2-fluoro-N-hydroxybenzamide
172	(E)-3-(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide
173	2-(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacetamide
174	4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)-2-fluoro-N-hydroxybenzamide
175	(E)-3-(4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide
176	2-(4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacetamide
177	phenyl (2S,6R)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylpiperazine-1-carboxylate
183	4-(((2S,6R)-2,6-dimethyl-4-phenethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
184	4-(((3R,5S)-3,5-dimethyl-4-phenethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
185	(3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-N-(1-methyl-1H-indol-5-yl)piperazine-1-carboxamide
186	(3R,5S)-N-(3-(1H-pyrrol-1-yl)phenyl)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethylpiperazine-1-carboxamide
187	(3R,5S)-N-(2,3-dihydrobenzofuran-5-yl)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethylpiperazine-1-carboxamide
188	4-(((3R,5S)-3,5-dimethyl-4-(3-phenylpropanoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

No.	Name of Compound
189	4-(((2S,6R)-2,6-dimethyl-4-(m-tolylcarbamothioyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
193	4-(((2S,6R)-4-(2-fluoro-2-methylpropyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
194	6-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxynicotinamide
195	6-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxynicotinamide
196	(3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-N,3,5-trimethyl-N-phenylpiperazine-1-carboxamide
197	N-hydroxy-4-(((2S,6R)-4-(indoline-1-carbonyl)-2,6-dimethylpiperazin-1-yl)methyl)benzamide
198	(3R,5S)-N-butyl-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-N-phenylpiperazine-1-carboxamide
204	4-(((3R,5S)-3,5-dimethyl-4-(4,4,4-trifluorobutyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
211	4-(((3R,5S)-4-(2-fluorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
212	1-(((3R,5S)-1-(2,5-difluorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
213	4-(((3R,5S)-3,5-dimethyl-4-(2,4,5-trifluorobenzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
214	4-(((3R,5S)-4-(3,5-bis(trifluoromethyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
215	4-(((2S,6R)-2,6-dimethyl-4-(2,4,5-trifluorobenzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
218	4-(2-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)ethyl)-N-hydroxybenzamide
219	4-(1-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)ethyl)-N-hydroxybenzamide
220	4-(((2S,6R)-2,6-dimethyl-4-(1-phenylethyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
222	4-(((3R,5S)-4-(2-(3-fluorophenyl)acetyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
223	4-(((3R,5S)-3,5-dimethyl-4-(2-(3-(trifluoromethyl)phenyl)acetyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
224	4-(((3R,5S)-4-(2-(3-chlorophenyl)acetyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
225	4-(((3R,5S)-4-(3-fluorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

No.	Name of Compound
230	(3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-N-(3-methoxybenzyl)-3,5-dimethylpiperazine-1-carboxamide (Trifluoroacetic acid salt)
231	(3R,5S)-N-(3-fluorobenzyl)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethylpiperazine-1-carboxamide
232	(2S,6R)-N-(3-fluorobenzyl)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylpiperazine-1-carboxamide
233	4-(((2S,6R)-4-(2-(3-chlorophenyl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
234	4-(((3R,5S)-4-(2-([1,1'-biphenyl]-3-yl)acetyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
242	4-(((3R,5S)-4-(3-(furan-2-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
243	4-(((3R,5S)-4-(3-(furan-3-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
244	4-(((3R,5S)-4-(3-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
245	4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-4-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)
246	4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
247	4-(((3R,5S)-4-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
248	4-(((3R,5R)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
249	4-(((3R,5R)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
250	4-(((2S,6R)-4-(2-([1,1'-biphenyl]-3-yl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)
251	4-(((2S,6R)-2,6-dimethyl-4-(2-(3-(pyridin-4-yl)phenyl)acetyl)piperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)
252	4-(((2S,6R)-4-(2-(3-(3,6-dihydro-2H-pyran-4-yl)phenyl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
253	4-(((2S,6R)-4-(2-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-yl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)
255	4-(((3R,5S)-4-(3-(1H-pyrrol-1-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
256	4-(((2S,6R)-4-(3-(1H-pyrrol-1-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

No.	Name of Compound
257	4-(((2S,6R)-4-(3-(furan-2-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
258	4-(((2S,6R)-4-(3-(furan-3-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
259	4-(((2S,6R)-4-(3-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
260	4-(((2S,6R)-2,6-dimethyl-4-(3-(pyridin-4-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
261	4-(((2S,6R)-2,6-dimethyl-4-(3-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
262	4-(((2S,6R)-4-(3-(2-fluoropyridin-4-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
263	4-(((2S,6R)-4-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-carbonyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
265	4-(((3R,5S)-3,5-dimethyl-4-(naphthalen-2-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
266	4-(((3R,5S)-3,5-dimethyl-4-(pyridin-4-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)
267	4-(((3R,5S)-4-(3-chloro-2-(trifluoromethyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
268	4-(((2S,6R)-2,6-dimethyl-4-(naphthalen-2-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
270	N-hydroxy-4-(((3R,5S)-4-isopentyl-3,5-dimethylpiperazin-1-yl)methyl)benzamide (Trifluoroacetic acid salt)
271	N-hydroxy-4-(((2S,6R)-4-isopentyl-2,6-dimethylpiperazin-1-yl)methyl)benzamide (Trifluoroacetic acid salt)
272	4-(((3R,5S)-3,5-dimethyl-4-(3-methylbut-2-en-1-yl)piperazin-1-yl)methyl)-N-hydroxybenzamide
273	N-hydroxy-4-(((2S,6R)-4-isopropyl-2,6-dimethylpiperazin-1-yl)methyl)benzamide (Trifluoroacetic acid salt)
274	4-(((2S,6R)-4-butyl-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)
275	4-(((3R,5S)-4-butyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)
276	4-(((2S,6R)-4-(2-(furan-2-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
277	4-(((2S,6R)-4-(2-(furan-3-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
278	4-(((2S,6R)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

No.	Name of Compound
279	4-(((2S,6R)-2,6-dimethyl-4-(2-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
280	4-(((2S,6R)-4-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-carbonyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
283	4-(((3R,5S)-4-(2-(furan-2-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
284	4-(((3R,5S)-4-(2-(furan-3-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
285	4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-4-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
286	4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
288	4-(((3R,5S)-4-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
290	4-(((3R,5S)-3,5-dimethyl-4-(4-methylbenzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)
291	N-hydroxy-4-(((3R,5S)-4-(4-methoxybenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamide (Trifluoroacetic acid salt)
292	4-(((3R,5S)-3,5-dimethyl-4-pivaloylpiperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)
293	4-(((3R,5S)-3,5-dimethyl-4-propionylpiperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)
294	4-(((3R,5S)-4-butyryl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)
295	4-(((3R,5S)-4-(cyclopropanecarbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)
296	N-hydroxy-4-(((3R,5S)-4-isobutyryl-3,5-dimethylpiperazin-1-yl)methyl)benzamide (Trifluoroacetic acid salt)
297	4-(((3R,5S)-3,5-dimethyl-4-(3-methylbutanoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)
298	4-(((2S,6R)-2,6-dimethyl-4-(3-(trifluoromethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
299	4-(((2S,6R)-4-(4-(dimethylamino)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
300	4-(((2S,6R)-2,6-dimethyl-4-(4-(methylsulfonyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
301	4-(((2S,6R)-4-(4-(1H-imidazol-1-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
302	4-(((2S,6R)-2,6-dimethyl-4-(4-thiophen-2-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

No.	Name of Compound
303	4-(((2S,6R)-4-(4-(furan-2-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
304	4-(((2S,6R)-4-(4-(4H-1,2,4-triazol-4-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
305	4-(((2S,6R)-2,6-dimethyl-4-(2-(2-methyl-1H-imidazol-1-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
309	4-(((3R,5S)-4-(4-(furan-3-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
321	(2S,6R)-N-(3-(1H-pyrrol-1-yl)phenyl)-4-(4-((E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)benzyl)-2,6-dimethylpiperazine-1-carboxamide
322	(E)-3-(4-(((3R,5S)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide
323	(E)-3-(4-(((3R,5S)-3,5-dimethyl-4-(2-phenylacetyl)piperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide
326	4-(((3R,5S)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
327	1-(((3R,5S)-1-(2-(furan-2-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
328	4-(((3R,5S)-4-(2-(furan-3-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
329	4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
330	4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
331	4-(((3R,5S)-4-((4',4'-dimethyl-2',3',-4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
332	4-(((3R,5S)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
340	4-(((3R,5S)-4-(4-(furan-2-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
342	4-(((3R,5S)-4-(3-(furan-2-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
343	4-(((3R,5S)-4-(3-(furan-3-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
344	4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
345	4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
346	4-(((3R,5S)-4-(3-(3,6-dihydro-2H-pyran-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

No.	Name of Compound
347	4-(((3R,5S)-4-((4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-yl)methyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
348	4-(((2S,6R)-4-(2-(furan-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
349	4-(((2S,6R)-2,6-dimethyl-4-(2-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
350	4-(((2S,6R)-2,6-dimethyl-4-(2-(pyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
351	4-(((2S,6R)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
352	4-(((2S,6R)-4-((4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
354	4-(((3R,5S)-3,5-dimethyl-4-(oxazol-4-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
355	4-(((3R,5S)-3,5-dimethyl-4-(pyrimidin-5-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
356	4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
376	4-(((3R,5S)-3,5-dimethyl-4-(4-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
380	4-(((3R,5S)-4-(3-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
382	4-(((3R,5S)-3,5-dimethyl-4-(3-(piperidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
383	4-(((3R,5S)-4-(3-(((R)-3-fluoropyrrolidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
384	4-(((3R,5S)-4-(3-((3,3-difluoroazetidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
385	4-(((3R,5S)-4-(3-((4-benzylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
386	N-hydroxy-4-(((3R,5S)-4-(3-((4-(2-hydroxy-2-methylpropyl)piperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamide
387	4-(((3R,5S)-4-(3-((4-(2-fluoro-2-methylpropyl)piperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
388	4-(((3R,5S)-4-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

No.	Name of Compound
396	4-(((2S,6R)-4-(3-(furan-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
400	4-(((2S,6R)-4-((4',4'-dimethyl-2',3',4',5'-(tetrahydro-[1,1'-biphenyl]-4-yl)methyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
101	4-(((2S,6R)-4-(4-(3,6-dihydro-2H-pyran-4-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
402	4-(((3R,5S)-3,5-dimethyl-4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
403	4-(((3R,5S)-3,5-dimethyl-4-(1H-pyrazole-3-carbonyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
404	4-(((3R,5S)-3,5-dimethyl-4-(pyrazine-2-carbonyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
405	N-hydroxy-4-(((3R,5S)-4-isonicotinoyl-3,5-dimethylpiperazin-1-yl)methyl)benzamide
411	1-(((3R,5S)-1-(1-(((R)-3-fluoropyrrolidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
412	4-(((3R,5S)-4-(4-((3,3-difluoroazetidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
113	4-(((3R,5S)-4-(4-((4-benzylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
423	4-(((3R,5S)-3,5-dimethyl-4-(3-(pyrrolidin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
424	4-(((3R,5S)-3,5-dimethyl-4-(3-(piperidin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
425	4-(((3R,5S)-4-(3-((diethylamino)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
426	4-(((3R,5S)-4-(3-((diethylamino)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
427	4-(((3R,5S)-3,5-dimethyl-4-(3-(pyrrolidin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
428	4-(((3R,5S)-3,5-dimethyl-4-(3-((4-methylpiperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
429	4-(((3R,5S)-4-(3-((4-ethylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
430	N-hydroxy-4-(((3R,5S)-4-(3-((4-isopropylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamide
431	4-(((3R,5S)-4-(3-((4-acetyl piperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
432	1-(((3R,5S)-3,5-dimethyl-4-(3-((4-methylpiperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

No.	Name of Compound
433	4-(((3R,5S)-4-(3-((4-ethylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
434	N-hydroxy-4-(((3R,5S)-4-(3-((4-isopropylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamide
435	4-(((3R,5S)-4-(3-((4-acetyl piperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
439	4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
440	4-(((3R,5S)-4-(3-(((1-(diethylamino)propan-2-yl)amino)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
441	4-(((3R,5S)-4-(3-(((1-(benzyl(methyl)amino)propan-2-yl)amino)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
442	N-hydroxy-4-(((3R,5S)-4-(3-((4-isopentylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamide
443	4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
444	4-(((3R,5S)-3,5-dimethyl-4-(3-((1-(methylsulfonyl)piperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
446	4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholine-4-carbonyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
452	4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(methylsulfonyl)piperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
453	4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
454	N-hydroxy-1-(((3R,5S)-1-(3-((1-isopentylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamide
455	4-(((3R,5S)-4-(3-(((1-(diethylamino)propan-2-yl)amino)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
456	4-(((3R,5S)-4-(3-(((1-(benzyl(methyl)amino)propan-2-yl)amino)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
457	4-(((3R,5S)-3,5-dimethyl-4-(2-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
458	4-(((3R,5S)-3,5-dimethyl-4-(4-(morpholinomethyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
459	4-(((3R,5S)-3,5-dimethyl-4-(4-(piperidin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

No.	Name of Compound
460	4-(((3R,5S)-4-(4-(((R)-3-fluoropyrrolidin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
461	4-(((3R,5S)-3,5-dimethyl-4-(4-(pyrrolidin-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
462	4-(((3R,5S)-3,5-dimethyl-4-(4-((4-methylpiperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
463	4-(((3R,5S)-3,5-dimethyl-4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
466	4-(((3R,5S)-3,5-dimethyl-4-(4-(pyrrolidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
467	4-(((3R,5S)-3,5-dimethyl-4-(4-(piperidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
468	4-(((3R,5S)-3,5-dimethyl-4-(4-((4-methylpiperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
472	(E)-3-(4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide
475	(E)-3-(4-(((2S,6R)-2,6-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide
476	(E)-3-(4-(((2S,6S)-4-(3-((diethylamino)methyl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide
477	(E)-3-(4-(((2S,6R)-4-(4-(furan-2-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide
478	4-(((2S,6R)-4-(3-((diethylamino)methyl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide (hydrochloride salt)
479	4-(((2S,6R)-2,6-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
480	(E)-3-(4-(((2S,6R)-2,6-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide
481	4-(((3R,5S)-3,5-dimethyl-4-(2-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
482	4-(((3R,5S)-4-(2-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
483	4-(((3R,5S)-3,5-dimethyl-4-(2-(1-(2,2,2-trifluoroethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide
484	N-hydroxy-4-(((3R,5S)-4-(2-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamide

No.	Name of Compound
485	4-(((3R,5S)-4-(2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide
486	4-(((3R,5S)-4-(4-((4-acetylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide (hydrochloride salt)
487	(E)-3-(4-(((2S,6R)-4-(3-((diethylamino)methyl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide
520	3-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxy-1H-indole-6-carboxamide
569	5-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxy-1H-indole-2-carboxamide
571	5-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzofuran-2-carboxamide
573	6-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxy-1H-indole-2-carboxamide
574	2-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzofuran-5-carboxamide
609	5-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxypicolinamide
652	4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N,2-dihydroxybenzamide
653	4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-N,2-dihydroxybenzamide
696	4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-3-fluoro-N-hydroxybenzamide
812	5-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxypicolinamide
813	4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-3-fluoro-N-hydroxybenzamide
814	4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazine-1-carbonyl)-N-hydroxybenzamide
818	4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)sulfonyl)-N-hydroxybenzamide
820	2-(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)sulfonyl)phenyl)-N-hydroxyacetamide
822	4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxycyclohexane-1-carboxamide
823	2-(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazine-1-carbonyl)phenyl)-N-hydroxyacetamide
824	3-(4-(((3R,6S)-4-benzyl-3,5-dimethylpiperazine-1-carbonyl)phenyl)-N-hydroxypropanamide

[0069] Preferably, the compounds represented by formula I or pharmaceutically acceptable salts thereof according to the present invention may be selected from the group consisting of compounds 081, 082, 083, 084, 098, 099, 100, 106, 107, 108, 109, 110, 112, 120, 121, 122, 123, 125, 126, 127, 128, 145, 146, 147, 148, 149, 159, 160, 161, 171, 173, 174, 175, 177, 186, 188, 193, 194, 195, 196, 198, 211, 214, 219, 248, 249, 250, 251, 252, 255, 265, 266, 267, 272, 283, 284, 285, 286, 292, 295, 297, 305, 326, 328, 329, 330, 332, 342, 343, 344, 345, 346, 349, 354, 356, 376, 380, 382, 383, 384, 385, 386, 387, 388, 403, 411, 413, 430, 431, 432, 433, 434, 435, 439, 440, 441, 442, 443, 444, 452, 453, 454, 455, 456, 467, 468, 481, 482, 483, 484, 485, 486, 569, 696, 813 and 823. More preferably, the compounds represented by formula I or pharmaceutically acceptable salts thereof according to the present invention may be selected from the group consisting of compounds 082, 083, 084, 098, 100, 120, 121, 122, 123, 125, 126, 127, 128, 145, 146, 148, 149, 159, 160, 161, 171, 174, 177, 194, 211, 249, 255, 283, 305, 326, 328, 329, 330, 332, 342, 343, 344, 345, 346, 349, 354, 356, 376, 382, 383, 387, 388, 411, 413, 431, 439, 441, 444, 452, 453, 454, 467, 468, 481, 482, 483, 484, 485, 696 and 813.

[0070] As used herein, the term "pharmaceutically acceptable salt" means any salt that is generally used in the pharmaceutical field. Examples of the pharmaceutically acceptable salt include, but are not limited to, salts with inorganic ions such as calcium, potassium, sodium or magnesium ions, salts with inorganic acids such as hydrochloric acid, nitric acid, phosphoric acid, bromic acid, iodic acid, perchloric acid, tartaric acid or sulfuric acid, salts with organic acids such as acetic acid, trifluoroacetic acid, citric acid, maleic acid, succinic acid, oxalic acid, benzoic acid, tartaric acid, fumaric acid, mandelic acid, propionic acid, citric acid, lactic acid, glycolic acid, gluconic acid, galacturonic acid, glutamic acid, glutaric acid, glucuronic acid, aspartic acid, ascorbic acid, carbonic acid, vanillic acid, hydroiodic acid or the like, salts with sulfonic acids such as methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid or naphthalenesulfonic acid, salts with amino acids such as glycine, arginine or lysine, and salts with amines such as trimethylamine, triethylamine, ammonia, pyridine or picoline.

[0071] In the present invention, preferred salts include salts with hydrochloric acid, trifluoroacetic acid, citric acid, bromic acid, maleic acid, phosphoric acid, sulfuric acid, tartaric acid or the like, and preferred examples of such compounds include compounds 230, 245, 250, 251, 253, 266, 270, 271, 273, 274, 275, 290, 291, 292, 293, 294, 295, 296, 297, 478 and 486 as disclosed herein.

[0072] The compounds represented by formula I may contain one or more asymmetrical carbon atoms, and thus may exist in the form of racemates, racemic mixtures, single enantiomers, diastereomeric mixtures, and individual diastereomers. The compounds of formula I can be separated into such isomers by methods known in the art, for example, column chromatography or HPLC. Alternatively, stereoisomers of the compounds of formula I may be synthesized by stereospecific synthesis using optically pure starting materials and/or

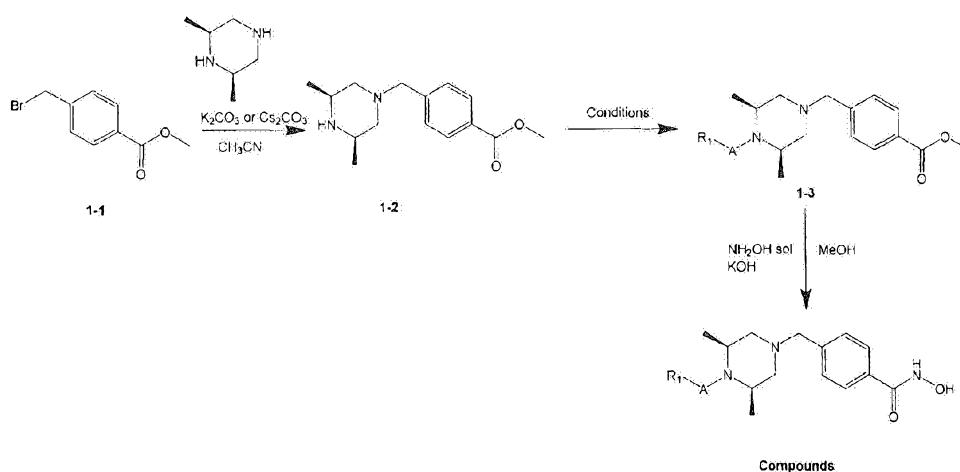
reagents of known configuration.

Methods for preparation of novel HDAC6 inhibitors

[0073] The present invention provides methods for the preparation of the novel compounds of formula I, stereoisomers thereof, or pharmaceutically acceptable salts thereof.

[0074] Preferred methods for the preparation of the novel compounds of formula I, stereoisomers thereof, or pharmaceutically acceptable salts thereof are as shown in reaction schemes 1 to 23 below, and also include modifications obvious to those skilled in the art.

Reaction Scheme I



[0075] Conditions: a) R_1-CH_2-Br (or $-I$, $-Cl$, $-OTf$, $-OMs$), K_2CO_3 (or Cs_2CO_3)/ CH_3CN (or DMF); b) R_1-CHO , $Na(CN)BH_3$, $AcOH/THF$; c) R_1-COCl , TEA/CH_2Cl_2 ; d) R_1CO_2H , $HOBt$, $EDCI$, $DIPEA/CH_2Cl_2$; e) R_1-NCO , TEA/CH_2Cl_2 ; f) 4-nitrophenyl 3-fluorobenzylcarbamate, TEA/DMF ; g) Ac_2O , TEA/CH_2Cl_2 ; h) R_1-SO_2Cl , TEA/CH_2Cl_2 ; i) R_1CO_2H , $HATU$, $DIPEA/DMF$.

Table 2

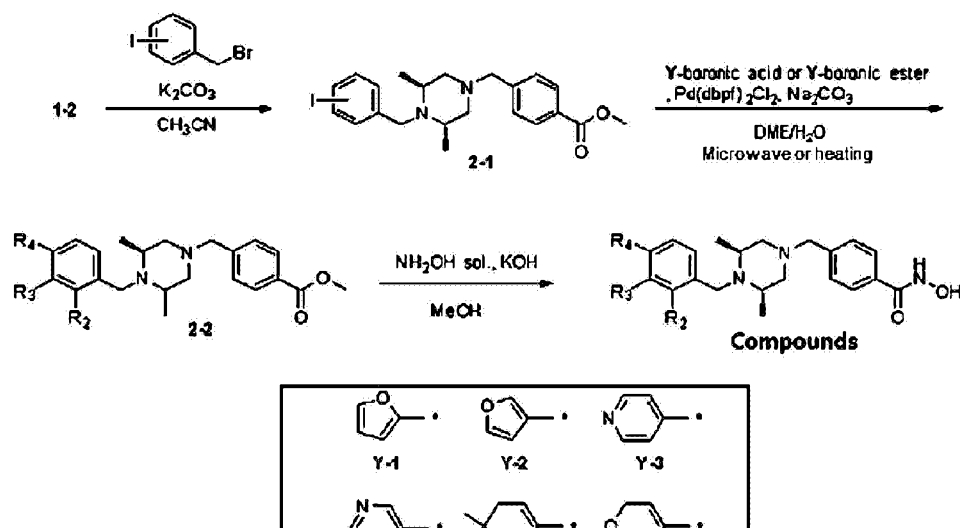
Compounds	A	R_1	conditions
82	$C=O$	methyl	g
83	$C=O$	phenyl	c
84	CH_2	phenyl	a
98	$NH(C=O)$	2-propyl	e
99	$NH(C=O)$	3-chlorophenyl	e
100	SO_2	phenyl	h
120	$C=O$	2-chlorophenyl	c
121	$C=O$	3-chlorophenyl	c
122	$C=O$	4-chlorophenyl	c

Compounds	A	R ₁	conditions
123	C=O	2-pyridyl	c
125	C=O	2-furanyl	c
126	C=O	2-thiophenyl	c
127	CH ₂	2-chlorophenyl	a
128	CH ₂	3-chlorophenyl	a
145	CH ₂	furan-2-yl	b
146	C=O	benzyl	c
147	CH ₂	methyl	a
148	CH ₂	ethyl	a
149	CH ₂	1,1,1-trifluoromethyl	a
159	NH(C=O)	phenyl	e
160	NH(C=O)	2-methylphenyl	e
161	NH(C=O)	benzyl	e
177	C=O	phenol	c
184	CH ₂	benzyl	b
188	C=O	phenethyl	c
204	CH ₂	1,1,1,-trifluoropropyl	a
211	CH ₂	2-fluorophenyl	a
212	CH ₂	2,5-difluorophenyl	a
213	CH ₂	2,4,5-trifluorophenyl	a
214	CH ₂	3,5-bis(trifluoromethyl)phenyl	a
222	C=O	3-fluorobenzyl	d
223	C=O	3-(trifluoromethyl)benzyl	d
224	C=O	3-chlorobenzyl	d
225	CH ₂	3-fluorophenyl	a
232	NH(C=O)	3-fluorobenzyl	f
255	CH ₂	3-(1H-pyrrol-1-yl)phenyl	a
265	CH ₂	naphthalen-2-yl	a
266	CH ₂	pyridin-4-yl	a
267	CH ₂	3-chloro-2-(trifluoromethyl)phenyl	a
270	CH ₂	4-isobutyl	a
272	CH ₂	2-methylprop-1-en-1-yl	a

Compounds	A	R ₁	conditions
275	CH ₂	propyl	a
290	C=O	4-methylphenyl	c
291	C=O	4-methoxyphenyl	c
292	C=O	tert-butyl	c
293	C=O	ethyl	c
294	C=O	propyl	c
295	C=O	cyclopropyl	c
296	C=O	isopropyl	c
297	C=O	isobutyl	c
354	CH ₂	oxazol-4-yl	a
355	CH ₂	pyrimidin-5-yl	a
403	C=O	1H-pyrazol-3-yl	i
404	C=O	2-pyrazinyl	i
405	C=O	4-pyridyl	c

[0076] As shown in reaction scheme 1 above, an amine of (2S,6R)-2,6-dimethylpiperazine is subjected to an alkylation reaction with methyl(4-bromomethyl)benzoate to prepare compound 1-2, which is then subjected to an alkylation reaction, an acylation reaction or a reductive amination reaction under conditions a) to i), thereby preparing compounds 1-3. Finally, the prepared compounds 1-3 are reacted with an aqueous hydroxylamine solution and potassium hydroxide to prepare compounds 82, 83, 84, 98, 99, 100, 120, 121, 122, 123, 125, 126, 127, 128, 145, 146, 147, 148, 149, 159, 160, 161, 177, 184, 188, 204, 211, 212, 213, 214, 222, 223, 224, 225, 232, 255, 265, 266, 267, 270, 272, 275, 290, 291, 292, 293, 294, 295, 296, 297, 354, 355, 403, 404 and 405.

Reaction Scheme 2



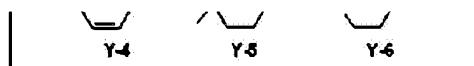
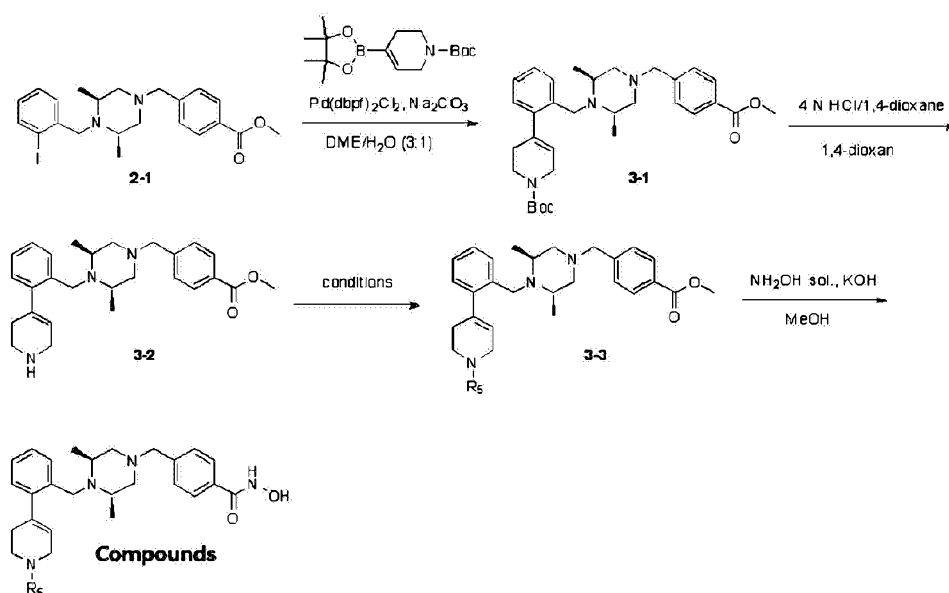


Table 3

Compounds	R ₂	R ₃	R ₄
309	H	H	Y-2
327	Y-1	H	H
328	Y-2	H	H
329	Y-3	H	H
330	Y-4	H	H
331	Y-5	H	H
332	Y-6	H	H
342	H	Y-1	H
343	H	Y-2	H
344	H	Y-4	H
345	H	Y-3	H
346	H	Y-6	H
347	H	Y-5	H

[0077] As shown in reaction scheme 2 above, compound 1-2 is alkylated to prepare compound 2-1, which is then subjected to a Suzuki reaction with a boronic acid or boronic ester containing each of compounds Y-1 to Y-6, thereby preparing compounds 2-2. Finally, the prepared compounds 2-2 are reacted with an aqueous hydroxylamine solution and potassium hydroxide to prepare compounds 309, 327, 328, 329, 330, 331, 332, 342, 343, 344, 345, 346 and 347.

Reaction Scheme 3



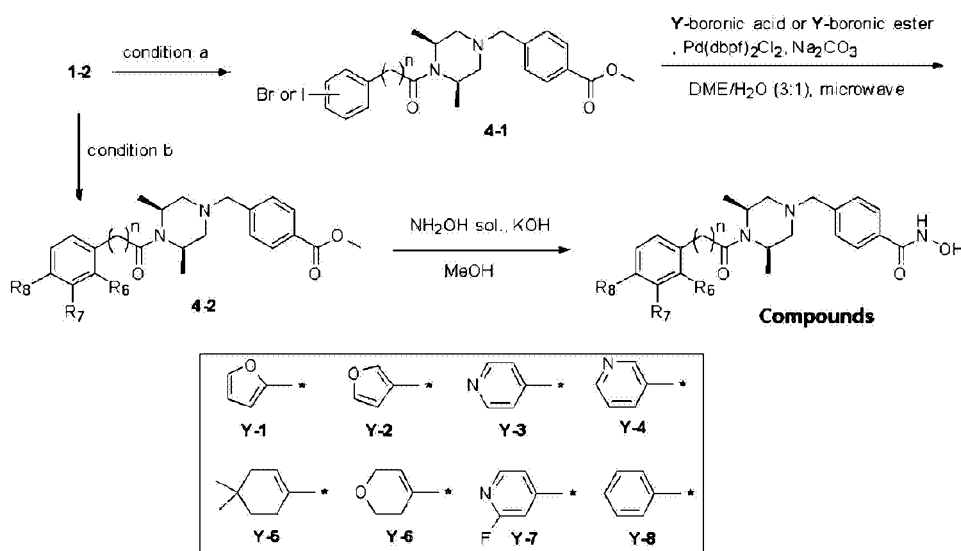
[0078] Conditions: a) MsCl, TEA/CH₂Cl₂; b) Ac₂O, TEA/CH₂Cl₂; c) R₅-OTf, K₂CO₃/CH₃ CN; d) R₅-X, TEA/CH₂Cl₂.

Table 4

Compounds	R ₅	conditions
481	methanesulfonyl	a
482	acetyl	b
483	2,2,2-trifluoroethyl	c
484	isopropyl	d
485	ethyl	d

[0079] As shown in reaction scheme 3 above, compound 2-1 is subjected to a Suzuki reaction with tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate to prepare compound 3-1, which is then deprotected under an acidic condition, thereby preparing compound 3-2. The prepared compound 3-2 is subjected to substitution reactions under conditions a) to d) above to prepare compounds 3-3, which are then reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compounds 481, 482, 483, 484 and 485.

Reaction Scheme 4



[0080] Conditions: a) (iodo, chloro or bromo)benzoyl chloride, TEA/CH₂Cl₂; b) 2-([1,1'-biphenyl]-3-yl)acetic acid, HOBt, EDCI, DIPEA/CH₂Cl₂.

Table 5

Compounds	n	R ₆	R ₇	R ₈	conditions
234	1	H	Y-8	H	b
242	0	H	Y-1	H	a

Compounds	n	R ₆	R ₇	R ₈	conditions
243	0	H	Y-2	H	a
244	0	H	Y-6	H	a
245	0	H	Y-3	H	a
246	0	H	Y-4	H	a
247	0	H	Y-5	H	a
283	0	Y-1	H	H	a
284	0	Y-2	H	H	a
285	0	Y-3	H	H	a
286	0	Y-4	H	H	a
288	0	Y-5	H	H	a
326	0	Y-6	H	H	a
340	0	H	H	Y-1	a

[0081] As shown in reaction scheme 4 above, compound 1-2 is reacted with benzoyl chloride or benzoyl bromide to prepare compound 4-1, which is then subjected to a Suzuki reaction with a boronic acid or boronic ester containing each of compounds Y-1 to Y-8, thereby preparing compounds 4-2. Alternatively, compound 1-2 is subjected to an amide coupling reaction with 2-([1,1'-biphenyl]-3-yl)acetic acid, thereby preparing compounds 4-2. The prepared compounds 4-2 are reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compounds 234, 242, 243, 244, 245, 246, 247, 283, 284, 285, 286, 288, 326 and 340.

Reaction Scheme 5

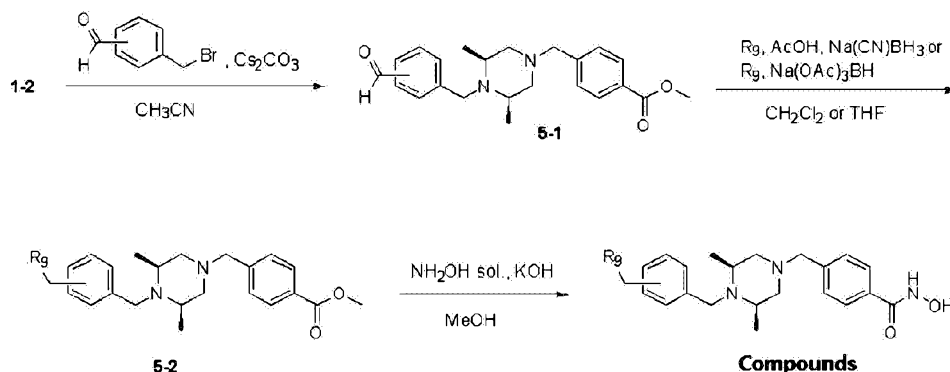


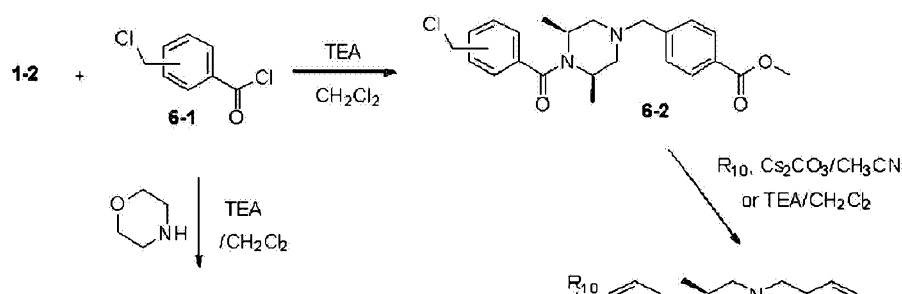
Table 6

Compounds	Position	R ₉
356	meta	morpholine
376	para	morpholine
382	meta	piperidine
383	meta	(R)-3-fluoropyrrolidine

Compounds	Position	R ₉
384	meta	3,3-difluoroazetidine
385	meta	4-benzylpiperazine
411	para	(R)-3-fluoropyrrolidine
412	para	3,3-difluoroazetidine
413	para	4-benzylpiperazine
426	meta	N,N-diethylamine
427	meta	pyrrolidine
428	meta	4-methylpiperazine
429	meta	4-ethylpiperazine
430	meta	4-isopropylpiperazine
431	meta	4-acetylpiperazine
452	meta	4-methansulfonylpiperazine
453	meta	4-(2,2,2-trifluoroethyl)piperazine
454	meta	4-isopentylpiperazine
455	meta	N,N-diethylpropane-1,2-diamine
456	meta	N-benzyl-N-methylpropane-1,2-diamine
457	ortho	morpholine
466	para	pyrrolidine
467	para	piperidine
468	para	4-methylpiperazine
486	para	4-acetylpiperazine

[0082] As shown in reaction scheme 5 above, compound 1-2 is subjected to a substitution reaction with ortho-, meta- or para-(bromomethyl)benzaldehyde to prepare compounds 5-1, which are then subjected to a reductive amination reaction with amine compounds, thereby preparing compounds 5-2. Finally, the prepared amine compounds 5-2 are reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compounds 356, 376, 382, 383, 384, 385, 411, 412, 413, 426, 427, 428, 429, 430, 431, 452, 453, 454, 455, 456, 457, 466, 467, 468 and 486.

Reaction Scheme 6



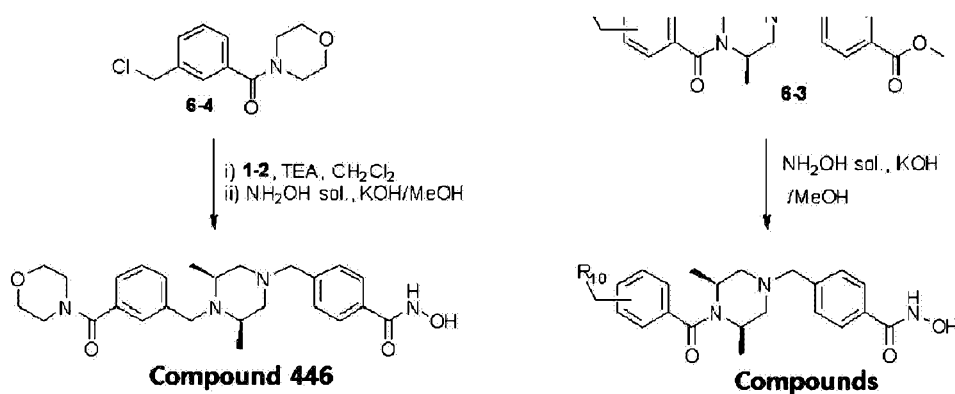


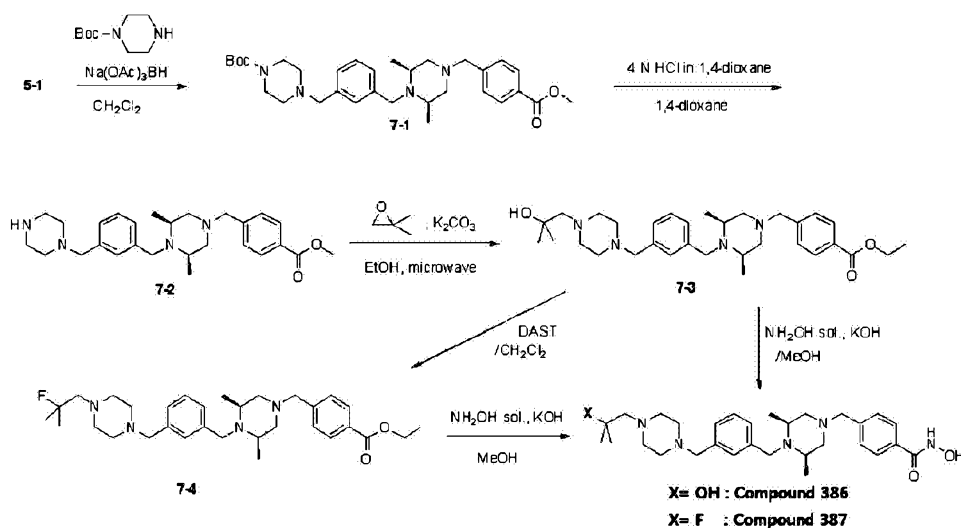
Table 7

Compounds	Position	R ₁₀
423	meta	pyrrolidine
424	meta	piperidine
425	meta	N,N-diethylamine
432	meta	4-methylpiperazine
433	meta	4-ethylpiperazine
434	meta	4-isopropylpiperazine
435	meta	4-acetyl piperazine
439	meta	morpholine
440	meta	N,N-diethylpropane-1,2-diamine
441	meta	N-benzyl-N-methylpropane-1,2-diamine
442	meta	4-isopentylpiperazine
443	meta	4-(2,2,2-trifluoroethyl)piperazine
444	meta	4-methanesulfonylpiperazine
458	para	morpholine
459	para	piperidine
460	para	(R)-3-fluoropyrrolidine
461	para	pyrrolidine
462	para	4-methylpiperazine
463	para	4-methanesulfonylpiperazine

[0083] As shown in reaction scheme 6 above, compound 6-1 is prepared and subjected to an acylation reaction with compound 1-2 to prepare compound 6-2. The prepared compound 6-2 is subjected to a substitution reaction with amine compounds to prepare compounds 6-3, which are then reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compounds 423, 424, 425, 432, 433, 434, 435, 439, 440, 441, 442, 443, 444, 458, 459, 460, 461, 462 and 463.

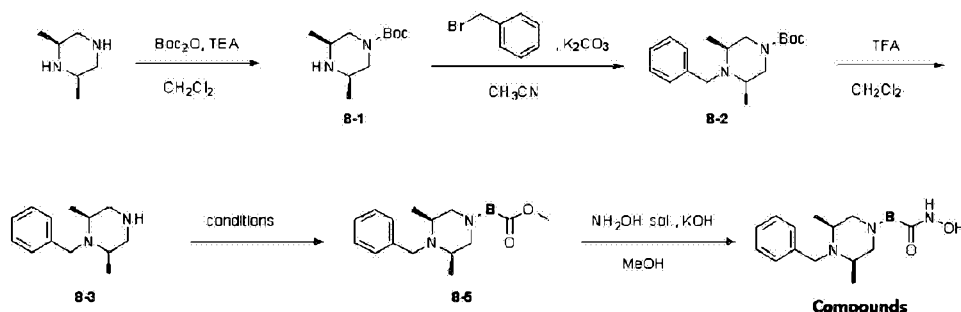
[0084] Alternatively, compound 6-1 is reacted with morpholine to prepare compound 6-4. The prepared compound 6-4 and compound 1-2 are subjected to a substitution reaction, and then reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compound 446.

Reaction Scheme 7

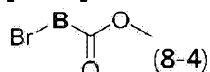


[0085] As shown in reaction scheme 7, compound 5-1 is subjected to a reductive amination reaction with 4-tert-butyl piperazine-1-carboxylate, and then deprotected under an acidic condition to prepare compound 7-2. The prepared compound 7-2 is reacted with 2,2-dimethyloxirane to prepare compound 7-3, which is then reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compound 386. Further, compound 7-3 is reacted with DAST to substitute the hydroxyl group with fluoride, thereby preparing compound 7-4. The prepared compound 7-4 is prepared with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compound 387.

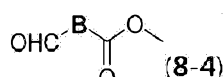
Reaction Scheme 8



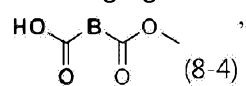
[0086] Conditions: a)



base/ CH_3CN or DCM; b)



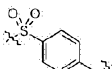
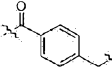
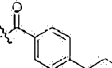
reducing agent/ CH_2Cl_2 . c)



EDC, HOBT, DIPEA,/ CH_2Cl_2

Table 8

Compound	B	Conditions
154		a
171		b
172		b
173		a
194		a
218		a
219		a
520		b ($\text{NaBH}(\text{OAc})_3$)
571		a (DIPEA)
574		a (DIPEA)
652		a (TEA)
812		b ($\text{NaBH}(\text{OAc})_3$)
813		a (K_2CO_3)
814		a (TEA)

Compound	B	Conditions
818		a (TEA)
820		a (TEA)
822		b (NaBH(OAc) ₃)
823		c
824		c

[0087] As shown in reaction scheme 8, (2S,6R)-2,6-dimethylpiperazine is protected with Boc and reacted with benzyl bromide, after which it is deprotected under an acidic condition, thereby preparing compound (8-3). The prepared compound 8-3 is subjected to an alkylation reaction or a reductive amination reaction with compound 8-4 shown in conditions a) to c), thereby preparing compounds 8-5. The prepared compounds 8-5 are reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compounds 154, 171, 172, 173, 194, 218, 219, 520, 571, 574, 652, 812, 813, 814, 818, 820, 822, 823 and 824.

Reaction Scheme 9

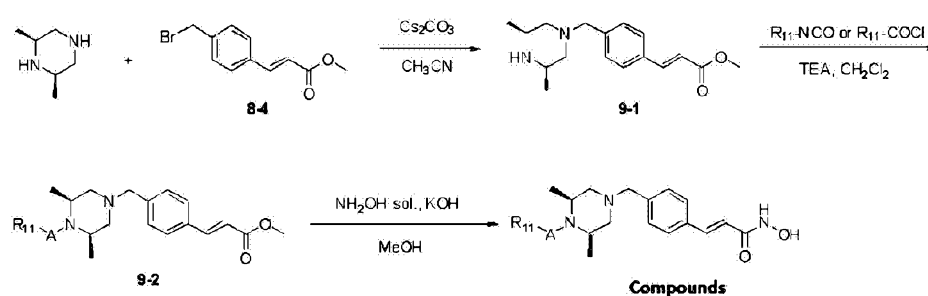


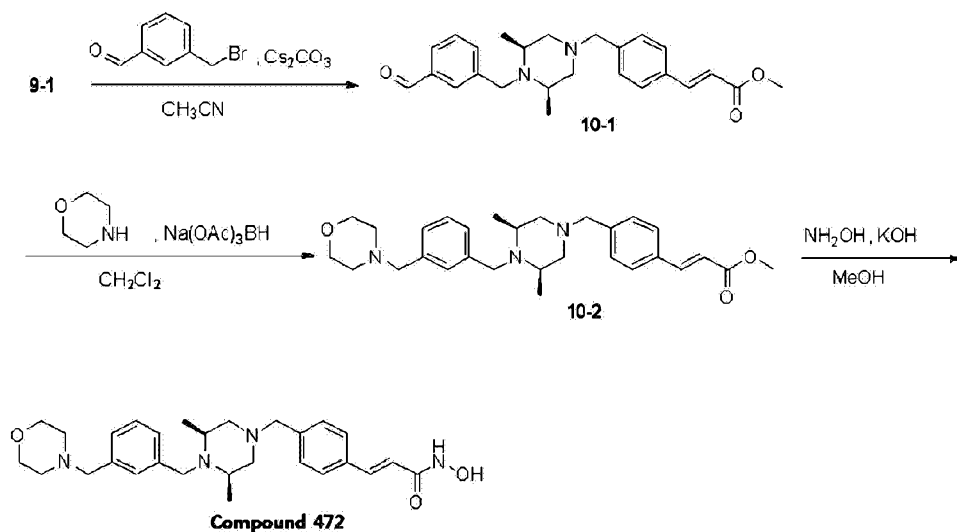
Table 9

Compounds	A	R ₁₁
321	NH(C=O)	3-(1H-pyrrol-1-yl)phenyl
322	C=O	2-furanyl
323	C=O	benzyl

[0088] As shown in reaction scheme 9 above, compound 8-4 is reacted with (2S,6R)-2,6-dimethylpiperazine to prepare compound 9-1, which is then subjected to a substitution reaction with an isocyanate or carbonyl chloride containing substituents represented by R₁₁, thereby

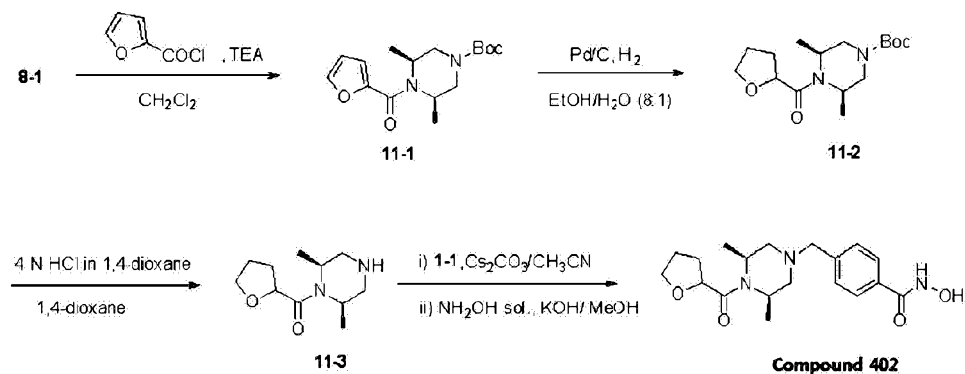
preparing compound 9-2. The prepared compounds 9-2 are reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compounds 321, 322 and 323.

Reaction Scheme 10



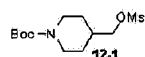
[0089] As shown in reaction scheme 10 above, compound 9-1 is subjected to an alkylation reaction with 3-(bromomethyl)benzaldehyde to prepare compound 10-1. The prepared compound 10-1 is subjected to a reductive amination reaction with morpholine to prepare compound 10-2, which is then reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compound 472.

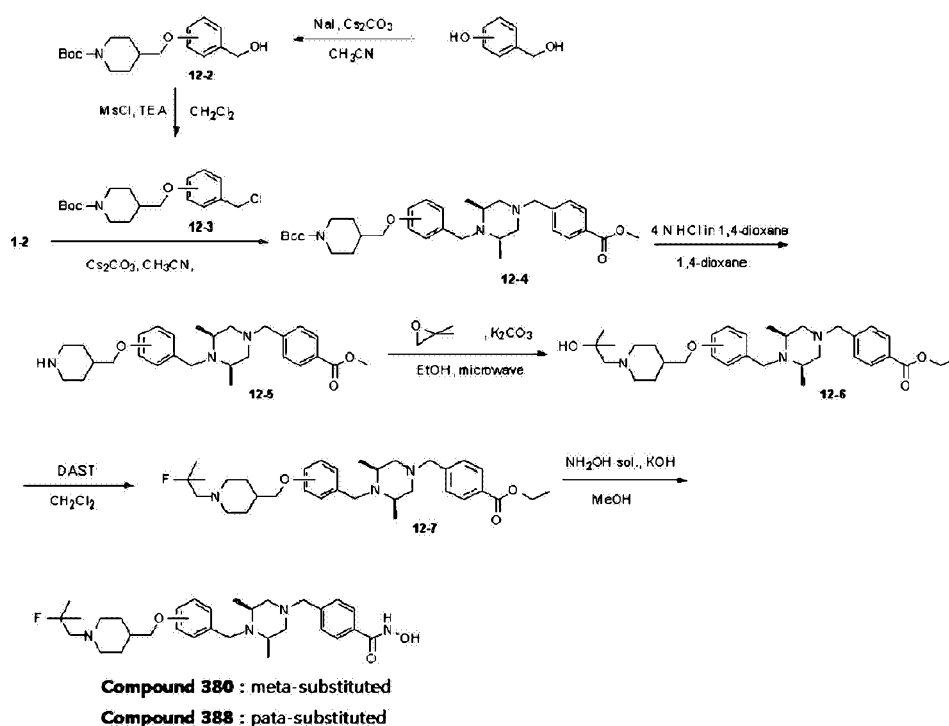
Reaction Scheme 11



[0090] As shown in reaction scheme 11 above, compound 8-1 is reacted with furan-2-carbonyl chloride to prepare compound 11-1. The prepared compound 11-1 is hydrogenated to prepare compound 11-2, which is then Boc deprotected under an acidic condition to prepare compound 11-3. The prepared compound 11-3 is reacted with compound 1-1, and then reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compound 402.

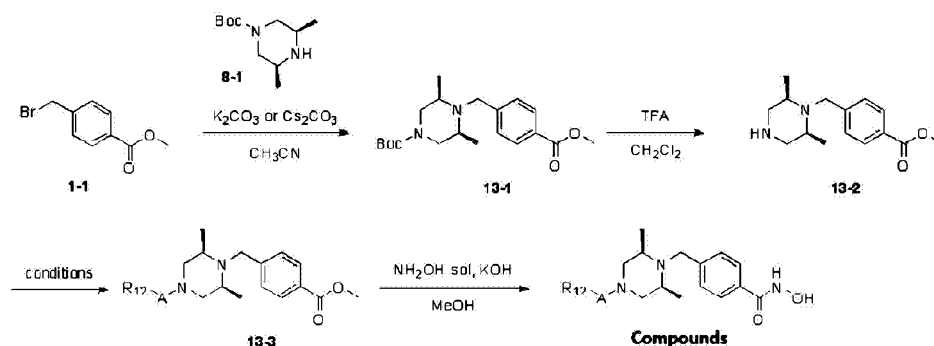
Reaction Scheme 12



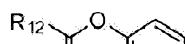


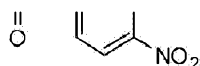
[0091] As shown in reaction scheme 12 above, 3-hydroxybenzylalcohol and 4-hydroxybenzylalcohol are subjected to a substitution reaction with compound 12-1 to prepare compounds 12-2, which are then reacted with MsCl to prepare compounds 12-3. Compounds 12-3 are reacted with compound 1-2 to prepare compounds 12-4, which are deprotected under an acidic condition and reacted with 2,2-dimethyloxirane to prepare compounds 12-6. The prepared compounds 12-6 are reacted with DAST to substitute the hydroxyl group with fluoride to thereby prepare compounds 12-7. Finally, the prepared compounds 12-7 are reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compounds 380 and 388.

Reaction Scheme 13



[0092] Conditions: a) $R_{12}-CH_2-Br$ (I or -Cl), K_2CO_3 (or Cs_2CO_3)/ CH_3CN (or DMF); b) $R_{12}-CHO$, $NaCNBH_3$, $AcOH/THF$ or $AcOH/CH_2ClCH_2Cl$; c) $R_{12}-COX$, TEA/CH_2Cl_2 ; d) $R_{12}CO_2H$, $HOBT$, $EDCI$, $DIPEA/CH_2Cl_2$; e) $R_{12}-NCO$, TEA/CH_2Cl_2 ; f) $R_{12}-NCS$, TEA/CH_2Cl_2 ; g)





DMF; h) R₁₂-SO₂Cl, TEA/CH₂Cl₂.

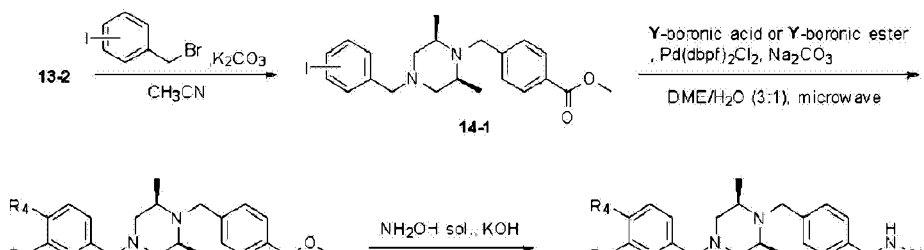
Table 10

Compounds	A	R ₁₂	conditions
80	C=O	phenyl	c
81	CH ₂	phenyl	a
103	NH(C=O)	2-propyl	e
104	NH(C=O)	3-chlorophenyl	e
105	SO ₂	phenyl	h
106	C=O	4-chlorophenyl	c
107	C=O	3-chlorophenyl	c
108	C=O	2-chlorophenyl	c
109	SO ₂	4-chlorophenyl	h
110	SO ₂	2-chlorophenyl	h
111	C=O	2-pyridinyl	c
112	C=O	3-pyridinyl	c
113	SO ₂	3-pyridinyl	h
114	C=O	2-thiophenyl	c
115	C=O	2-furanyl	c
118	CH ₂	2-chlorophenyl	a
162	NH(C=O)	phenyl	e
163	NH(C=O)	2-methoxyphenyl	e
164	NH(C=O)	3-methoxyphenyl	e
165	NH(C=O)	4-methoxyphenyl	e
166	NH(C=O)	2-methylphenyl	e
167	NH(C=O)	3-methylphenyl	e
168	NH(C=O)	benzyl	e
183	CH ₂	benzyl	b
185	NH(C=O)	1-methyl-1H-indole	e
186	NH(C=O)	3-(1H-pyrrol-1-yl)phenyl	e
187	NH(C=O)	2,3-dihydrobenzofuran-5-yl	e
189	C=S	3-methylphenylamine	f
196	NCH ₃ (C=O)	phenyl	g
197	C=O	indoline	g

Compounds	A	R ₁₂	conditions
215	CH ₂	2,4,5-trifluorophenyl	a
220	CH(CH ₃)	phenyl	a
230	NH(C=O)	3-methoxybenzyl	g
231	NH(C=O)	3-fluorobenzyl	g
233	C=O	3-chlorobenzyl	d
256	CH ₂	(3-pyrrole)phenyl	a
268	CH ₂	naphthalen-2-yl	a
271	CH ₂	isobutyl	a
273	CH(CH ₃)	methyl	a
274	CH ₂	propyl	a
298	CH ₂	3-trifluoromethylphenyl	b
299	CH ₂	4-(N,N-dimethylamino)phenyl	b
300	CH ₂	4-(methylsulfonyl)phenyl	b
301	CH ₂	4-(1H-imidazol-1-yl)phenyl	b
302	CH ₂	4-(thiophen-2-yl)phenyl	b
303	CH ₂	4-(furan-2-yl)phenyl	b
304	CH ₂	4-(4H-1,2,4-triazol-4-yl)phenyl	b
305	CH ₂	2-(2-methyl-1H-imidazol-1-yl)phenyl	b

[0093] As shown in reaction scheme 13 above, compound 8-1 and compound 1-1 are subjected to an alkylation reaction to prepare compound 13-1, which is then deprotected under an acidic condition to prepare compound 13-2. The prepared compound 13-2 is subjected to an alkylation reaction, an acylation reaction or a reductive amination reaction under conditions a) to h), thereby preparing compounds 13-3. Finally, the prepared compounds 13-3 are reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compounds 80, 81, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 118, 162, 163, 164, 165, 166, 167, 168, 183, 185, 186, 187, 189, 196, 197, 215, 220, 230, 231, 233, 256, 268, 271, 273, 274, 298, 299, 300, 301, 302, 303, 304 and 305.

Reaction Scheme 14



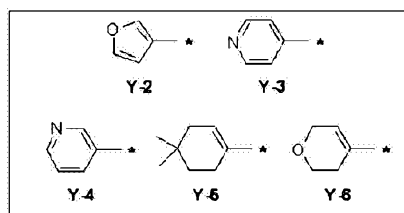
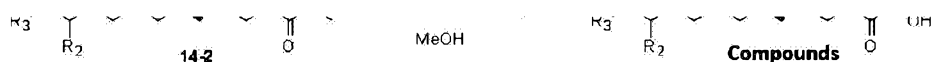


Table 11

Compounds	R ₂	R ₃	R ₄
348	Y-2	H	H
349	Y-4	H	H
350	Y-3	H	H
351	Y-6	H	H
352	Y-5	H	H
396	H	Y-2	H
400	H	H	Y-5
401	H	H	Y-6

[0094] As shown in reaction scheme 14 above, compound 13-2 is subjected to an alkylation reaction to prepare compound 14-1, which is then subjected to a Suzuki reaction with a boronic acid boronic ester containing each of Y-2 to Y-6, thereby preparing compounds 14-2. Finally, the prepared compounds 14-2 are reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compounds 348, 349, 350, 351, 352, 396, 400 and 401.

Reaction Scheme 15

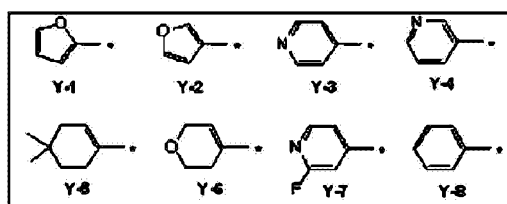
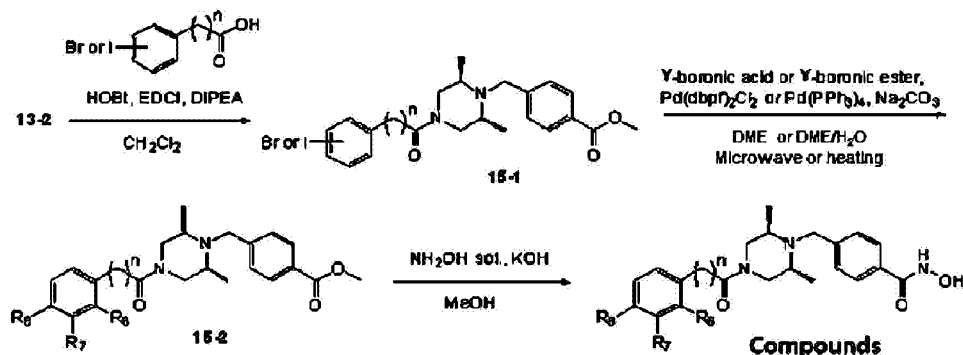


Table 12

Compounds	n	R ₆	R ₇	R ₈
250	1	H	Y-8	H
251	1	H	Y-3	H
252	1	H	Y-6	H
253	1	H	Y-5	H
257	0	H	Y-1	H
258	0	H	Y-2	H
259	0	H	Y-6	H
260	0	H	Y-3	H
261	0	H	Y-4	H
262	0	H	Y-7	H
263	0	H	Y-5	H
276	0	Y-1	H	H
277	0	Y-2	H	H
278	0	Y-6	H	H
279	0	Y-4	H	H
280	0	Y-5	H	H

[0095] As shown in reaction scheme 15 above, compound 13-2 is subjected to an amide coupling reaction with 2-, 3-, 4-iodobenzoic acid or 2-(3-bromophenyl)acetic acid to prepare compound 15-1, which is then subjected to a Suzuki reaction with a boronic acid or boronic ester containing each of Y-1 to Y-8, thereby preparing compounds 15-2. Finally, the prepared compounds 15-2 are reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compounds 250, 251, 252, 253, 257, 258, 259, 260, 261, 262, 263, 276, 277, 278, 279 and 280.

Reaction Scheme 16

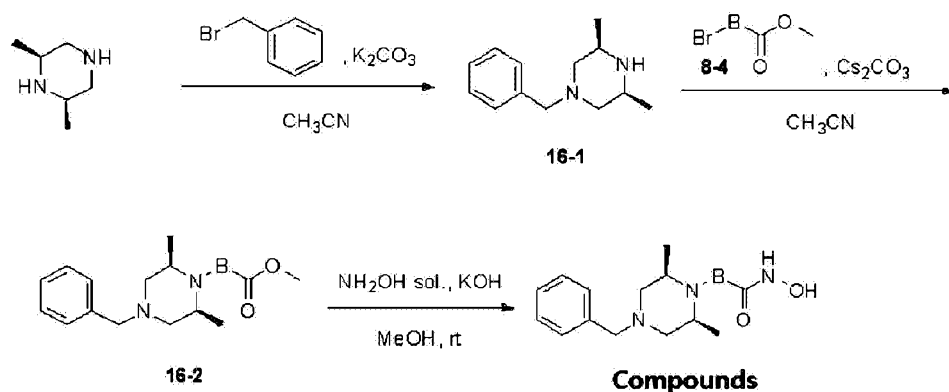
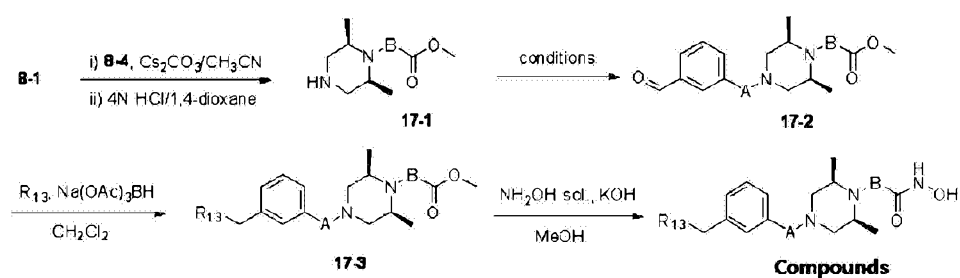


Table 13

Compounds	B
174	
175	
176	
195	

[0096] As shown in reaction scheme 16 above, (2S,6R)-2,6-dimethylpiperazine is reacted with benzyl bromide to introduce a benzyl group therein to thereby prepare compound 16-1, which is then subjected to an alkylation reaction with compound 8-4, thereby preparing compounds 16-2. Finally, the prepared compounds 16-2 are reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compounds 174, 175, 176 and 195.

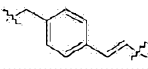
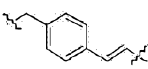
Reaction Scheme 17



[0097] Conditions: a) (3-bromomethyl)benzaldehyde, $\text{Cs}_2\text{CO}_3/\text{CH}_3\text{CN}$; b) 3-formylbenzoic acid, HOBt, EDCI, DIPEA/ CH_2Cl_2 .

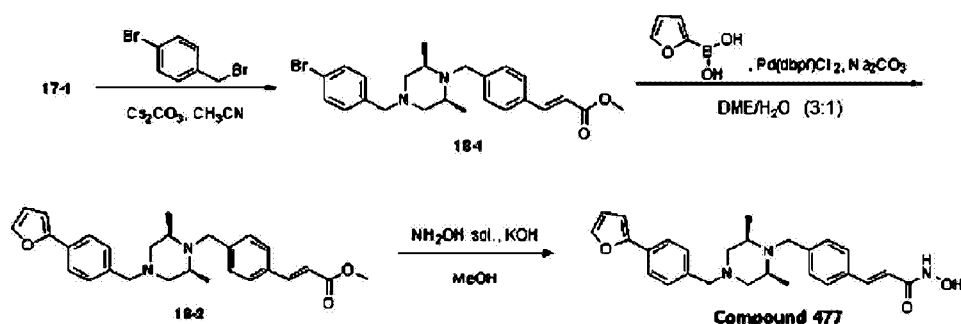
Table 14

Compounds	A	B	R_{13}	conditions
475	CH_2		pyrrolidine	a
476	CH_2		diethylamine	a
478	CH_2		diethylamine	a
479	CH_2		pyrrolidine	a

Compounds	A	B	R ₁₃	conditions
				
480	C=O		pyrrolidine	b
487	C=O		diethylamine	b

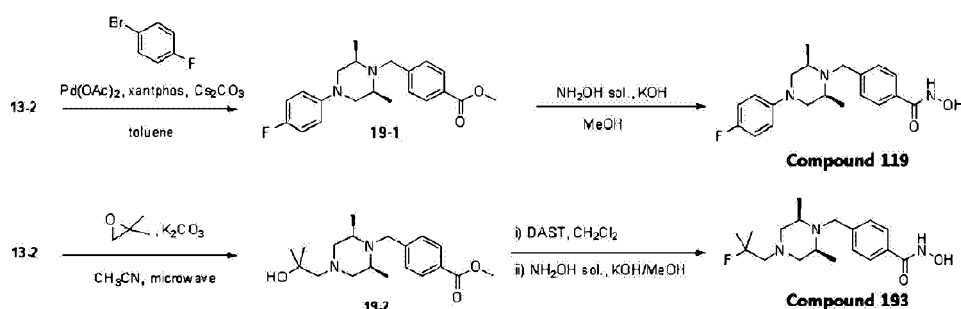
[0098] As shown in reaction scheme 17 above, compound 8-1 is subjected to an alkylation reaction with compound 8-4 and deprotected under an acidic condition, thereby preparing compound 17-1. The prepared compound 17-1 is subjected to an alkylation reaction or an amide coupling reaction under conditions a) or b) to prepare compounds 17-2, which are then subjected to a reductive amination reaction with pyrrolidine or diethylamine, thereby preparing compounds 17-3. Finally, the prepared compounds 17-3 are reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compounds 475, 476, 478, 479, 480 and 487.

Reaction Scheme 18



[0099] As shown in reaction scheme 18 above, compound 17-1 is subjected to an alkylation reaction with 4-bromobenzyl bromide to prepare compound 18-1, which is then subjected to a Suzuki reaction with furan-2-yl boronic acid, thereby preparing compound 18-2. Finally, the prepared compound 18-2 is reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compound 477.

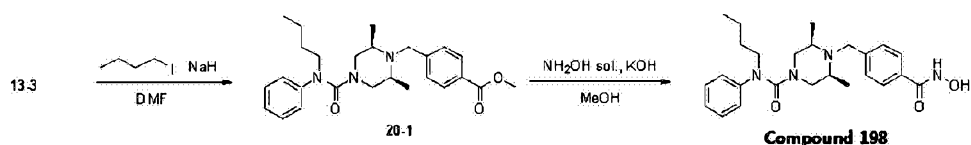
Reaction Scheme 19



[0100] As shown in reaction scheme 19 above, compound 13-2 is subjected to a Buchwald reaction with 1-bromo-4-fluorobenzene to prepare compound 19-1, which is then reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compound 119.

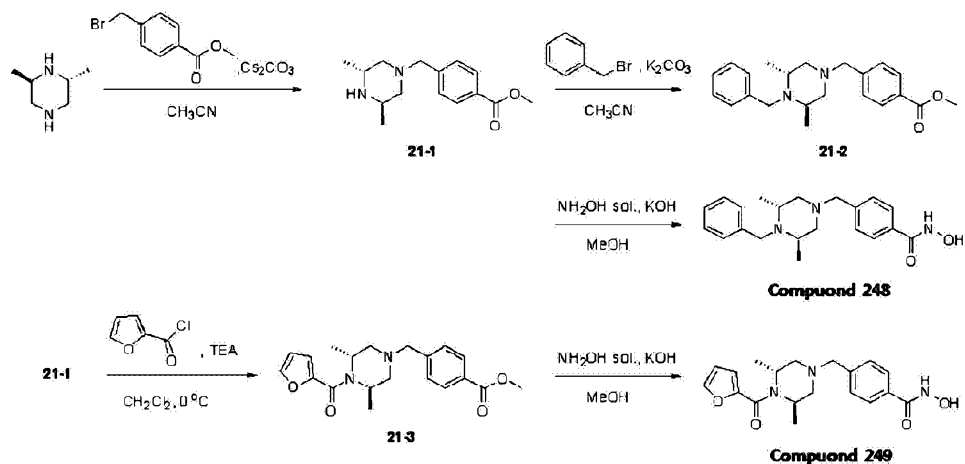
[0101] Alternatively, compound 13-2 is reacted with 2,2-dimethyloxirane to prepare compound 19-2, which is then reacted with DAST to substitute the hydroxyl group with fluoride and then reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compound 193.

Reaction Scheme 20



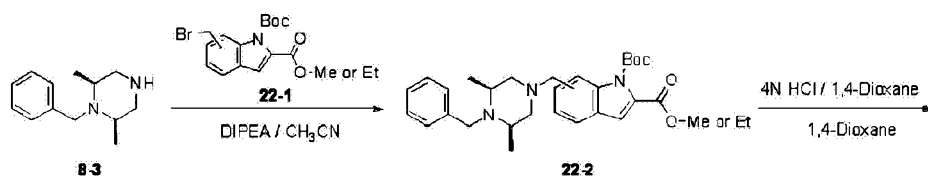
[0102] As shown in reaction scheme 20 above, compound 13-3 is subjected to an alkylation reaction with butyl iodide to prepare compound 20-1, which is then reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compound 198.

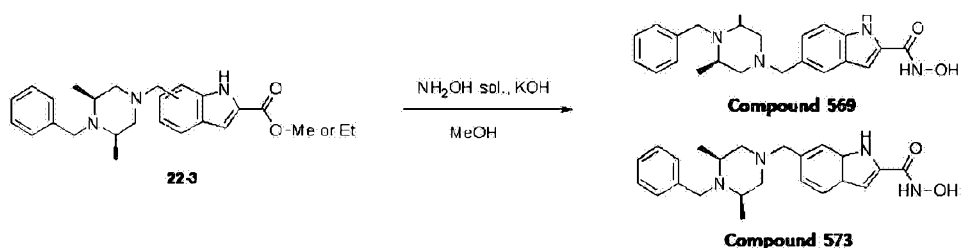
Reaction Scheme 21



[0103] As shown in reaction scheme 21 above, (2R,6R)-2,6-dimethylpiperazine is subjected to an alkylation reaction with compound 1-1 to prepare compound 21-1, which is then subjected to an alkylation reaction or an acylation reaction, thereby preparing compound 21-2 or compound 21-3. Finally, the prepared compound 21-2 or compound 21-3 is reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compounds 248 and 249.

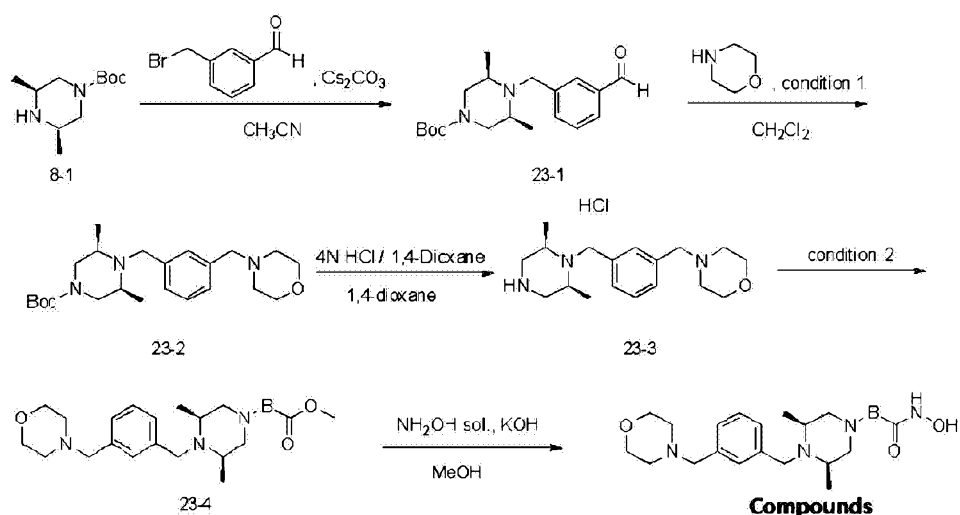
Reaction Scheme 22





[0104] As shown in reaction scheme 22 above, (2S,6R)-1-benzyl-2,6-dimethylpiperazine is subjected to an alkylation reaction with compound 8-3 and compound 22-1 to prepare compounds 22-2, which are then deprotected to remove the tert-butyloxycarbonyl group, thereby preparing compounds 22-3. Finally, compounds 22-3 are reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compounds 569 and 573.

Reaction Scheme 23



[0105] Conditions: a),

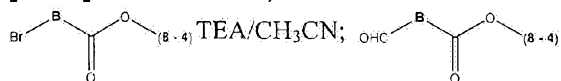


Table 15

Compounds	B	Condition 1	Condition 2
609		$\text{NaCNBH}_3/\text{AcOH}$	B (NaCNBH_3)
653		$\text{NaBH}(\text{OAc})_3$	a
696		$\text{NaBH}(\text{OAc})_3$	a

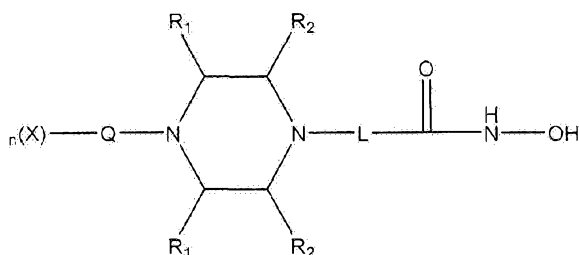
Compounds	B	Condition 1	Condition 2
			

[0106] As shown in reaction scheme 23 above, compound 8-1 is subjected to an alkylation reaction to prepare compound 23-1, which is then subjected to a reductive amination reaction with morpholine to prepare compound 23-2, which is then deprotected to remove the tert-butyloxycarbonyl group, thereby preparing compound 23-3. Compound 23-3 is subjected to an alkylation reaction with compound 8-4 to prepare compounds 23-4. Finally, the prepared compounds 23-4 are reacted with an aqueous hydroxylamine solution and potassium hydroxide, thereby preparing compounds 609, 653 and 696.

Compositions comprising novel compounds having HDAC6 inhibitory activity, and said compositions for use in treating diseases

[0107] The present invention provides a pharmaceutical composition for use in preventing or treating histone deacetylase 6 (HDAC6) activity-associated diseases, which contains, as an active ingredient, a compound represented by the following formula I, a stereoisomer thereof or a pharmaceutically acceptable salt thereof:

Formula I



wherein L, R₁, R₂, Q, X and n are as defined above.

inflammatory diseases, autoimmune diseases, neurological diseases and neurodegenerative disorders. Specifically, these histone deacetylase 6 (HDAC6) activity-associated diseases include lung cancer, colon cancer, breast cancer, prostate cancer, liver cancer, brain cancer, ovarian cancer, stomach cancer, skin cancer, pancreatic cancer, glioma, glioblastoma, leukaemia, lymphoma, multiple myeloma, solid cancer, Wilson's disease, Spinocerebellar ataxia, prion disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, amyloidosis, Alzheimer's disease, alcoholic liver disease, spinal muscular atrophy, rheumatoid arthritis, and osteoarthritis, as well as disorders or diseases associated with the abnormal function of histone deacetylase.

[0108] In an embodiment, the compound represented by formula I according to the present invention may be a compound represented by formula II or formula III. In another embodiment, the compound represented by formula I according to the present invention may be any one of the compounds represented by formula I-1 to I-23. In still another embodiment, the compound represented by formula I according to the present invention may be any one of compounds

080 to 824.

[0109] The pharmaceutically acceptable salt is as described above with respect to a pharmaceutically acceptable salt of the compound represented by formula I according to the present invention.

[0110] For administration, the pharmaceutical composition according to the present invention may further contain at least one pharmaceutically acceptable carrier in addition to the compound of formula I, a stereoisomer thereof or a pharmaceutically acceptable salt thereof. The pharmaceutically acceptable carrier that is used in the present invention may be at least one of physiological saline, sterile water, Ringer solution, buffered saline, dextrose solution, maltodextrin solution, glycerol, ethanol, and a mixture of two or more thereof. If necessary, the composition may contain other conventional additives such as an antioxidant, a buffer or a bacteriostatic agent. In addition, the composition can be formulated into injectable formulations such as solutions, suspensions, turbid fluid, etc, pills, capsules, granules and tablets using a diluent, a dispersing agent, a surfactant, a binder and a lubricant. Thus, the composition of the present invention may be in the form of patches, liquids, pills, capsules, granules, tablets, suppositories, etc. These formulations can be prepared either by conventional methods that are used for formulation in the art or by the method disclosed in Remington's Pharmaceutical Science (the latest edition), Mack Publishing Company, Easton PA. In addition, the composition of the present invention can be prepared as various formulations depending on diseases or components.

[0111] The composition of the present invention may be administered orally or parenterally (e.g., intravenously, subcutaneously, intraperitoneally or topically) depending on the intended use. The dose of the pharmaceutical composition varies depending on the patient's weight, age, sex, health conditions, diet, the time of administration, the mode of administration, excretion rate, the severity of the disease, and the like.

[0112] The pharmaceutical composition of the present invention may further contain, in addition to the compound represented by formula I, a stereoisomer thereof or a pharmaceutically acceptable salt thereof, one or more active ingredients that exhibit medical efficacy identical or similar thereto.

[0113] The present invention provides a compound represented by formula I, a stereoisomer thereof or a pharmaceutically acceptable salt thereof for use in preventing or treating histone deacetylase 6 activity-associated diseases.

[0114] As used herein, the term "therapeutically effective amount" refers to the amount of the compound represented by formula I, which is effective for the prevention or treatment of histone deacetylase 6 activity-associated diseases.

[0115] Described herein is a method of selectively inhibiting HDAC6, which comprises administering the compound of formula I, a stereoisomer thereof or a pharmaceutically

acceptable salt thereof to mammals including humans.

[0116] The method of preventing or treating histone deacetylase 6 activity-associated disease described herein includes inhibiting or averting the disease as well as addressing the disease itself, prior to the onset of symptoms by administering the compound represented by formula I. In the management of diseases, the magnitude of a prophylactic or therapeutic dose of a particular active ingredient will vary with the nature and severity of the disease or condition, and may also vary according to the route by which the active ingredient is administered. The dose and the dose frequency will also vary according to the age, body weight, and response of the individual patient. Suitable dosing regimens can be readily selected by those skilled in the art with due consideration of such factors. In addition, the method of preventing or treating histone deacetylase 6 activity-associated disease described herein may further comprise administering a therapeutically effective amount of an additional active agent helpful for the treatment of the disease together with the compound represented by formula I, in which the additional active agent can exhibit a synergistic effect with the compound of formula I or an assistant effect.

[0117] Further described herein is the use of the compound represented by formula I, a stereoisomer thereof or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating histone deacetylase 6 activity-associated disease. For the preparation of the medicament, the compound represented by formula I may be mixed with a pharmaceutically acceptable adjuvant, diluent, carrier or the like, and combined with other active agents such that the active ingredients can have synergistic effects.

[0118] The particulars mentioned in the use, composition and treatment method of the present invention may be appropriately combined unless contradictory to one another.

Advantageous Effects of Invention

[0119] The compounds represented by formula I, stereoisomers thereof or pharmaceutically acceptable salts thereof can selectively inhibit HDAC6, and thus exhibit excellent effects on the prevention or treatment of histone deacetylase 6 activity-associated diseases.

Mode for the Invention

[0120] Hereinafter, the present invention will be described in further detail with reference to Examples, Preparation Examples and Experimental Examples.

Preparation of novel dimethylpiperazine derivative compounds

[0121] Specific methods for preparing the compounds of formula I are as follows.

Example 1: Synthesis of compound 80

(4-(((2S,6R)-4-benzoyl-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-benzoyl-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0122] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (3 mL), and then benzoyl chloride (0.049 mL, 0.420 mmol) and TEA (0.106 mL, 0.763 mmol) were added thereto. The mixture was stirred at 0 °C for 1 hour, and saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was separated and concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/ methylene chloride = 5 %) and concentrated to afford the desired compound (0.124 g, 88.7 %) as a pale yellow oil.

Step 2: Synthesis of compound 80

[0123] Methyl 4-(((2S,6R)-4-benzoyl-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.060 g, 0.164 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.2 mL, 3.275 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.091 g, 1.637 mmol) were added thereto. The mixture was stirred at room temperature for 20 minutes, and saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was concentrated under reduced pressure to afford **compound 80** (0.045 g, 74.8 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.68 (d, 2 H, *J* = 8.2 Hz), 7.46 - 7.39 (m, 5 H), 7.34 (d, 2 H, *J* = 8.8 Hz), 3.67 (s, 2 H), 3.17 (s, 2 H), 2.69 - 2.61 (m, 2 H), 2.60 - 2.57 (m, 2 H), 1.82 - 1.76 (m, 2 H), 0.83 (d, 6 H, *J* = 6.12 Hz); LRMS (ES) *m/z* 368.0 (*M*⁺ +1).

Example 2: Synthesis of compound 81

(4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl**4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)benzoate**

[0124] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.050 g, 0.191 mmol) was dissolved in acetonitrile (2 mL), and then benzyl bromide (0.023 mL, 0.210 mmol) and K_2CO_3 (0.053 g, 0.381 mmol) were added thereto. The mixture was heated and stirred at 80 °C for 1 hour, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 30 %) and concentrated to afford the desired compound (0.022 g, 32.8 %) as a colorless oil.

Step 2: Synthesis of compound 81

[0125] Methyl 4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.022 g, 0.062 mmol) was dissolved in methanol (2 mL), and then hydroxylamine (0.023 mL, 0.210 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.053 g, 0.381 mmol) were added thereto. The mixture was stirred at room temperature for 20 minutes, and water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. **Compound 81** (0.003 g, 13.6 %) was obtained as a white solid.

^1H NMR (400 MHz, $DMSO-d_6$) δ 7.65 (d, 2 H, J = 8.1 Hz), 7.34 - 7.23 (m, 7 H), 3.73 (s, 2 H), 3.39 (s, 2 H), 2.64 (d, 2 H, J = 10.4 Hz), 2.56 - 2.54 (m, 2 H), 1.79 (t, 2 H, J = 10.6 Hz), 0.88 (d, 6 H, J = 6.1 Hz); LRMS (ES) m/z 354.2 ($M^+ + 1$).

Example 3: Synthesis of compound 82**(4-(((3R,5S)-4-acetyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)****Step 1: Synthesis of methyl****4-(((3R,5S)-4-acetyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0126] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (2 mL), and then acetic anhydride (0.072 mL, 0.763 mmol) and TEA (0.266 mL, 1.907 mmol) were added thereto. The mixture was stirred at 0 °C for 1 hour, and saturated sodium hydrogen carbonate was added thereto, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to afford the desired compound (0.115 g, 99.1 %) as a white solid.

Step 2: Synthesis of compound 82

[0127] Methyl 4-(((3R,5S)-4-acetyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.052 g, 0.171 mmol) was dissolved in methanol (0.5 mL), and then hydroxylamine (0.209 mL, 3.417 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.096 g, 1.708 mmol) were added thereto. The mixture was stirred at room temperature for 20 minutes, and then concentrated under reduced pressure. Saturated sodium hydrogen carbonate was added to the concentrate, followed by extraction with ethyl acetate. The organic layer was dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. The concentrate was purified by PTLC (100 % ethyl acetate) to afford the desired **compound 82** (0.016 g, 30.7 %) as a white solid.

¹H NMR (400 MHz, CD₃OD) δ 7.73 (d, 2 H, *J* = 8.3 Hz), 7.50 (d, 2 H, *J* = 8.3 Hz), 4.51 - 4.50 (m, 1 H), 4.11 - 4.10 (m, 1 H), 3.57 (s, 2 H), 2.71 (d, 2 H, *J* = 11.5 Hz), 2.21 - 2.20 (m, 2 H), 2.11 (s, 3 H), 1.40 - 1.38 (m, 6 H); LRMS (ES) *m/z* 306.2 (*M*⁺ +1).

Example 4: Synthesis of compound 83

(4-(((3R,5S)-4-benzoyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-benzoyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0128] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (3 mL), and then benzoyl chloride (0.049 mL, 0.420 mmol) and TEA (0.106 mL, 0.763 mmol) were added thereto. The mixture was stirred at 0 °C for 1 hour, and saturated sodium hydrogen carbonate was added to the reaction mixture, followed by methylene chloride. The organic layer was separated and concentrated under

reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 30 %) and concentrated to afford the desired compound (0.124 g, 88.7 %) as a pale yellow oil.

Step 2: Synthesis of compound 83

[0129] Methyl 4-(((3R,5S)-4-benzoyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.060 g, 0.164 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.2 mL, 3.275 mmol, 50.00% aqueous solution) and potassium hydroxide (0.091 g, 1.637 mmol) were added thereto. The mixture was stirred at room temperature for 20 minutes, and saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was concentrated under reduced pressure to yield **compound 83** (0.045 g, 74.8 %) as a white solid.

¹H NMR (400 MHz, CD₃OD) δ 7.72 (d, 2 H, *J* = 8.3 Hz), 7.49 (d, 2 H, *J* = 8.2 Hz), 7.46 - 7.44 (m, 3 H), 7.36 - 7.34 (m, 2 H), 3.59 (s, 2 H), 2.71 (d, 2 H, *J* = 10.7 Hz), 2.26 (dd, 2 H, *J* = 10.2, 3.6 Hz), 1.39 (d, 6 H, *J* = 6.7 Hz).

Example 5: Synthesis of compound 84

(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0130] (2S,6R)-2,6-dimethylpiperazine (50.000 g, 437.867 mmol) and Cs₂CO₃ (171.199 g, 525.440 mmol) were dissolved in acetonitrile (200 mL) at 0 °C, and methyl 4-(bromomethyl)benzoate (formula 1-1, 80.242 g, 350.293 mmol) was added to the solution, followed by stirring at room temperature for 5 hours. The reaction mixture was filtered through a glass filter to remove solids, and the filtrate was concentrated under reduced pressure to remove the solvent. Water was added to the concentrate, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Hexane (100 mL) was added to the concentrate and stirred, and the precipitated solid was filtered, washed with hexane, and dried to yield the desired compound (85.200 g, 74.2 %) as a white solid.

Step 2: Synthesis of methyl

4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0131] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 30.000 g, 114.351 mmol), benzyl bromide (14.961 mL, 125.786 mmol) and K₂CO₃ (23.707g, 171.527 mmol) were dissolved in acetonitrile (150 mL) at room temperature, and the solution was stirred at the same temperature for 17 hours. The reaction mixture was filtered through a glass filter to remove solids, and the filtrate was concentrated under reduced pressure to remove the solvent. Water was added to the concentrate, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; 120 g cartridge; ethyl acetate/ hexane = from 0 % to 30 %) and concentrated to afford the desired compound (22.400 g, 55.6 %) as a white solid.

Step 3: Synthesis of compound 84

[0132] Methyl 4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 15.000 g, 42.557 mmol), hydroxylamine (52.061 mL, 851.136 mmol, 50.00 % aqueous solution) and potassium hydroxide (23.879 g, 425.568 mmol) were dissolved in methanol (300 mL) at 0 °C, and the solution was stirred at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; 120 g cartridge; methanol/ methylene chloride = from 0 % to 20 %) and concentrated, and then the obtained material was crystallized from diethyl ether (200 mL) and methylene chloride (50 mL) at 25 °C and filtered. The resulting solid was washed with diethyl ether and dried to yield **compound 84** (12.580 g, 83.6 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.18 (brs, 1 H), 9.03 (brs, 1 H), 7.70 (d, 2 H, *J* = 8.2 Hz), 7.36 - 7.33 (m, 4 H), 7.28 (dd, 2 H, *J* = 7.5, 7.5 Hz), 7.18 (dd, 1 H, *J* = 7.2, 7.2 Hz), 3.73 (s, 2 H), 3.44 (s, 2 H), 2.64 (d, 2 H, *J* = 10.6 Hz), 2.61 - 2.53 (m, 2 H), 1.81 (t, 2 H, *J* = 10.5 Hz), 0.90 (d, 6 H, *J* = 6.1 Hz); LRMS (ES) *m/z* 354.2 (M⁺+1).

Example 6: Synthesis of compound 98

((2S,6R)-4-(4-(hydroxycarbamoyl)benzyl)-N-isopropyl-2,6-dimethylpiperazine-1-carboxamide)

Step 1: Synthesis of methyl**4-(((3R,5S)-4-isopropylcarbamoyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0133] Methyl 4-(((3R,SS)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (3 mL), and then 2-isocyanatopropane (0.041 mL, 0.419 mmol) and TEA (0.080 mL, 0.572 mmol) were added thereto. The mixture was stirred at 0 °C for 2 hours, and water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was concentrated under reduced pressure to yield the desired compound (0.120 g, 90.6 %) as a yellow solid.

Step 2: Synthesis of compound 98

[0134] Methyl 4-(((3R,5S)-4-isopropylcarbamoyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.060 g, 0.173 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.211 mL, 3.454 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.097 g, 1.727 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and saturated sodium hydrogen carbonate was added thereto, followed by extraction with ethyl acetate. The organic layer was dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. **Compound 98** (0.040 g, 66.5 %) was obtained as a white solid.

¹H NMR (400 MHz, CD₃OD) δ 7.72 (d, 2 H, *J* = 8.3 Hz), 7.46 (d, 2 H, *J* = 8.2 Hz), 4.06 - 4.03 (m, 2 H), 3.96 - 3.93 (m, 1 H), 3.54 (s, 2 H), 2.68 (d, 2 H, *J* = 11.1 Hz), 2.15 (dd, 2 H, *J* = 10.2, 3.6 Hz), 1.29 (d, 6 H, *J* = 6.8 Hz), 1.14 (d, 6 H, *J* = 6.6 Hz); LRMS (ES) *m/z* 349.1 (*M*⁺+1).

Example 7: Synthesis of compound 99**((2S,6R)-N-(3-chlorophenyl)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylpiperazine -1-carboxamide)****Step 1: Synthesis of methyl****4-(((4-(3-chlorophenylcarbamoyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0135] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (3 mL), and then 3-chlorophenylisocyanate (0.051 mL, 0.419 mmol) and TEA (0.080 mL, 0.572 mmol) were added thereto. The mixture was stirred at 0 °C for 2 hours, and water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was concentrated under reduced pressure to yield the desired compound (0.018 g, 68.1 %) as a white solid.

Step 2: Synthesis of compound 99

[0136] Methyl 4-((4-(3-chlorophenylcarbamoyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.050 g, 0.120 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.147 mL, 2.404 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.067 g, 1.202 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and the reaction mixture was concentrated under reduced pressure. Saturated sodium hydrogen carbonate was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 99** (0.040 g, 66.5 %) as a white solid.

¹H NMR (400 MHz, CD₃OD) δ 7.74 (d, 2 H, *J* = 8.0 Hz), 7.53 - 7.52 (m, 1 H), 7.45 (d, 2 H, *J* = 8.1 Hz), 7.29 - 7.28 (m, 1 H), 7.24 - 7.22 (m, 1 H), 7.01 (d, 1 H, *J* = 7.8 Hz), 4.21 - 4.20 (m, 2 H), 3.56 (s, 2 H), 2.74 (d, 2 H, *J* = 11.4 Hz), 2.22 (dd, 2 H, *J* = 10.2, 3.6 Hz), 1.25 (d, 6 H, *J* = 6.5 Hz).

Example 8: Synthesis of compound 100

4-(((3R,5S)-3,5-dimethyl-4-(phenylsulfonyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethylpiperazine-4-(phenylsulfonyl-1-yl)methyl)benzoate

[0137] Methyl 4-(((3R,SS)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (3 mL), and then benzenesulfonyl chloride (0.054 mL, 0.419 mmol) and TEA (0.080 mL, 0.572 mmol) were added thereto. The mixture was stirred at 0 °C for 2 hours, and then stirred at room temperature for 3 hours. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 25 %) and concentrated to afford the desired compound (0.048 g, 31.3 %) as a pale yellow solid.

Step 2: Synthesis of compound 100

[0138] Methyl 4-(((3R,5S)-3,5-dimethylpiperazine-4-(phenylsulfonyl-1-yl)methyl)benzoate (formula 1-3, 0.048 g, 0.119 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.146 mL, 2.385 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.067 g, 1.193 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried with anhydrous sodium sulfate, and then concentrated under reduced pressure to yield **compound 100** (0.034 g, 70.7 %) as a white solid.

¹H NMR (400 MHz, CD₃OD) δ 7.84 (d, 2 H, *J* = 8.1 Hz), 7.68 (d, 2 H, *J* = 8.3 Hz), 7.63 - 7.61 (m, 1 H), 7.58 - 7.54 (m, 2 H), 7.41 (d, 2 H, *J* = 8.3 Hz), 4.06 - 4.03 (m, 2 H), 3.41 (s, 2 H), 2.53 (d, 2 H, *J* = 11.3 Hz), 1.85 - 1.81 (m, 2 H), 1.43 (d, 6 H, *J* = 6.9 Hz); LRMS (ES) *m/z* 404.1 (*M*⁺+1).

Example 9: Synthesis of compound 103

(((3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-N-isopropyl-3,5-dimethylpiperazine-1-carboxamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(isopropylcarbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0139] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (3 mL), and then 2-isocyanatopropane (0.041 mL, 0.419 mmol) and TEA (0.079 mL, 0.572 mmol) were added thereto. The mixture was stirred for 2 hours while elevating the temperature from 0 °C to room temperature, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield the desired compound (0.094 g, 70.1 %).

Step 2: Synthesis of compound 103

[0140] Methyl 4-(((2S,6R)-4-(isopropylcarbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

(formula 13-3, 0.045 g, 0.130 mmol) was dissolved in methanol (0.5 mL), and then hydroxylamine (0.158 mL, 2.590 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.073 g, 1.295 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. **Compound 103** (0.020 g, 44.3 %) was obtained as a white solid.

^1H NMR (400 MHz, CD_3OD) δ 7.69 (d, 2 H, $J = 8.2$ Hz), 7.50 (d, 2 H, $J = 8.2$ Hz), 3.91 - 3.82 (m, 5 H), 2.67 - 2.61 (m, 2 H), 2.55 - 2.50 (m, 2 H), 1.13 (d, 6 H, $J = 6.6$ Hz), 1.03 (d, 6 H, $J = 6.0$ Hz); LRMS (ES) m/z 349.2 ($\text{M}^+ + 1$).

Example 10: Synthesis of compound 104

((3R,5S)-N-(3-chlorophenyl)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethylpiperazine -1-carboxamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(3-chlorophenylcarbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0141] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (3 mL), and then 3-chlorophenyl isocyanate (0.051 mL, 0.419 mmol) and TEA (0.079 mL, 0.572 mmol) were added thereto. The mixture was stirred for 2 hours while elevating the temperature from 0 °C to room temperature, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield the desired compound (0.094 g, 70.1 %).

Step 2: Synthesis of compound 104

[0142] Methyl 4-(((2S,6R)-4-(3-chlorophenylcarbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.065 g, 0.156 mmol) was dissolved in methanol (0.5 mL), and then hydroxylamine (0.191 mL, 3.126 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.088 g, 1.563 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and the reaction mixture was concentrated under reduced pressure. Saturated sodium hydrogen carbonate was added to the concentrate, which was then stirred. The precipitated solid was filtered and dried to yield **compound 104** (0.035 g, 53.7 %) as a

white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 8.67 (s, 1 H), 7.67 (d, 2 H, J = 8.2 Hz), 7.63 - 7.62 (m, 1 H), 7.41 - 7.38 (m, 3 H), 7.24 (dd, 1 H, J = 10.2, 3.6 Hz), 7.46 (dd, 1 H, J = 10.2, 3.6 Hz), 3.95 (d, 2 H, J = 12.8 Hz), 3.77 (s, 2 H), 2.68 - 2.65 (m, 2 H), 2.53 - 2.52 (m, 2 H), 0.97 (d, 6 H, J = 6.1 Hz).

Example 11: Synthesis of compound 105

4-(((2S,6R)-2,6-dimethyl-4-(phenylsulfonyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((2S,6R)-2,6-dimethyl-4-(phenylsulfonyl)piperazin-1-yl)methyl)benzoate

[0143] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (3 mL), and then phenylsulfonyl chloride (0.065 g, 0.306 mmol) and TEA (0.116 mL, 0.835 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 25 %) and concentrated to afford the desired compound (0.108 g, 88.8%) as a colorless oil.

Step 2: Synthesis of compound 105

[0144] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(phenylsulfonyl)piperazin-1-yl)methyl)benzoate (formula 13-3, 0.045 g, 0.115 mmol) was dissolved in methanol (0.5 mL), and then hydroxylamine (0.137 mL, 2.236 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.063 g, 1.118 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and the reaction mixture was concentrated under reduced pressure. Saturated sodium hydrogen carbonate was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 105** (0.027 g, 59.9 %) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 7.76 - 7.74 (m, 3 H), 7.69 - 7.68 (m, 2 H), 7.61 (d, 2 H, J = 8.3 Hz), 7.28 (d, 2 H, J = 8.1 Hz), 3.71 (s, 2 H), 3.44 (d, 2 H, J = 10.5 Hz), 2.65 - 2.64 (m, 2 H), 2.02 (t, 2 H, J = 10.8 Hz), 0.91 (d, 6 H, J = 6.2 Hz); LRMS (ES) m/z 404.1 ($M^+ + 1$).

[0145] Example 12: Synthesis of compound 106

(4-(((2S,6R)-4-(4-chlorobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((4-(4-chlorobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0146] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (3 mL), and then 4-chlorobenzoyl chloride (0.054 mL, 0.419 mmol) and TEA (0.159 mL, 1.144 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 30%) and concentrated to afford the desired compound (0.142 g, 92.9 %) as a brown oil.

Step 2: Synthesis of compound 106

[0147] Methyl 4-(((4-(4-chlorobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.070 g, 0.175 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.214 mL, 3.492 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.098 g, 1.746 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was concentrated under reduced pressure to yield **compound 106** (0.028 g, 39.9%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.69 (d, 2 H, *J* = 8.3 Hz), 7.51 (d, 2 H, *J* = 8.4 Hz), 7.48 (d, 2 H, *J* = 8.3 Hz), 7.41 (d, 2 H, *J* = 8.4 Hz), 4.38 - 4.37 (m, 1 H), 3.88 (s, 2 H), 3.51 - 3.50 (m, 1 H), 3.06 - 3.05 (m, 1 H), 2.82 - 2.80 (m, 1 H), 2.67 - 2.58 (m, 2 H), 1.10 (s, 3 H), 0.92 - 0.88 (m, 3 H); LRMS (ES) *m/z* 402.1 (*M*⁺+1).

Example 13: Synthesis of compound 107

(4-(((2S,6R)-4-(3-chlorobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl**4-(((4-(3-chlorobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate**

[0148] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.278 mmol) was dissolved in methylene chloride (3 mL), and then 3-chlorobenzoyl chloride (0.039 mL, 0.306 mmol) and TEA (0.116 mL, 0.835 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 30 %) and concentrated to afford the desired compound (0.100 g, 89.6 %) as a yellow oil.

Step 2: Synthesis of compound 107

[0149] Methyl 4-(((4-(3-chlorobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.050 g, 0.125 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.153 mL, 2.494 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.070 g, 1.247 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was concentrated under reduced pressure to yield **compound 107** (0.025 g, 49.9 %) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 7.68 (d, 2 H, J = 8.2 Hz), 7.54 (d, 1 H, J = 7.9 Hz), 7.52 - 7.46 (m, 2 H), 7.42 (d, 2 H, J = 8.0 Hz), 7.36 (d, 1 H, J = 7.5 Hz), 4.25 (d, 1 H, J = 9.4 Hz), 3.78 (s, 2 H), 2.98 - 2.96 (m, 2 H), 2.71 - 2.68 (m, 3 H), 1.02 (s, 3 H), 0.84 (s, 3 H); LRMS (ES) m/z 402.1 ($M^+ + 1$).

Example 14: Synthesis of compound 108**(4-(((2S,6R)-4-(2-chlorobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenza**

mide)

Step 1: Synthesis of methyl

4-(((4-(2-chlorobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0150] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.278 mmol) was dissolved in methylene chloride (3 mL), and then 2-chlorobenzoyl chloride (0.039 mL, 0.306 mmol) and TEA (0.116 mL, 0.835 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was concentrated under reduced pressure to yield the desired compound (0.110 g, 98.6%) as a yellow oil.

Step 2: Synthesis of compound 108

[0151] Methyl 4-(((4-(2-chlorobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.055 g, 0.137 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.168 mL, 2.744 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.077 g, 1.372 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was concentrated under reduced pressure to yield **compound 108** (0.025 g, 45.3 %) as a white solid.

¹H NMR (400 MHz, CD₃OD) δ 11.13 (s, 1 H), 8.97 (s, 1 H), 7.68 (d, 2 H, *J* = 8.0 Hz), 7.53 (d, 1 H, *J* = 7.2 Hz), 7.44 - 7.35 (m, 5 H), 4.28 (d, 2 H, *J* = 11.9 Hz), 3.78 (s, 2 H), 3.06 (d, 1 H, *J* = 12.8 Hz), 2.92 - 2.89 (m, 1 H), 2.74 - 2.61 (m, 3 H), 1.02 (d, 3 H, *J* = 5.9 Hz), 0.81 - 0.78 (m, 3 H); LRMS (ES) *m/z* 402.1 (*M*⁺+1).

Example 15: Synthesis of compound 109**4-(((2S,6R)-4-((4-chlorophenyl)sulfonyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide****Step 1: Synthesis of methyl****4-(((2S,6R)-4-((4-chlorophenyl)sulfonyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate**

[0152] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g,

0.381 mmol) was dissolved in methylene chloride (3 mL), and then 4-chlorobenzene-1-sulfonyl chloride (0.065 g, 0.306 mmol) and TEA (0.116 mL, 0.835 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/ hexane = 30 %) and concentrated to afford the desired compound (0.108 g, 88.8 %) as a colorless oil.

Step 2: Synthesis of compound 109

[0153] Methyl 4-(((2S,6R)-4-((4-chlorophenyl)sulfonyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.05 g, 0.114 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.140 mL, 2.289 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.064 g, 1.144 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried with anhydrous sodium sulfate, and then concentrated under reduced pressure to yield **compound 109** (0.035 g, 69.8 %) as a white solid.

¹H NMR (400 MHz, CD₃OD) δ 7.78 (d, 2 H, *J* = 8.4 Hz), 7.66 (d, 4 H, *J* = 7.2 Hz), 7.43 (d, 2 H, *J* = 7.9 Hz), 3.83 (s, 2 H), 3.52 (d, 2 H, *J* = 11.3 Hz), 2.21 - 2.20 (m, 2 H), 3.52 (d, 2 H, *J* = 11.3 Hz), 1.01 (d, 6 H, *J* = 6.1 Hz); LRMS (ES) *m/z* 438.0 (*M*⁺+1).

Example 16: Synthesis of compound 110

(4-(((2S,6R)-4-((2-chlorophenyl)sulfonyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-((2-chlorophenyl)sulfonyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0154] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (3 mL), and then 2-chlorobenzene-1-sulfonyl chloride (0.042 mL, 0.306 mmol) and TEA (0.116 mL, 0.835 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon

dioxide; ethyl acetate/ hexane = 30 %) and concentrated to afford the desired compound (0.105 g, 68.3%) as a colorless oil.

Step 2: Synthesis of compound 110

[0155] Methyl 4-(((2S,6R)-4-((2-chlorophenyl)sulfonyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.060 g, 0.137 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.168 mL, 2.746 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.077 g, 1.373 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. **Compound 110** (0.037 g, 61.5 %) was obtained as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 11.10 (s, 1 H), 9.00 (s, 1 H), 7.98 (d, 1 H, J = 7.3 Hz), 7.71 - 7.64 (m, 4 H), 7.60 - 7.52 (m, 1 H), 7.37 (d, 2 H, J = 8.1 Hz), 3.75 (s, 2 H), 3.52 (d, 2 H, J = 11.3 Hz), 2.60 - 2.56 (m, 4 H), 0.93 (d, 6 H, J = 5.8 Hz); LRMS (ES) m/z 438.1 ($M^+ + 1$).

Example 17: Synthesis of compound 111

(4-(((2S,6R)-2,6-dimethyl-4-picolinoylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-2,6-dimethyl-4-picolinoylpiperazin-1-yl)methyl)benzoate

[0156] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (3 mL), and then picolinoyl chloride (0.075 g, 0.419 mmol) and TEA (0.159 mL, 1.144 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate = 100 %) and concentrated to afford the desired compound (0.046 g, 32.8 %) as a yellow oil.

Step 2: Synthesis of compound 111

[0157] Methyl 4-(((2S,6R)-2,6-dimethyl-4-picolinoylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.02 g, 0.054 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.067 mL, 1.089 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.03 g, 0.544 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was concentrated under reduced pressure to yield **compound 111** (0.001 g, 5.0 %) as a colorless oil.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.65 (dd, 1 H, *J* = 10.2, 3.6 Hz), 8.62 (d, 1 H, *J* = 3.0 Hz), 7.90 (dd, 1 H, *J* = 10.2, 3.6 Hz), 7.70 (d, 2 H, *J* = 8.4 Hz), 7.55 - 7.51 (m, 3 H), 4.42 (d, 1 H, *J* = 12.3 Hz), 3.89 (s, 2 H), 3.49 (d, 1 H, *J* = 12.7 Hz), 3.12 - 3.11 (m, 1 H), 2.85 - 2.84 (m, 1 H), 2.72 - 2.63 (m, 2 H), 1.12 (d, 3 H, *J* = 3.6 Hz), 0.92 (d, 3 H, *J* = 5.2 Hz).

Example 18: Synthesis of compound 112

4-(((2S,6R)-2,6-dimethyl-4-nicotinoylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

(((2S,6R)-2,6-dimethyl-4-nicotinoylpiperazin-1-yl)methyl)benzoate

[0158] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (3 mL), and then nicotinoyl chloride (0.075 g, 0.419 mmol) and TEA (0.159 mL, 1.144 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.119 g, 85.0 %) as a yellow oil.

Step 2: Synthesis of compound 112

[0159] Methyl (((2S,6R)-2,6-dimethyl-4-nicotinoylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.060 g, 0.163 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.200 mL, 3.266 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.092 g, 1.633 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was concentrated under reduced pressure and

extracted with ethyl acetate and water. The organic layer was concentrated under reduced pressure to yield **compound 112** (0.001 g, 1.7 %) as a colorless oil.

^1H NMR (400 MHz, DMSO- d_6) δ 8.65 (dd, 1 H, J = 10.2, 3.6 Hz), 8.62 (d, 1 H, J = 3.0 Hz), 7.90 (dd, 1 H, J = 10.2, 3.6 Hz), 7.70 (d, 2 H, J = 8.4 Hz), 7.55 - 7.51 (m, 3 H), 4.42 (d, 1 H, J = 12.3 Hz), 3.89 (s, 2 H), 3.49 (d, 1 H, J = 12.7 Hz), 3.12 - 3.11 (m, 1 H), 2.85 - 2.84 (m, 1 H), 2.72 - 2.63 (m, 2 H), 1.12 (d, 3 H, J = 3.6 Hz), 0.92 (d, 3 H, J = 5.2 Hz); LRMS (ES) m/z 369.2 ($M^+ + 1$).

Example 19: Synthesis of compound 113

4-(((2S,6R)-2,6-dimethyl-4-(pyridin-3-ylsulfonyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((2S,6R)-2,6-dimethyl-4-(pyridin-3-ylsulfonyl)piperazin-1-yl)methyl)benzoate

[0160] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (3 mL), and then pyridine-3-sulfonyl chloride (0.090 g, 0.419 mmol) and TEA (0.159 mL, 1.144 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.105 g, 68.3 %) as a white solid.

Step 2: Synthesis of compound 113

[0161] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(pyridin-3-ylsulfonyl)piperazin-1-yl)methyl)benzoate (formula 13-3, 0.600 g, 0.149 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.182 mL, 2.974 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.830 g, 1.487 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. **Compound 113** (0.033 g, 54.9 %) was obtained as a white solid.

^1H NMR (400 MHz, CD_3OD) δ 8.93 (d, 1 H, J = 2.3 Hz), 8.84 (dd, 1 H, J = 10.2, 3.6 Hz), 8.22 - 8.20 (m, 1 H), 7.66 - 7.65 (m, 1 H), 7.65 (d, 2 H, J = 8.3 Hz), 7.42 (d, 2 H, J = 8.2 Hz), 3.83 (s, 2 H), 3.58 (d, 2 H, J = 11.5 Hz), 2.74 - 2.72 (m, 2 H), 2.24 (t, 2 H, J = 10.8 Hz), 1.01 (d, 6 H, J = 6.2 Hz); LRMS (ES) m/z 405.1 ($\text{M}^+ + 1$).

Example 20: Synthesis of compound 114

4-(((2S,6R)-2,6-dimethyl-4-(thiophene-2-carbonyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((2S,6R)-2,6-dimethyl-4-(thiophene-2-carbonyl)piperazin-1-yl)methyl)benzoate

[0162] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (3 mL), and then thiophene-2-carbonyl chloride (0.046 mL, 0.419 mmol) and TEA (0.159 mL, 1.144 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 30 %) and concentrated to afford the desired compound (0.127 g, 89.5 %) as a yellow oil.

Step 2: Synthesis of compound 114

[0163] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(thiophene-2-carbonyl)piperazin-1-yl)methyl)benzoate (formula 13-3, 0.070 g, 0.188 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.230 mL, 3.759 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.105 g, 1.879 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was concentrated under reduced pressure to yield compound **114** (0.013 g, 18.5 %) as a white solid.

^1H NMR (400 MHz, CD_3OD) δ 7.70 (d, 2 H, J = 8.4 Hz), 7.65 (dd, 1 H, J = 10.2, 3.6 Hz), 7.52 (d, 2 H, J = 8.4 Hz), 7.40 (dd, 1 H, J = 10.2, 3.6 Hz), 7.12 (dd, 1 H, J = 10.2, 3.6 Hz), 4.20 - 4.19 (m, 2 H), 3.89 (s, 2 H), 3.03 - 2.97 (m, 2 H), 2.70 - 2.62 (m, 2 H), 1.05 (d, 6 H, J = 5.6 Hz); LRMS (ES) m/z 374.1 ($\text{M}^+ + 1$).

Example 21: Synthesis of compound 115

(4-(((2S,6R)-4-(furan-2-carbonyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(furan-2-carbonyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0164] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (3 mL), and furan-2-carbonyl chloride (0.040 mL, 0.419 mmol) and TEA (0.159 mL, 1.144 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 30 %) and concentrated to afford the desired compound (0.115 g, 84.7 %) as a pale yellow oil.

Step 2: Synthesis of compound 115

[0165] Methyl 4-(((2S,6R)-4-(furan-2-carbonyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.060 g, 0.168 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.206 mL, 3.367 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.095 g, 1.683 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was concentrated under reduced pressure to yield **compound 115** (0.007 g, 11.6 %) as a pale yellow solid.

¹H NMR (400 MHz, CD₃OD) δ 7.71 - 7.69 (m, 3 H), 7.53 (d, 2 H, *J* = 8.4 Hz), 7.04 (dd, 1 H, *J* = 10.2, 3.6 Hz), 6.59 (dd, 1 H, *J* = 10.2, 3.6 Hz), 4.31 (d, 2 H, *J* = 13.1 Hz), 3.90 (s, 2 H), 2.85 - 2.82 (m, 2 H), 2.69 - 2.65 (m, 2 H), 1.08 (d, 6 H, *J* = 5.4 Hz); LRMS (ES) *m/z* 358.1 (*M*⁺+1).

Example 22: Synthesis of compound 118

(4-(((2S,6R)-4-(2-chlorobenzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl**4-(((2S,6R)-4-(2-chlorobenzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate**

[0166] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.278 mmol) was dissolved in acetonitrile (2 mL), and then 2-chlorobenzyl bromide (0.038 mL, 0.292 mmol) and K₂CO₃ (0.096 g, 0.696 mmol) were added thereto. The mixture was stirred at room temperature for 2 hours, and then the reaction mixture was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 25 %) and concentrated to afford the desired compound (0.080 g, 74.3 %) as a pale yellow oil.

Step 2: Synthesis of compound 118

[0167] Methyl 4-(((2S,6R)-4-(2-chlorobenzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.040 g, 0.103 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.126 mL, 2.068 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.058 g, 1.034 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then the reaction mixture was concentrated under reduced pressure. Saturated sodium hydrogen carbonate was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 118** (0.018 g, 43.3 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.65 (d, 2 H, *J* = 8.2 Hz), 7.37 - 7.33 (m, 4 H), 7.33 - 7.31 (m, 2 H), 3.74 (s, 2 H), 3.41 (s, 2 H), 2.65 - 2.62 (m, 2 H), 2.55 - 2.51 (m, 2 H), 1.83 - 1.82 (m, 2 H), 0.88 (d, 6 H, *J* = 6.1 Hz); LRMS (ES) *m/z* 388.1 (M⁺+1).

Example 23: Synthesis of compound 119**(4-(((2S,6R)-4-(4-fluorophenyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)****Step 1: Synthesis of methyl**

4-(((2S,6R)-4-(4-fluorophenyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0168] Pd(OAc)₂ (0.006 g, 0.028 mmol) and xantphos (0.003 g, 0.006 mmol) were dissolved in toluene, and then 1-bromo-4-fluorobenzene (0.049 g, 0.278 mmol), methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.278 mmol) and Cs₂CO₃ (0.227 g, 0.696 mmol) were added thereto. The mixture was heated and stirred at 100 °C for 17 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 15 %) and concentrated to afford the desired compound (0.007 g, 7.1 %) as a white solid.

Step 2: Synthesis of compound 119

[0169] Methyl 4-(((2S,6R)-4-(4-fluorophenyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 19-1, 0.007 g, 0.020 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.024 mL, 0.393 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.011 g, 0.196 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Saturated sodium hydrogen carbonate was added to the concentrate, followed by extraction with ethyl acetate. The organic layer was concentrated under reduced pressure to yield **compound 119** (0.003 g, 58.0 %) as a pale brown solid.

¹H NMR (400 MHz, CD₃OD) δ 7.71 (d, 2 H, *J* = 8.2 Hz), 7.53 (d, 2 H, *J* = 8.2 Hz), 6.98 - 6.95 (m, 4 H), 4.12 (s, 2 H), 3.41 (d, 2 H, *J* = 11.4 Hz), 2.81 - 2.78 (m, 2 H), 2.51 (t, 2 H, *J* = 11.1 Hz), 1.12 (d, 6 H, *J* = 6.1 Hz); LRMS (ES) *m/z* 358.1 (M⁺+1).

Example 24: Synthesis of compound 120**4-(((3R,5S)-4-(2-chlorobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide****Step 1: Synthesis of methyl****4-(((3R,5S)-4-(2-chlorobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0170] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g,

0.381 mmol) was dissolved in methylene chloride (1 mL), and then 2-chlorobenzoyl chloride (0.058 mL, 0.801 mmol) and TEA (0.106 mL, 0.762 mmol) were added thereto. The mixture was stirred at room temperature for 2 hours, and then water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was separated and concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.076 g, 49.7 %) as a yellow oil.

Step 2: Synthesis of compound 120

[0171] Methyl 4-(((3R,5S)-4-(2-chlorobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.070 g, 0.175 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.214 mL, 3.492 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.098 g, 1.746 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was concentrated under reduced pressure to yield **compound 120** (0.029 g, 41.3 %) as a pale yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.69 (d, 2 H, *J* = 8.1 Hz), 7.41 - 7.40 (m, 3 H), 7.33 (d, 2 H, *J* = 8.0 Hz), 3.51 (s, 2 H), 2.79 - 2.61 (m, 4 H), 2.14 - 2.13 (m, 2 H), 1.36 (d, 3 H, *J* = 6.8 Hz), 1.24 - 1.18 (m, 3 H).

Example 25: Synthesis of compound 121

4-(((3R,5S)-4-(3-chlorobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-chlorobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0172] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (1 mL), and then 3-chlorobenzoyl chloride (0.080 g, 0.457 mmol) and TEA (0.106 mL, 0.762 mmol) were added thereto. The mixture was stirred at room temperature for 2 hours, and then water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was separated and concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound

(0.062 g, 40.6 %) as a pale yellow oil.

Step 2: Synthesis of compound 121

[0173] Methyl 4-(((3R,5S)-4-(3-chlorobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.050 g, 0.125 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.153 mL, 2.494 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.070 g, 1.247 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was concentrated under reduced pressure to yield **compound 121** (0.021 g, 41.9 %) as a pale yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.68 (d, 2 H, *J* = 8.0 Hz), 7.47 - 7.41 (m, 3 H), 7.32 (d, 2 H, *J* = 8.0 Hz), 7.29 (s, 1 H), 3.49 (s, 2 H), 2.61 - 2.50 (m, 4 H), 2.16 - 2.12 (m, 2 H), 1.28 (d, 6 H, *J* = 5.6 Hz).

Example 26: Synthesis of compound 122

4-(((3R,5S)-4-(4-chlorobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(4-chlorobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0174] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (1 mL), and then 4-chlorobenzoyl chloride (0.080 g, 0.457 mmol) and TEA (0.106 mL, 0.762 mmol) were added thereto. The mixture was stirred at room temperature for 2 hours, and then water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was separated and concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.059 g, 38.6 %) as a pale yellow oil.

Step 2: Synthesis of compound 122

[0175] Methyl 4-(((3R,5S)-4-(4-chlorobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

(formula 1-3, 0.050 g, 0.125 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.153 mL, 2.494 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.070 g, 1.247 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was concentrated under reduced pressure to yield **compound 122** (0.014 g, 27.9 %) as a pale yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.10 (brs, 1 H), 9.05 (brs, 1 H), 7.72 (d, 2 H, *J* = 8.1 Hz), 7.50 (d, 2 H, *J* = 8.3 Hz), 7.43 (d, 2 H, *J* = 8.1 Hz), 7.38 (d, 2 H, *J* = 8.4 Hz), 4.10 (brs, 2 H), 3.54 (s, 2 H), 2.63 (d, 2 H, *J* = 11.1 Hz), 2.15 (dd, 2 H, *J* = 11.3, 4.1 Hz), 1.29 (d, 6 H, *J* = 6.1 Hz); LRMS (ES) *m/z* 402.8 (*M*⁺+1).

Example 27: Synthesis of compound 123

(4-(((3R,5S)-3,5-dimethyl-4-picolinoylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-picolinoylpiperazin-1-yl)methyl)benzoate

[0176] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (1 mL), and then picolinoyl chloride (0.065 g, 0.457 mmol) and TEA (0.106 mL, 0.762 mmol) were added thereto. The mixture was stirred at room temperature for 2 hours, and then water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was separated and concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.042 g, 30.0 %) as a white solid.

Step 2: Synthesis of compound 123

[0177] Methyl 4-(((3R,5S)-3,5-dimethyl-4-picolinoylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.035 g, 0.095 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.117 mL, 1.905 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.053 g, 0.953 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was concentrated under reduced pressure to yield **compound 123** (0.011 g, 31.3 %) as a pale yellow solid.

^1H NMR (400 MHz, DMSO- d_6) δ 8.56 - 8.55 (m, 1 H), 7.82 (d, 2 H, J = 8.0 Hz), 3.71 (s, 2 H), 2.96 (brs, 2 H), 2.56 (brs, 2 H), 1.02 (brs, 3 H), 0.88 (brs, 3 H); LRMS (ES) m/z 369.4 ($M^+ + 1$).

Example 28: Synthesis of compound 125

4-(((3R,5S)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0178] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 6.000 g, 22.870 mmol) and TEA (4.781 mL, 34.305 mmol) were dissolved in methylene chloride (120 mL) at 0 °C, and furan-2-carbonyl chloride (2.488 mL, 25.157 mmol) was added to the solution, which was then stirred at the same temperature for 1 hour. A saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; 80 g cartridge; ethyl acetate/ hexane = from 0 % to 30 %) and concentrated to afford the desired compound (7.440 g, 91.3 %) as a white solid.

Step 2: Synthesis of compound 125

[0179] Methyl 4-(((3R,5S)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 7.440 g, 20.874 mmol), hydroxylamine (25.536 mL, 417.485 mmol, 50.00 % aqueous solution) and potassium hydroxide (11.713 g, 208.742 mmol) were dissolved in methanol (150 mL) at 0 °C, and the solution was stirred at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure to afford **compound 125** (5.330 g, 71.4 %) as an apricot solid.

^1H NMR (400 MHz, DMSO- d_6) δ 11.23 (brs, 1 H), 9.06 (brs, 1 H), 7.81 (s, 1 H), 7.74 (d, 2 H, J

= 7.6 Hz), 7.42 (d, 2 H, J = 5.8 Hz), 6.95 (d, 1 H, J = 3.3 Hz), 6.61 - 6.60 (m, 1 H), 4.49 (brs, 2 H), 3.54 (s, 2 H), 2.68 (d, 2 H, J = 11.0 Hz), 2.14 (d, 2 H, J = 8.2 Hz), 1.25 (d, 6 H, J = 5.6 Hz); LRMS (ES) m/z 358.2 ($M^+ + 1$).

Example 29: Synthesis of compound 126

(4-(((3R,5S)-3,5-dimethyl-4-(thiophene-2-carbonyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(thiophene-2-carbonyl)piperazin-1-yl)methyl)benzoate

[0180] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (1 mL), and then thiophene-2-carbonyl chloride (0.067 g, 0.457 mmol) and TEA (0.106 mL, 0.762 mmol) were added thereto. The mixture was stirred at room temperature for 2 hours, and then water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was separated and concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.061 g, 43.0 %) as a pale yellow oil.

Step 2: Synthesis of compound 126

[0181] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(thiophene-2-carbonyl)piperazin-1-yl)methyl)benzoate (formula 1-3, 0.050 g, 0.134 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.164 mL, 2.685 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.075 g, 1.342 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was concentrated under reduced pressure to yield **compound 126** (0.019 g, 37.9 %) as a pale yellow solid.

^1H NMR (400 MHz, DMSO- d_6) δ 7.72 - 7.71 (m, 3 H), 7.41 - 7.36 (m, 3 H), 7.10 (brs, 1 H), 4.43 (brs, 2 H), 3.52 (s, 2 H), 2.67 - 2.64 (m, 2 H), 2.14 - 2.12 (m, 2 H), 1.36 (d, 6 H, J = 5.5 Hz).

Example 30: Synthesis of compound 127

4-(((3R,5S)-4-(2-chlorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide**Step 1: Synthesis of methyl****4-(((3R,5S)-4-(2-chlorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0182] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol) was dissolved in acetonitrile (2 mL), and then 1-(bromomethyl)-2-chlorobenzene (0.094 g, 0.457 mmol) and K₂CO₃ (0.105 g, 0.762 mmol) were added thereto. The mixture was stirred at room temperature for 16 hours, and then water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.035 g, 23.7 %) as a white oil.

Step 2: Synthesis of compound 127

[0183] Methyl 4-(((3R,5S)-4-(2-chlorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.030 g, 0.078 mmol) was dissolved in methanol (0.5 mL), and then hydroxylamine (0.095 mL, 1.551 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.044 g, 0.775 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. **Compound 127** (0.011 g, 36.6 %) was obtained as a pale yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.78 - 7.68 (m, 3 H), 7.32 - 7.19 (m, 6 H), 3.68 (s, 2 H), 3.44 (s, 2 H), 2.69 - 2.66 (m, 4 H), 1.86 - 1.83 (m, 2 H), 0.78 (brs, 6 H).

Example 31: Synthesis of compound 128**4-(((3R,5S)-4-(3-chlorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide**

Step 1: Synthesis of methyl**4-(((3R,5S)-4-(3-chlorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0184] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol) was dissolved in acetonitrile (2 mL), and then 1-(bromomethyl)-3-chlorobenzene (0.094 g, 0.457 mmol) and K₂CO₃ (0.105 g, 0.762 mmol) were added thereto. The mixture was stirred at room temperature for 16 hours, and then water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.041 g, 27.8 %) as a white oil.

Step 2: Synthesis of compound 128

[0185] Methyl 4-(((3R,5S)-4-(3-chlorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.035 g, 0.090 mmol) was dissolved in methanol (0.5 mL), and then hydroxylamine (0.111 mL, 1.809 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.051 g, 0.905 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. **Compound 128** (0.015 g, 42.7 %) was obtained as a pale yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.68 (d, 2 H, *J* = 9.6 Hz), 7.38 (s, 1 H), 7.30 (d, 2 H, *J* = 4.0 Hz), 7.27 - 7.20 (m, 3 H), 3.69 (s, 2 H), 3.40 (s, 2 H), 2.64 - 2.54 (m, 4 H), 1.82 - 1.75 (m, 2 H), 0.84 (d, 6 H, *J* = 8.0 Hz).

Example 32: Synthesis of compound 145**(4-(((3R,5S)-4-(furan-2-ylmethyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)****Step 1: Synthesis of methyl**

4-(((3R,5S)-4-(furan-2-ylmethyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0186] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.300 g, 1.144 mmol) and 2-furaldehyde (0.104 mL, 1.258 mmol) were dissolved in methylene chloride (5 mL), and acetic acid (0.069 mL, 1.144 mmol) was added thereto at 40 °C, followed by stirring for 1 hour. Na(CN)BH₃ (0.072 g, 1.144 mmol) was added to the reaction mixture, followed by stirring at the same temperature for 3 days. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 25 %) and concentrated to afford the desired compound (0.028 g, 7.2 %) as a pale yellow oil.

Step 2: Synthesis of compound 145

[0187] Methyl 4-(((3R,5S)-4-(furan-2-ylmethyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.028 g, 0.082 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.100 mL, 1.635 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.046 g, 0.818 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. **Compound 145** (0.013 g, 46.3 %) was obtained as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.10 (brs, 1 H), 9.00 (brs, 1 H), 7.67 (d, 2 H, *J* = 8.1 Hz), 7.59 (d, 1 H, *J* = 2.4 Hz), 7.30 (d, 2 H, *J* = 8.1 Hz), 6.41 - 6.40 (m, 1 H), 6.28 - 6.27 (m, 1 H), 3.86 (s, 2 H), 3.38 (s, 2 H), 2.60 (d, 2 H, *J* = 10.0 Hz), 2.44 - 2.40 (m, 2 H), 1.74 (t, 2 H, *J* = 10.6 Hz), 0.87 (d, 6 H, *J* = 6.4 Hz).

Example 33: Synthesis of compound 146**4-(((3R,5S)-3,5-dimethyl-4-(2-phenylacetyl)piperazin-1-yl)methyl)-N-hydroxybenzamide****Step 1: Synthesis of methyl**

4-(((3R,5S)-3,5-dimethyl-4-(2-phenylacetyl)piperazin-1-yl)methyl)benzoate

[0188] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol) was dissolved in methylene chloride (1 mL), and then 2-phenylacetyl chloride (0.065 g, 0.419 mmol) and TEA (0.106 mL, 0.762 mmol) were added thereto. The mixture was stirred at room temperature for 15 hours, and then water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was separated and concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.042 g, 29.0 %) as a white solid.

Step 2: Synthesis of compound 146

[0189] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(2-phenylacetyl)piperazin-1-yl)methyl)benzoate (formula 1-3, 0.030 g, 0.079 mmol) was dissolved in methanol (0.5 mL), and hydroxylamine (0.096 mL, 1.577 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.044 g, 0.788 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was concentrated under reduced pressure to yield **compound 146** (0.014 g, 46.5 %) as a pale yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.69 (d, 2 H, *J* = 8.0 Hz), 7.34 (d, 2 H, *J* = 8.0 Hz), 7.31 - 7.27 (m, 2 H), 7.22 - 7.20 (m, 3 H), 4.41 (brs, 1 H), 4.12 (brs, 1 H), 3.47 - 3.33 (m, 2 H), 3.31 (s, 2 H), 2.62 - 2.59 (m, 2 H), 2.02 - 2.01 (m, 2 H), 1.22 (brs, 6 H).

Example 34: Synthesis of compound 147**4-(((3R,5S)-4-ethyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)****Step 1: Synthesis of methyl****4-(((3R,5S)-4-ethyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0190] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), iodoethane (0.037 mL, 0.457 mmol) and K₂CO₃ (0.105 g, 0.762 mmol) were

dissolved in acetonitrile (1mL) and stirred at room temperature for 7 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/ methylene chloride = 5 %) and concentrated to afford the desired compound (0.059 g, 53.3 %) as a pale yellow solid.

Step 2: Synthesis of compound 147

[0191] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.040 g, 0.174 mmol) was dissolved in methanol (0.5 mL), and then hydroxylamine (0.213 mL, 3.487 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.098 g, 1.744 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. **Compound 147** (0.010 g, 19.7 %) was obtained as a brown solid.

^1H NMR (400 MHz, DMSO- d_6) δ 7.65 (d, 2 H, J = 7.8 Hz), 7.20 (d, 2 H, J = 7.9 Hz), 2.73 (q, 2 H, J = 7.6 Hz), 2.61 - 2.55 (m, 4 H), 1.70 - 1.66 (m, 2 H), 0.90 (d, 6 H, J = 5.9 Hz), 0.81 (t, 3 H, J = 7.0 Hz).

Compound 35: Synthesis of compound 148

4-(((3R,5S)-3,5-dimethyl-4-propylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-propylpiperazin-1-yl)methyl)benzoate

[0192] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), iodopropane (0.045 mL, 0.457 mmol) and K_2CO_3 (0.105 g, 0.762 mmol) were dissolved in acetonitrile (1 mL) and stirred at room temperature for 7 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and

concentrated to afford the desired compound (0.054 g, 46.5 %) as a white solid.

Step 2: Synthesis of compound 148

[0193] Methyl 4-(((3R,5S)-3,5-dimethyl-4-propylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.040 g, 0.131 mmol) was dissolved in methanol (0.5 mL), and then hydroxylamine (0.161 mL, 3.487 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.074 g, 1.314 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. **Compound 148** (0.017 g, 42.4 %) was obtained as a brown solid.

^1H NMR (400 MHz, DMSO- d_6) δ 7.66 (d, 2 H, J = 8.0 Hz), 7.21 (d, 2 H, J = 8.0 Hz), 3.35 (s, 2 H), 2.60 - 2.52 (m, 6 H), 1.68 (t, 2 H, J = 10.4 Hz), 1.32 - 1.30 (m, 2 H), 0.90 (d, 6 H, J = 6.0 Hz), 0.76 (t, 3 H, J = 7.4 Hz).

Example 36: Synthesis of compound 149

4-(((3R,5S)-3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl)benzoate

[0194] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), 2,2,2-trifluoroethyl trifluoromethane sulfonate (0.066 mL, 0.457 mmol) and K_2CO_3 (0.105 g, 0.762 mmol) were dissolved in acetonitrile (1 mL) and stirred at room temperature for 12 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.062 g, 47.2 %) as a white oil.

Step 2: Synthesis of compound 149

[0195] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl)benzoate (formula 1-3, 0.030 g, 0.087 mmol) was dissolved in methanol (0.5 mL), and then hydroxylamine (0.107 mL, 1.742 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.049 g, 1.744 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. **Compound 149** (0.011 g, 36.6 %) was obtained as a brown solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.68 (d, 2 H, *J* = 7.9 Hz), 7.31 (d, 2 H, *J* = 8.0 Hz), 3.41 (s, 2 H), 3.28 (s, 2 H), 2.70 - 2.63 (m, 2 H), 2.60 - 2.49 (m, 2 H), 1.73 (t, 2 H, *J* = 10.5 Hz), 0.96 (d, 6 H, *J* = 6.2 Hz).

Example 37: Synthesis of compound 154

6-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)-N-hydroxyhexanamide)

Step 1: Synthesis of ethyl 6-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)hexanoate

[0196] (2S,6R)-1-benzyl-2,6-dimethylpiperazin (formula 8-3, 0.100 g, 0.489 mmol) was dissolved in acetonitrile (1 mL), and then ethyl 6-bromohexanoate (formula 8-4, 0.131 g, 0.587 mmol) and Cs₂CO₃ (0.319 g, 0.979 mmol) were added thereto. The mixture was stirred at room temperature for 20 hours, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 20 %) and concentrated to afford the desired compound (0.090 g, 53.1 %) as a white oil.

Step 2: Synthesis of compound 154

[0197] Ethyl 6-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)hexanoate (formula 8-5, 0.040 g, 0.115 mmol) was dissolved in methanol (0.5 mL), and hydroxylamine (0.141 mL, 2.309 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.065 g, 1.154 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then the reaction mixture

was concentrated under reduced pressure to remove the solvent. Saturated sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure to yield **compound 154** (0.021 g, 54.6 %) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 7.33 - 7.24 (m, 4 H), 7.17 - 7.15 (m, 1 H), 3.69 (s, 2 H), 2.68 - 2.53 (m, 4 H), 2.13 (t, 2 H, $J = 7.2$ Hz), 1.86 (t, 2 H, $J = 7.4$ Hz), 1.66 (t, 2 H, $J = 10.6$ Hz), 1.45 - 1.34 (m, 4 H), 1.20 - 1.18 (m, 2 H), 0.84 (d, 6 H, $J = 8.0$ Hz).

Example 38: Synthesis of compound 159

((2S,6R)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-phenylpiperazine-1-carboxamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(phenylcarbamoyl)piperazin-1-yl)methyl)benzoate

[0198] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (compound 1-2, 0.150 g, 0.572 mmol) was dissolved in methylene chloride (2 mL), and then phenyl isocyanate (0.069 mL, 0.629 mmol) and TEA (0.119 mL, 0.858 mmol) were added thereto. The mixture was stirred at 0 °C for 2 hours, and then stirred at room temperature for 2 hours. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 30 %) and concentrated to afford the desired compound (0.171 g, 78.4 %) as a white solid.

Step 2: Synthesis of compound 159

[0199] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(phenylcarbamoyl)piperazin-1-yl)methyl)benzoate (formula 1-3, 0.100 g, 0.262 mmol) was dissolved in methanol (2 mL), and then hydroxylamine (0.321 mL, 5.243 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.147 g, 2.621 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Saturated sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of

sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure to yield **compound 159** (0.030 g, 29.9 %) as a white solid.

¹H NMR (400 MHz, CD₃OD) δ 8.22 (s, 1 H), 7.69 (d, 2 H, *J* = 8.1 Hz), 7.44 (d, 2 H, *J* = 7.4 Hz), 7.34 - 7.32 (m, 2 H), 6.92 - 6.89 (m, 1 H), 4.20 - 4.17 (m, 2 H), 7.50 (s, 2 H), 2.64 (d, 2 H, *J* = 11.1 Hz), 2.12 - 2.08 (m, 2 H), 1.26 (d, 6 H, *J* = 6.7 Hz); LRMS (ES) *m/z* 383.2 (*M*⁺+1).

Example 39: Synthesis of compound 160

((2S,6R)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-o-tolylpiperazine-1-carboxamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(o-tolylcarbamoyl)piperazin-1-yl)methyl)benzoate

[0200] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.200 g, 0.762 mmol) was dissolved in methylene chloride (3 mL), and then o-tolyl isocyanate (0.103 mL, 0.839 mmol) and TEA (0.159 mL, 1.144 mmol) were added thereto. The mixture was stirred at 0 °C for 2 hours, and then stirred at room temperature for 1 hour. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.030 g, 10.0 %) as a white solid.

Step 2: Synthesis of compound 160

[0201] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(o-tolylcarbamoyl)piperazin-1-yl)methyl)benzoate (formula 1-3, 0.030 g, 0.076 mmol) was dissolved in methanol (2 mL), and hydroxylamine (0.093 mL, 1.517 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.043 g, 0.759 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Saturated sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure to yield **compound 160** (0.010 g, 33.3 %) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 11.10 (s, 1 H), 9.00 (s, 1 H), 7.85 (s, 1 H), 7.72 (d, 2 H, J = 8.2 Hz), 7.43 (d, 2 H, J = 8.0 Hz), 7.17 - 7.10 (m, 3 H), 7.03 (dd, 1 H, J = 10.2, 3.6 Hz), 3.54 (s, 2 H), 2.65 (d, 2 H, J = 11.2 Hz), 2.16 (s, 3 H), 2.12 - 2.13 (m, 1 H), 1.30 (d, 6 H, J = 6.6 Hz); LRMS (ES) m/z 397.2 ($M^+ + 1$).

Example 40: Synthesis of compound 161

((2S,6R)-N-benzyl-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylpiperazine-1-carboxamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(benzylcarbamoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0202] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.150 g, 0.572 mmol) was dissolved in methylene chloride (2 mL), and then benzyl isocyanate (0.078 mL, 0.629 mmol) and TEA (0.119 mL, 0.858 mmol) were added thereto at 0 °C. The mixture was stirred at room temperature for 1 hour. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/ hexane = 30 %) and concentrated to afford the desired compound (0.517 g, 69.4 %) as a white solid.

Step 2: Synthesis of compound 161

[0203] Methyl 4-(((3R,5S)-4-(benzylcarbamoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.100 g, 0.253 mmol) was dissolved in methanol (2 mL), and hydroxylamine (0.309 mL, 5.057 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.114 g, 2.529 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Saturated sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure to yield **compound 161** (0.062 g, 61.8 %) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 11.10 (s, 1 H), 9.10 (s, 1 H), 7.71 (d, 2 H, J = 8.0 Hz), 7.41 (d,

2 H, $J = 7.9$ Hz), 7.31 - 7.27 (m, 2 H), 7.24 - 7.18 (m, 3 H), 6.91 - 6.90 (m, 1 H), 4.25 (d, 2 H, $J = 5.5$ Hz), 4.04 - 4.03 (m, 2 H), 3.51 (s, 2 H), 2.60 (d, 2 H, $J = 11.0$ Hz), 2.08 - 2.05 (m, 2 H), 1.22 (d, 6 H, $J = 6.6$ Hz).

Example 41: Synthesis of compound 162

((3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-N-phenylpiperazine-1-carboxamide)

Step 1: Synthesis of

4-(((2S,6R)-2,6-dimethyl-4-(phenylcarbamoyl)piperazin-1-yl)methyl)benzoate

[0204] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.150 g, 0.572 mmol) was dissolved in methylene chloride (4 mL), and then phenyl isocyanate (0.069 mL, 0.629 mmol) and TEA (0.119 mL, 0.858 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/ hexane = 25 %) and concentrated to afford the desired compound (0.217 g, 99.5 %) as a pale yellow oil.

Step 2: Synthesis of compound 162

[0205] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(phenylcarbonyl)piperazin-1-yl)methyl)benzoate (formula 13-3, 0.107 g, 0.280 mmol) was dissolved in methanol (3 mL), and then hydroxylamine (0.343 mL, 5.610 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.157 g, 2.805 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then the reaction mixture was concentrated under reduced pressure. Saturated sodium hydrogen carbonate was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 162** (0.041 g, 38.2 %) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 11.20 (s, 1 H), 9.00 (s, 1 H), 8.48 (s, 1 H), 7.68 (d, 2 H, $J = 8.0$ Hz), 7.45 - 7.42 (m, 4 H), 7.22 (dd, 2 H, $J = 10.2, 3.6$ Hz), 6.93 - 6.91 (m, 1 H), 3.97 (d, 2 H, $J = 13.3$ Hz), 3.78 (s, 2 H), 2.63 - 2.60 (m, 1 H), 0.97 (d, 6 H, $J = 6.0$ Hz); LRMS (ES) m/z 383.2 ($M^+ + 1$).

Example 42: Synthesis of compound 163**((3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-N-(2-methoxyphenyl)-3,5-dimethylpiperazine-1-carboxamide)****Step 1: Synthesis of methyl****4-(((2S,6R)-4-(2-methoxyphenylcarbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate**

[0206] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.150 g, 0.572 mmol) was dissolved in methylene chloride (4 mL), and then 2-methoxyphenyl isocyanate (0.094 g, 0.629 mmol) and TEA (0.119 mL, 0.858 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 25 %) and concentrated to afford the desired compound (0.169 g, 71.8 %) as a pale yellow oil.

Step 2: Synthesis of compound 163

[0207] Methyl 4-(((2S,6R)-4-(2-methoxyphenylcarbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.100 g, 0.243 mmol) was dissolved in methanol (3 mL), and then hydroxylamine (0.297 mL, 4.860 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.136 g, 2.430 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. **Compound 163** (0.060 g, 59.9 %) was obtained as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.68 - 7.65 (m, 3 H), 7.56 (d, 1 H, *J* = 8.0 Hz), 7.39 (d, 2 H, *J* = 8.2 Hz), 7.00 - 6.98 (m, 2 H), 6.87 - 6.85 (m, 1 H), 3.88 (d, 2 H, *J* = 11.6 Hz), 3.78 (s, 3 H), 3.76 (s, 2 H), 2.69 - 2.63 (m, 2 H), 2.55 - 2.52 (m, 2 H), 0.96 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 413.2 (*M*⁺+1).

Example 43: Synthesis of compound 164

((3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-N-(3-methoxyphenyl)-3,5-dimethylpiperazin-1-carboxamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(3-methoxyphenylcarbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0208] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.150 g, 0.572 mmol) was dissolved in methylene chloride (4 mL), and then 3-methoxyphenyl isocyanate (0.094 g, 0.629 mmol) and TEA (0.119 mL, 0.858 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 25 %) and concentrated to afford the desired compound (0.210 g, 89.3 %) as a pale yellow oil.

Step 2: Synthesis of compound 164

[0209] Methyl 4-(((2S,6R)-4-(3-methoxyphenylcarbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.100 g, 0.243 mmol) was dissolved in methanol (3 mL), and then hydroxylamine (0.297 mL, 4.860 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.136 g, 2.430 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. **Compound 164** (0.025 g, 24.9 %) was obtained as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 11.10 (s, 1 H), 9.00 (s, 1 H), 8.46 (s, 1 H), 7.67 (d, 2 H, J = 8.2 Hz), 7.43 (d, 2 H, J = 8.2 Hz), 7.14 - 7.11 (m, 1 H), 7.09 - 7.02 (m, 1 H), 6.57 (dd, 1 H, J = 10.2, 3.6 Hz), 3.95 (d, 2 H, J = 12.8 Hz), 3.77 (s, 2 H), 3.69 (s, 3 H), 2.35 - 2.54 (m, 2 H), 2.50 - 2.48 (m, 2 H), 0.96 (d, 6 H, J = 6.0 Hz); LRMS (ES) m/z 413.2 ($M^+ + 1$).

Example 44: Synthesis of compound 165

((3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-N-(4-methoxyphenyl)-3,5-dimethylpiperazine-1-carboxamide)Step 1: Synthesis of methyl4-(((2S,6R)-4-(4-methoxyphenylcarbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0210] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.150 g, 0.572 mmol) was dissolved in methylene chloride (4 mL), and then 4-methoxyphenyl isocyanate (0.094 g, 0.629 mmol) and TEA (0.119 mL, 0.858 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 30 %) and concentrated to afford the desired compound (0.022 g, 9.4 %) as a pale yellow oil.

Step 2: Synthesis of compound 165

[0211] Methyl 4-(((2S,6R)-4-(4-methoxyphenylcarbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.022 g, 0.053 mmol) was dissolved in methanol (3 mL), and then hydroxylamine (0.065 mL, 1.069 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.03 g, 0.535 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then the reaction mixture was concentrated under reduced pressure. Saturated sodium hydrogen carbonate was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 165** (0.008 g, 36.3 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.31 (s, 1 H), 7.67 (d, 2 H, *J* = 8.2 Hz), 7.40 (d, 2 H, *J* = 8.2 Hz), 7.31 (d, 2 H, *J* = 9.1 Hz), 6.80 (d, 2 H, *J* = 9.1 Hz), 6.80 (d, 2 H, *J* = 9.1 Hz), 3.94 (d, 2 H, *J* = 12.3 Hz), 3.76 (s, 2 H), 3.69 (s, 3 H), 2.66 - 2.25 (m, 4 H), 0.96 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 413.2 (*M*⁺+1).

Example 45: Synthesis of compound 166((3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-N-o-tolylpiperazine-1-carboxamide)

Step 1: Synthesis of methyl**4-(((2S,6R)-2,6-dimethyl-4-(o-tolylcarbamoyl)piperazin-1-yl)methyl)benzoate**

[0212] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.150 g, 0.572 mmol) was dissolved in methylene chloride (4 mL), and then o-tolyl isocyanate (0.078 mL, 0.629 mmol) and TEA (0.119 mL, 0.858 mmol) were added thereto at 0 °C. The mixture was stirred at room temperature for 1 hour, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 30 %) and concentrated to afford the desired compound (0.182 g, 80.5 %) as a white solid.

Step 2: Synthesis of compound 166

[0213] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(o-tolylcarbamoyl)piperazin-1-yl)methyl)benzoate (formula 13-3, 0.082 g, 0.207 mmol) was dissolved in methanol (3 mL), and then hydroxylamine (0.254 mL, 4.147 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.116 g, 2.073 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then the reaction mixture was concentrated under reduced pressure. Saturated sodium hydrogen carbonate was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 166** (0.010 g, 12.2 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.04 (s, 1 H), 7.66 (d, 2 H, *J* = 8.1 Hz), 7.34 (d, 2 H, *J* = 8.1 Hz), 7.16 - 7.10 (m, 3 H), 7.04 - 7.02 (m, 1 H), 3.90 (d, 2 H, *J* = 13.6 Hz), 3.76 (s, 2 H), 2.69 - 2.63 (m, 2 H), 2.54 - 2.50 (m, 2 H), 2.12 (s, 3 H), 0.97 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 397.2 (*M*⁺+1).

Example 46: Synthesis of compound 167**((3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-N-m-tolylpiperazine-1-carboxamide)****Step 1: Synthesis of methyl**

4-(((2S,6R)-2,6-dimethyl-4-(m-tolylcarbamoyl)piperazin-1-yl)methyl)benzoate

[0214] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.150 g, 0.572 mmol) was dissolved in methylene chloride (4 mL), and then m-tolyl isocyanate (0.084 mL, 0.629 mmol) and TEA (0.119 mL, 0.858 mmol) were added thereto at 0 °C. The mixture was stirred at room temperature for 1 hour, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 30 %) and concentrated to afford the desired compound (0.170 g, 75.2 %) as a white solid.

Step 2: Synthesis of compound 167

[0215] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(m-tolylcarbamoyl)piperazin-1-yl)methyl)benzoate (formula 13-3, 0.070 g, 0.177 mmol) was dissolved in methanol (3 mL), and then hydroxylamine (0.217 mL, 3.540 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.099 g, 1.770 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then the reaction mixture was concentrated under reduced pressure. Saturated sodium hydrogen carbonate was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 167** (0.008 g, 36.3 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.40 (s, 1 H), 7.68 (d, 2 H, *J* = 8.2 Hz), 7.41 (d, 2 H, *J* = 8.2 Hz), 7.26 - 7.24 (m, 2 H), 7.11 (dd, 1 H, *J* = 10.2, 3.6 Hz), 6.74 (d, 2 H, *J* = 7.2 Hz), 3.96 (d, 2 H, *J* = 13.0 Hz), 3.77 (s, 2 H), 2.65 - 2.59 (m, 4 H), 2.24 (s, 3 H), 0.96 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 397.2 (*M*⁺+1).

Example 47: Synthesis of compound 168**((3R,5S)-N-benzyl-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethylpiperazine-1-carboxamide)****Step 1: Synthesis of methyl****4-(((2S,6R)-4-(benzylcarbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate**

[0216] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.150 g, 0.572 mmol) was dissolved in methylene chloride (4 mL), and then benzyl isocyanate (0.078 mL, 0.629 mmol) and TEA (0.119 mL, 0.858 mmol) were added thereto at 0 °C. The mixture was stirred at room temperature for 1 hour, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 30 %) and concentrated to afford the desired compound (0.115 g, 50.9 %) as a pale yellow solid.

Step 2: Synthesis of compound 168

[0217] Methyl 4-(((2S,6R)-4-(benzylcarbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.060 g, 0.152 mmol) was dissolved in methanol (3 mL), and then hydroxylamine (0.186 mL, 3.034 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.085 g, 1.517 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then the reaction mixture was concentrated under reduced pressure. Saturated sodium hydrogen carbonate was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 168** (0.045 g, 74.8 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.05 (s, 1 H), 9.00 (s, 1 H), 7.67 (d, 2 H, *J* = 8.2 Hz), 7.42 (d, 2 H, *J* = 8.2 Hz), 7.30 - 7.19 (m, 5 H), 7.04 - 7.06 (m, 1 H), 4.22 (d, 2 H, *J* = 5.8 Hz), 3.83 (d, 2 H, *J* = 12.1 Hz), 3.75 (s, 2 H), 2.56 - 2.54 (m, 2 H), 2.45 - 2.43 (m, 2 H), 0.92 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 397.2 (*M*⁺+1).

Example 48: Synthesis of compound 171

(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-2-fluoro-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-2-fluorobenzoate

[0218] (2S,6R)-1-benzyl-2,6-dimethylpiperazin (formula 8-3, 0.200 g, 0.979 mmol) and methyl

4-formyl-2-fluorobenzoate (formula 8-4, 0.178 g, 0.979 mmol) were dissolved in tetrahydrofuran (5 mL), and acetic acid (0.028 mL, 0.979 mmol) was added thereto at room temperature, followed by stirring for 1 hour. Next, Na(CN)BH₃ (0.062 g, 0.979 mmol) was added to the reaction mixture, followed by stirring at the same temperature for 2 hours. Then, water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 25 %) and concentrated to afford the desired compound (0.028 g, 7.2 %) as a pale yellow oil.

Step 2: Synthesis of compound 171

[0219] Methyl 4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-2-fluorobenzoate (formula 8-5, 0.100 g, 0.264 mmol) was dissolved in methanol (3 mL), and then hydroxylamine (0.323 mL, 5.284 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.148 g, 2.642 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour and 40 minutes, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. **Compound 171** (0.034 g, 33.9 %) was obtained as a pale orange solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.00 (brs, 1 H), 9.10 (brs, 1 H), 7.47 (dd, 1 H, *J* = 7.5, 7.5 Hz), 7.32 (d, 2 H, *J* = 7.6 Hz), 7.26 (dd, 2 H, *J* = 7.5, 7.5 Hz), 7.17 - 7.13 (m, 2 H), 3.71 (s, 2 H), 3.42 (s, 2 H), 2.63 - 2.53 (m, 4 H), 1.81 (t, 2 H, *J* = 10.4 Hz), 0.88 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 372.2 (M⁺+1).

Example 49: Synthesis of compound 172

((E)-3-(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide)

Step 1: Synthesis of (E)-methyl 3-(4-(dimethoxymethyl)phenyl)acrylate

[0220] (E)-3-(4-formylphenyl)acrylic acid (1.000 g, 5.676 mmol) was dissolved in methanol (10 mL), and SOCl₂ (0.824 mL, 11.353 mmol) was added thereto at 0 °C, followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure to remove the solvent. Water was added to the concentrate, followed by extraction with

methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield the desired compound (0.870 g, 64.9 %) as a pale yellow solid.

Step 2: Synthesis of (E)-methyl 3-(4-formylphenyl)acrylate

[0221] (E)-methyl 3-(4-(dimethoxymethyl)phenyl)acrylate (0.870 g, 3.682 mmol) was dissolved in methanol (15 mL) at room temperature, and HCl (15 mL, 1N methanol solution) was added thereto at the same temperature, followed by stirring for 2 hours and 30 minutes. The reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate. The precipitated solid was filtered and dried to yield the desired compound (0.695 g, 99.2 %) as a pale yellow solid.

Step 3: Synthesis of (E)-methyl

3-(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)phenyl)acrylate

[0222] (2S,6R)-1-benzyl-2,6-dimethylpiperazine (formula 8-3, 0.050 g, 0.245 mmol) and (E)-methyl 3-(4-formylphenyl)acrylate (0.047 g, 0.245 mmol) were dissolved in tetrahydrofuran (1 mL), and acetic acid (0.007 mL, 0.245 mmol) was added thereto at room temperature, followed by stirring for 1 hour. Na(CN)BH₃ (0.015 g, 0.245 mmol) was added to the reaction mixture, followed by stirring at the same temperature for 2 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 25 %) and concentrated to afford the desired compound (0.012 g, 13.0 %) as a white solid.

Step 4: Synthesis of compound 172

[0223] (E)-methyl 3-(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 8-5, 0.050 g, 0.135 mmol) was dissolved in methanol (3 mL), and then hydroxylamine (0.165 mL, 2.699 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.076 g, 1.350 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Saturated sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure to yield **compound 172** (0.024 g, 47.9 %) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 9.60 (brs, 1 H), 7.44 (d, 2 H, J = 8.0 Hz), 7.32 - 7.24 (m, 7 H), 7.15 (dd, 1 H, J = 7.1, 7.1 Hz), 6.39 (d, 1 H, J = 15.8 Hz), 3.70 (s, 2 H), 3.37 (s, 2 H), 2.62 (d, 2 H, J = 10.7 Hz), 2.56 - 2.52 (m, 2 H), 1.77 (t, 2 H, J = 10.5 Hz), 0.87 (d, 6 H, J = 6.1 Hz); LRMS (ES) m/z 380.5 ($M^+ + 1$).

Example 50: Synthesis of compound 173

2-(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacetamide

Step 1: Synthesis of methyl 2-(4-(bromomethyl)phenyl)acetate

[0224] 2-(4-(bromomethyl)phenyl)acetic acid (3.000 g, 13.096 mmol) was dissolved in methanol (30 mL), and SOCl_2 (1.900 mL, 26.193 mmol) was added thereto at 0 °C, followed by stirring at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield the desired compound (3.140 g, 98.6 %) as a colorless oil.

Step 2: Synthesis of methyl

2-(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)phenyl)acetate

[0225] (2S,6R)-1-benzyl-2,6-dimethylpiperazine (formula 8-3, 0.200 g, 0.979 mmol), methyl 2-(4-(bromomethyl)phenyl)acetate (formula 8-4, 0.238 g, 0.979 mmol) and Cs_2CO_3 (0.478 g, 1.468 mmol) were dissolved in acetonitrile (5 mL) at room temperature. The reaction solution was stirred at the same temperature for 2 hours, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Water was added to the concentrate, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/ hexane = 25 %) and concentrated to afford the desired compound (0.273 g, 76.1 %) as a pale yellow oil.

Step 3: Synthesis of compound 173

[0226] Methyl 2-(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)phenyl)acetate (formula 8-5, 0.173 g, 0.472 mmol) was dissolved in methanol (3 mL), and then hydroxylamine (0.577 mL, 9.441 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.265 g, 4.720 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Saturated sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 173** (0.140g, 80.7 %) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 10.60 (brs, 1 H), 8.80 (brs, 1 H), 7.31 (d, 2 H, $J = 7.3$ Hz), 7.27 - 7.24 (m, 2 H), 7.17 - 7.15 (m, 5 H), 3.69 (s, 2 H), 3.33 (s, 2 H), 3.22 (s, 2 H), 2.61 (d, 2 H, $J = 10.1$ Hz), 2.53 - 2.49 (m, 2 H), 1.75 (t, 2 H, $J = 10.5$ Hz), 0.87 (d, 6 H, $J = 6.1$ Hz); LRMS (ES) m/z 368.4 ($M^+ + 1$).

Example 51: Synthesis of compound 174

(4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)-2-fluoro-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)-2-fluorobenzoate

[0227] (3R,5S)-1-benzyl-3,5-dimethylpiperazine (formula 16-1, 0.200 g, 0.979 mmol) was dissolved in acetonitrile (3 mL), and then methyl 4-(bromomethyl)-2-fluorobenzoate (formula 8-4, 0.254 g, 1.028 mmol) and Cs_2CO_3 (0.478 g, 1.468 mmol) were added thereto. The mixture was stirred at 80 °C for 2 hours, and then water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 15 %) and concentrated to afford the desired compound (0.211 g, 58.2 %) as a pale yellow oil.

Step 2: Synthesis of compound 174

[0228] Methyl 4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)-2-fluorobenzoate (formula 16-2, 0.100 g, 0.270 mmol) was dissolved in methanol (3 mL), and then

hydroxylamine (0.330 mL, 5.339 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.151 g, 2.699 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Saturated sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield **compound 174** (0.058 g, 57.8 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.46 - 7.44 (m, 1 H), 7.31 - 7.23 (m, 5 H), 7.20 - 7.16 (m, 2 H), 3.72 (s, 2 H), 3.40 (s, 2 H), 2.65 (d, 2 H, *J* = 10.4 Hz), 2.56 - 2.54 (m, 2 H), 1.82 - 1.80 (m, 2 H), 0.85 (d, 6 H, *J* = 6.1 Hz); LRMS (ES) *m/z* 372.4 (*M*⁺+1).

Example 52: Synthesis of compound 175

((E)-3-(4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide)

Step 1: Synthesis of (3R,5S)-1-benzyl-3,5-dimethylpiperazine

[0229] (2S,6R)-2,6-dimethylpiperazine (1.000 g, 8.757 mmol) and K₂CO₃ (1.724 g, 13.136 mmol) were dissolved in acetonitrile (50mL), and benzylbromide (1.092 mL, 9.195 mmol) was added thereto at 0 °C, and the mixture was stirred at the same temperature for 1 hour and 30 minutes. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (1.170 g, 65.4 %) as a yellow oil.

Step 2: Synthesis of (E)-methyl 3-(4-(hydroxymethyl)phenyl)acrylate

[0230] (E)-3-(4-(hydroxymethyl)phenyl)acrylic acid (0.300 g, 1.577 mmol) was dissolved in methanol (5 mL), and NaBH₄ (0.063 g, 1.656 mmol) was added thereto at room temperature, followed by stirring at the same temperature for 50 minutes. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield the desired compound (0.284 g, 93.7%) as a white solid.

Step 3: Synthesis of (E)-methyl 3-(4-(bromomethyl))phenyl)acrylate

[0231] (E)-methyl 3-(4-(hydroxymethyl)phenyl)acrylate (0.284 g, 1.478 mmol) was dissolved in toluene (10 mL), and PBr_3 (0.042 mL, 0.443 mmol) was added thereto at 0 °C, followed by stirring at the room temperature for 30 minutes. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield the desired compound (0.260 g, 69.0 %) as a white solid.

[0232] Step 4: Synthesis of (E)-methyl**3-(4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acrylate**

[0233] (3R,5S)-1-benzyl-3,5-dimethylpiperazine (formula 16-1, 0.200 g, 0.979 mmol), (E)-methyl 3-(4-(bromomethyl))phenyl)acrylate (formula 8-4, 0.250 g, 0.979 mmol) and Cs_2CO_3 (0.478 g, 1.468 mmol) were dissolved in acetonitrile (5 mL) at 80 °C, and the reaction solution was stirred at the same temperature for 1 hour and 40 minutes. Then, water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 15 %) and concentrated to afford the desired compound (0.078 g, 21.1 %) as a yellow oil.

Step 5: Synthesis of compound 175

[0234] (E)-methyl 3-(4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 16-2, 0.078 g, 0.206 mmol) was dissolved in methanol (1.5 mL), and then hydroxylamine (0.252 mL, 4.121 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.116 g, 2.061 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Saturated sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield **compound 175** (0.040 g, 51.1 %) as an orange solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.00 (s, 2 H), 7.45 (d, 2 H, $J = 8.0$ Hz), 7.36 - 7.21 (m, 8 H), 6.40 (d, 1 H, $J = 15.7$ Hz), 3.71 (s, 2 H), 3.39 (s, 2 H), 2.64 (d, 2 H, $J = 10.6$ Hz), 2.59 - 2.54

(m, 2 H), 1.81 - 1.76 (m, 2 H), 0.87 (d, 6 H, $J = 6.0$ Hz); LRMS (ES) m/z 380.4 ($M^+ + 1$).

Example 53: Synthesis of compound 176

(2-(4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacetamide)

Step 1: Synthesis of methyl

2-(4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acetate

[0235] (3R,5S)-1-benzyl-3,5-dimethylpiperazine (formula 16-1, 0.200 g, 0.979 mmol), methyl 2-(4-(bromomethyl)phenyl)acetate (formula 8-4, 0.238 g, 0.979 mmol) and Cs_2CO_3 (0.478 g, 1.468 mmol) were dissolved in acetonitrile (5 mL) at room temperature. The reaction solution was stirred at the same temperature for 5 hours, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Water was added to the resulting concentrate, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 30 %) and concentrated to yield the desired compound (0.274 g, 76.4 %) as a pale yellow oil.

Step 2: Synthesis of compound 176

[0236] Methyl 2-(4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acetate (formula 16-2, 0.143 g, 0.390 mmol) was dissolved in methanol (3 mL), and then hydroxylamine (0.477 mL, 7.804 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.219 g, 3.9902 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then the reaction mixture was concentrated under reduced pressure. Saturated sodium hydrogen carbonate (5 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 176** (0.105 g, 73.2 %) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.50 (s, 1 H), 9.00 (s, 1 H), 7.32 - 7.21 (m, 1 H), 7.16 (d, 2 H, $J = 7.9$ Hz), 3.69 (s, 2 H), 3.37 (s, 2 H), 3.22 (s, 2 H), 2.62 (d, 2 H, $J = 10.8$ Hz), 2.56 - 2.52 (m, 1 H), 1.80 - 1.75 (m, 1 H), 0.88 (d, 6 H, $J = 6.0$ Hz); LRMS (ES) m/z 368.5 ($M^+ + 1$).

Example 54: Synthesis of compound 177 (phenyl)

(2S,6R)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylpiperazine-1-carboxylate**Step 1: Synthesis of phenyl****(2S,6R)-4-(4-(methoxycarbonyl)benzyl)-2,6-dimethylpiperazine-1-carboxylate**

[0237] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.200 g, 0.762 mmol) was dissolved in methylene chloride (5 mL), and then phenylchloroformate (0.105 mL, 0.839 mmol) and TEA (0.211 mL, 1.525 mmol) were added thereto. The mixture was stirred at 0 °C for 2 hours, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 25 %) and concentrated to afford the desired compound (0.066 g, 22.6 %) as a colorless oil.

Step 2: Synthesis of compound 177

[0238] Phenyl (2S,6R)-4-(4-(methoxycarbonyl)benzyl)-2,6-dimethylpiperazine-1-carboxylate (formula 1-3, 0.066 g, 0.173 mmol) was dissolved in methanol (3 mL), and then hydroxylamine (0.211 mL, 3.451 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.097 g, 1.726 mmol) were added thereto. The mixture was stirred at room temperature for 10 minutes, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Saturated sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure to yield **177** (0.062 g, 61.8 %) as a pale orange solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.00 (s, 1 H), 9.00 (s, 1 H), 7.72 (d, 2 H, *J* = 8.0 Hz), 7.43 (d, 2 H, *J* = 8.0 Hz), 7.39 - 7.36 (m, 1 H), 7.22 (dd, 1 H, *J* = 10.2, 3.6 Hz), 7.10 (d, 2 H, *J* = 7.6 Hz), 4.15 - 4.13 (m, 1 H), 3.56 (s, 2 H), 2.66 (d, 2 H, *J* = 11.4 Hz), 2.21 - 2.17 (m, 1 H), 1.35 (d, 6 H, *J* = 6.7 Hz); LRMS (ES) *m/z* 384.2 (*M*⁺+1).

Example 55: Synthesis of compound 183

4-(((2S,6R)-2,6-dimethyl-4-phenethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)**Step 1: Synthesis of methyl****4-(((2S,6R)-2,6-dimethyl-4-phenethylpiperazin-1-yl)methyl)benzoate**

[0239] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol) and phenylacetaldehyde (0.049 mL, 0.419 mmol) were dissolved in tetrahydrofuran (2 mL), and acetic acid (0.021 mL, 0.381 mmol) was added thereto at room temperature, followed by stirring for 1 hour. Na(CN)BH₃ (0.024 g, 0.381 mmol) was added to the reaction mixture, followed by stirring at the same temperature for 17 hours. A saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; 4 g cartridge, ethyl acetate/hexane = 30 %) and concentrated to afford the desired compound (0.040 g, 28.6 %) as a pale yellow oil.

Step 2: Synthesis of compound 183

[0240] Methyl 4-(((2S,6R)-2,6-dimethyl-4-phenethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.045 g, 0.123 mmol) was dissolved in methanol (3 mL), and then hydroxylamine (0.150 mL, 2.456 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.069 g, 1.228 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Saturated sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The organic layer was dried with anhydrous sodium sulfate, and then concentrated under reduced pressure to yield **compound 183** (0.040 g, 88.7 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.66 (d, 2 H, *J* = 8.0 Hz), 7.38 (d, 2 H, *J* = 8.0 Hz), 7.26 - 7.17 (m, 5 H), 3.73 (s, 2 H), 2.80 (d, 2 H, *J* = 10.1 Hz), 2.71 (t, 2 H, *J* = 7.8 Hz), 2.55 - 2.53 (m, 2 H), 2.42 (t, 2 H, *J* = 7.8 Hz), 1.83 - 1.80 (m, 2 H), 0.91 (d, 6 H, *J* = 6.1 Hz).

Example 56: Synthesis of compound 184**4-(((3R,5S)-3,5-dimethyl-4-phenethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)**

Step 1: Synthesis of methyl**4-(((3R,5S)-3,5-dimethyl-4-phenethylpiperazin-1-yl)methyl)benzoate**

[0241] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol) and phenylacetaldehyde (0.049 mL, 0.419 mmol) were dissolved in tetrahydrofuran (2 mL), and acetic acid (0.021 mL, 0.381 mmol) was added thereto at room temperature, followed by stirring for 1 hour. Na(CN)BH₃ (0.024 g, 0.381 mmol) was added to the mixture, which was then stirred at the same temperature for 17 hours. The reaction mixture was washed with an aqueous solution of sodium chloride, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 30 %) and concentrated to afford the desired compound (0.010 g, 7.2 %) as a colorless oil.

Step 2: Synthesis of compound 184

[0242] Methyl 4-(((3R,5S)-3,5-dimethyl-4-phenethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.010 g, 0.027 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.033 mL, 0.546 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.015 g, 0.273 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Saturated sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield **compound 184** (0.007 g, 69.8 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.50 (s, 1 H), 9.00 (s, 1 H), 7.70 (d, 2 H, *J* = 8.2 Hz), 7.35 (d, 2 H, *J* = 8.0 Hz), 7.28 (d, 2 H, *J* = 8.0 Hz), 7.18 (d, 2 H, *J* = 8.2 Hz), 3.43 (s, 1 H), 2.83 - 2.79 (m, 2 H), 2.72 - 2.59 (m, 6 H), 1.77 - 1.72 (m, 2 H), 1.00 (d, 6 H, *J* = 6.1 Hz).

Example 57: Synthesis of compound 185**((3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-N-(1-methyl-1H-indol-5-yl)piperazine-1-carboxamide)****Step 1: Synthesis of methyl**

4-(((2S,6R)-2,6-dimethyl-4-(1-methyl-1H-indol-5-ylcarbamoyl)piperazin-1-yl)methyl)benzoate

[0243] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol), 5-isocyanato-1-methyl-1H-indole (0.079 g, 0.457 mmol) and TEA (0.106 mL, 0.762 mmol) were dissolved in methylene chloride (1 mL), and then stirred at room temperature for 3 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.061 g, 36.8 %) as a white solid.

Step 2: Synthesis of compound 185

[0244] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(1-methyl-1H-indol-5-ylcarbamoyl)piperazin-1-yl)methyl) benzoate (formula 13-3, 0.040 g, 0.092 mmol) was dissolved in methanol (0.5 mL), and then hydroxylamine (0.113 mL, 1.841 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.052 g, 0.921 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Saturated sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure to yield **compound 185** (0.018 g, 44.9 %) as a pale yellow solid.

^1H NMR (400 MHz, DMSO- d_6) δ 8.30 (s, 1 H), 7.67 (d, 2 H, J = 8.2 Hz), 7.57 (d, 1 H, J = 1.7 Hz), 7.38 (d, 2 H, J = 8.2 Hz), 7.27 (d, 1 H, J = 8.8 Hz), 7.23 - 7.22 (m, 1 H), 7.17 (dd, 1 H, J = 10.2, 3.6 Hz), 6.29 (dd, 1 H, J = 10.2, 3.6 Hz), 3.99 - 3.96 (m, 2 H), 3.77 (s, 2 H), 3.73 (s, 3 H), 2.62 - 2.52 (m, 4 H), 0.97 (d, 6 H, J = 6.0 Hz).

Example 58: Synthesis of compound 186

((3R,5S)-N-(3-(1H-pyrrol-1-yl)phenyl)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethylpiperazine-1-carboxamide)

Step 1: Synthesis of methyl 4-(((2S,6R)-4-(3-(1H-pyrrol-1-yl)phenylcarbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0245] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol), 1-(3-isocyanatophenyl)-1H-pyrrole (0.084 g, 0.457 mmol) and TEA (0.106 mL, 0.762 mmol) were dissolved in methylene chloride (1 mL), and then stirred at room temperature for 3 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.059 g, 34.7 %) as a white solid.

Step 2: Synthesis of compound 186

[0246] Methyl 4-(((2S,6R)-4-(3-(1H-pyrrol-1-yl)phenylcarbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.040 g, 0.090 mmol) was dissolved in methanol (0.5 mL), and then hydroxylamine (0.110 mL, 1.792 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.050 g, 0.896 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Saturated sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure to yield **compound 186** (0.013 g, 32.4 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.67 (brs, 1 H), 7.78 - 7.76 (m, 3 H), 7.36 - 7.22 (m, 6 H), 7.09 (d, 2 H, *J* = 8.0 Hz), 6.23 (s, 2 H), 3.97 (d, 2 H, *J* = 12.0 Hz), 3.75 (s, 2 H), 2.67 - 2.61 (m, 4 H), 0.84 (d, 6 H, *J* = 4.8 Hz).

Example 59: Synthesis of compound 187

((3R,5S)-N-(2,3-dihydrobenzofuran-5-yl)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethylpiperazine-1-carboxamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(2,3-dihydrobenzofuran-5-ylcarbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0247] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol), 5-isocyanato-2,3-dihydrobenzofuran (0.074 g, 0.457 mmol) and TEA (0.106 mL, 0.762 mmol) were dissolved in methylene chloride (1 mL), and then stirred at room temperature for 3 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.070 g, 43.4 %) as a white solid.

Step 2: Synthesis of compound 187

[0248] Methyl 4-(((2S,6R)-4-(2,3-dihydrobenzofuran-5-ylcarbonyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.040 g, 0.094 mmol) was dissolved in methanol (0.5 mL), and then hydroxylamine (0.116 mL, 1.889 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.053 g, 0.945 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Saturated sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure to yield **compound 187** (0.020 g, 49.9 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.27 (s, 1 H), 7.66 (d, 2 H, *J* = 8.1 Hz), 7.37 (d, 2 H, *J* = 20.0 Hz), 7.29 (d, 1 H, *J* = 1.2 Hz), 7.04 - 7.02 (m, 1 H), 6.60 (d, 1 H, *J* = 8.0 Hz), 4.45 (t, 2 H, *J* = 8.7 Hz), 3.92 (d, 2 H, *J* = 12.0 Hz), 3.74 (s, 2 H), 3.11 (t, 2 H, *J* = 8.6 Hz), 2.61 - 2.56 (m, 4 H), 0.96 (d, 6 H, *J* = 6.0 Hz).

Example 60: Synthesis of compound 188

4-(((3R,5S)-3,5-dimethyl-4-(3-phenylpropanoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-phenylpropanoyl)piperazin-1-yl)methyl)benzoate

[0249] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.070 g,

0.267 mmol) was dissolved in methylene chloride (1 mL), and then 3-phenylpropanoyl chloride (0.054 g, 0.320 mmol) and TEA (0.074 mL, 0.534 mmol) were added thereto. The mixture was stirred at room temperature for 3 hours, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was separated and concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/ methylene chloride = 5 %) and concentrated to afford the desired compound (0.097 g, 92.2 %) as a white oil.

Step 2: Synthesis of compound 188

[0250] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-phenylpropanoyl)piperazin-1-yl)methyl)benzoate (formula 1-3, 0.040 g, 0.101 mmol) was dissolved in methanol (0.5 mL), and then hydroxylamine (0.124 mL, 2.028 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.057 g, 1.014 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then saturated sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The organic layer was concentrated under reduced pressure to yield **compound 188** (0.019 g, 47.4 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.70 (d, 2 H, *J* = 8.4 Hz), 7.38 (d, 2 H, *J* = 8.0 Hz), 7.27 - 7.14 (m, 5 H), 4.39 (brs, 1 H), 4.00 (brs, 1 H), 3.48 (s, 2 H), 2.80 - 2.78 (m, 2 H), 2.69 - 2.66 (m, 2 H), 2.58 - 2.57 (m, 2 H), 2.01 - 1.98 (m, 2 H), 1.19 (brs, 6 H).

Example 61: Synthesis of compound 189

4-(((2S,6R)-2,6-dimethyl-4-(*m*-tolylcarbamothioyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-2,6-dimethyl-4-(*m*-tolylcarbamothioyl)piperazin-1-yl)methyl)benzoate

[0251] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (compound 13-2, 0.070 g, 0.267 mmol), 1-isothiocyanate-3-methylbenzene (0.048 g, 0.320 mmol) and TEA (0.106 mL, 0.762 mmol) were dissolved in methylene chloride (1 mL), and then stirred at the room temperature for 6 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide;

methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.092 g, 83.8 %) as a yellow solid.

Step 2: Synthesis of compound 189

[0252] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(m-tolylcarbamothioyl)piperazin-1-yl)methyl)benzoate (formula 13-3, 0.040 g, 0.097 mmol) was dissolved in methanol (0.5 mL), and then hydroxylamine (0.119 mL, 1.944 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.055 g, 0.972 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Saturated sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure to yield **compound 189** (0.021 g, 52.4 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.65 (d, 2 H, *J* = 8.0 Hz), 7.30 (d, 2 H, *J* = 8.0 Hz), 7.14 (t, 1 H, *J* = 8.0 Hz), 7.05 - 7.04 (m, 1 H), 6.88 (d, 1 H, *J* = 8.0 Hz), 4.55 (d, 2 H, *J* = 12.0 Hz), 3.75 (s, 2 H), 2.91 - 2.85 (m, 2 H), 2.55 - 2.51 (m, 2 H), 2.48 (s, 3 H), 0.98 (d, 6 H, *J* = 6.1 Hz).

Example 62: Synthesis of compound 193

(4-(((2S,6R)-4-(2-fluoro-2-methylpropyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(2-hydroxy-2-methylpropyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0253] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol) was dissolved in acetonitrile (2 mL), and 2,2-dimethyloxirane (0.041 g, 0.572 mmol) and K₂CO₃ (0.105 g, 0.762 mmol) were added thereto. The mixture was stirred at 80 °C for 48 hours, and then water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 50 %) and concentrated to afford the desired compound (0.040 g, 31.4 %) as a brown oil.

Step 2: Synthesis of methyl**4-(((2S,6R)-4-(2-fluoro-2-methylpropyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate**

[0254] Methyl 4-(((2S,6R)-4-(2-hydroxy-2-methylpropyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 19-2, 0.080 g, 0.239 mmol) was dissolved in methylene chloride (4 mL), and DAST (0.042 g, 0.263 mmol) was added thereto at 0 °C, followed by stirring at room temperature for 40 minutes. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 50 %) and concentrated to afford the desired compound (0.065 g, 80.8 %) as a yellow oil.

Step 3: Synthesis of compound 193

[0255] Methyl 4-(((2S,6R)-4-(2-fluoro-2-methylpropyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (0.065 g, 0.193 mmol) was dissolved in methanol (2 mL), and then hydroxylamine (0.236 mL, 3.864 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.108 g, 1.932 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Saturated sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield **compound 193** (0.030 g, 46.0%) as a pale orange solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.65 (d, 2 H, *J* = 8.2 Hz), 7.35 (d, 2 H, *J* = 8.2 Hz), 3.72 (s, 2 H), 2.74 (d, 2 H, *J* = 10.0 Hz), 2.57 - 2.53 (m, 2 H), 2.35 (d, 2 H, *J* = 22.1 Hz), 1.95 - 1.93 (m, 2 H), 1.29 (d, 6 H, *J* = 22.1 Hz), 0.89 (d, 6 H, *J* = 6.1 Hz); LRMS (ES) *m/z* 338.2 (*M*⁺+1).

Example 63: Synthesis of compound 194**(6-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxynicotinamide)****Step 1: Synthesis of methyl**

6-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)nicotinate

[0256] (2S,6R)-1-benzyl-2,6-dimethylpiperazine (formula 8-3, 0.200 g, 0.831 mmol) was dissolved in acetonitrile (4 mL), and then methyl 6-(bromomethyl)nicotinate (formula 8-4, 0.191 g, 0.831 mmol) and Cs_2CO_3 (0.541 g, 1.661 mmol) were added thereto. The mixture was stirred at room temperature for 17 hours, and then water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 25 %) and concentrated to afford the desired compound (0.183 g, 62.3 %) as a pale yellow solid.

Step 2: Synthesis of compound 194

[0257] Methyl 6-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)nicotinate (formula 8-5, 0.100 g, 0.283 mmol) was dissolved in methanol (2 mL), and then hydroxylamine (0.346 mL, 5.658 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.159 g, 2.829 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The organic layer was dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. **Compound 194** (0.032 g, 31.9 %) was obtained as a pale orange solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.75 (d, 1 H, J = 1.4 Hz), 7.94 (dd, 1 H, J = 10.2, 3.6 Hz), 7.35 - 7.33 (m, 2 H), 7.30 - 7.24 (m, 3 H), 7.17 - 7.15 (m, 1 H), 3.73 (s, 2 H), 3.48 (s, 2 H), 2.67 (d, 2 H, J = 9.9 Hz), 2.58 - 2.54 (m, 2 H), 1.88 - 1.83 (m, 2 H), 0.90 (d, 6 H, J = 6.1 Hz); LRMS (ES) m/z 355.2 ($\text{M}^+ + 1$).

Example 64: Synthesis of compound 195**6-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxynicotinamide)****Step 1: Synthesis of methyl****6-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)nicotinate**

[0258] (3R,5S)-1-benzyl-3,5-dimethylpiperazine (formula 16-1, 0.150 g, 0.734 mmol) was dissolved in acetonitrile (4 mL), and then methyl 4-(bromomethyl)nicotinate (formula 8-4, 0.169 g, 0.734 mmol) and Cs_2CO_3 (0.718 g, 2.203 mmol) were added thereto. The mixture was stirred at room temperature for 17 hours, and then water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 25 %) and concentrated to afford the desired compound (0.108 g, 41.6 %) as a yellow solid.

Step 2: Synthesis of compound 195

[0259] Methyl 6-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)nicotinate (formula 16-2, 0.050 g, 0.141 mmol) was dissolved in methanol (2 mL), and then hydroxylamine (0.173 mL, 2.829 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.079 g, 1.415 mmol) were added thereto. The mixture was stirred at room temperature for 20 minutes, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. Saturated sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield **compound 195** (0.022 g, 43.9 %) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.75 (s, 1 H), 7.99 (d, 1 H, J = 8.2 Hz), 7.50 (d, 1 H, J = 8.2 Hz), 7.35 - 7.21 (m, 5 H), 3.82 (s, 2 H), 3.44 (s, 2 H), 2.73 - 2.60 (m, 4 H), 1.78 (t, 2 H, J = 9.9 Hz), 0.88 (d, 6 H, J = 6.1 Hz); LRMS (ES) m/z 355.2 ($\text{M}^+ + 1$).

Example 65: Synthesis of compound 196

((3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-N,3,5-trimethyl-N-phenylpiperazine-1-carboxamide)

Step 1: Synthesis of 4-nitrophenyl methyl(phenyl)carbamate

[0260] N-methylaniline (0.300 g, 2.800 mmol) and TEA (0.776 mL, 5.600 mmol) were dissolved in methylene chloride (5 mL), and 4-nitrophenyl chloroformate (0.621 g, 3.080 mmol) was added thereto at 0 °C, followed by stirring at the same temperature for 2 hours. Then, water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield the desired

compound (0.709 g, 93.0 %) as a yellow oil.

Step 2: Synthesis of methyl

4-(((2S,6R)-2,6-dimethyl-4-(methyl(phenyl)carbamoyl)piperazin-1-yl)methyl)benzoate

[0261] 4-nitrophenyl methyl(phenyl)carbamate (0.500 g, 1.836 mmol), methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.549 g, 1.836 mmol) and TEA (0.382 mL, 2.755 mmol) were dissolved in N,N-dimethylformamide (20 mL). The reaction solution was stirred at 100 °C for 17 hours, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/ hexane = 50 %) and concentrated to afford the desired compound (0.373 g, 51.4 %) as a brown oil.

Step 3: Synthesis of compound 196

[0262] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(methyl(phenyl)carbamoyl)piperazin-1-yl)methyl)benzoate (formula 13-3, 0.110 g, 0.278 mmol) was dissolved in methanol (2 mL), and then hydroxylamine (0.340 mL, 5.563 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.156 g, 2.781 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure to yield **compound 196** (0.092 g, 83.4 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.90 (s, 1 H), 9.10 (s, 1 H), 7.64 (d, 2 H, *J* = 8.3 Hz), 7.35 - 7.30 (m, 4 H), 7.12 - 7.08 (m, 3 H), 3.65 (s, 2 H), 3.47 (d, 2 H, *J* = 12.8 Hz), 3.07 (s, 3 H), 2.41 (t, 1 H, *J* = 11.5 Hz), 2.33 - 2.28 (m, 2 H), 0.86 (d, 6 H, *J* = 6.4 Hz); LRMS (ES) *m/z* 397.2 (*M*⁺+1).

Example 66: Synthesis of compound 197

(N-hydroxy-4-(((2S,6R)-4-(indoline-1-carbonyl)-2,6-dimethylpiperazin-1-yl)methyl)benzamide)

Step 1: Synthesis of 4-nitrophenyl indoline-1-carboxylate

[0263] Indoline (0.300 g, 2.518 mmol) and TEA (0.698 mL, 5.035 mmol) were dissolved in methylene chloride (5 mL), and 4-nitrophenyl chloroformate (0.558 g, 2.769 mmol) was added thereto at 0 °C, followed by stirring at the same temperature for 30 minutes. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 25 %) and concentrated to afford the desired compound (0.668 g, 93.3 %) as a pale brown solid.

Step 2: Synthesis of methyl**4-(((2S,6R)-4-(indoline-1-carbonyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate**

[0264] 4-Nitrophenyl indoline-1-carboxylate (0.300 g, 1.055 mmol), methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.315 g, 1.055 mmol) and TEA (0.439 mL, 3.166 mmol) were dissolved in N,N-dimethylformamide (6 mL) at 100 °C, and then stirred at the same temperature for 17 hours. Then, water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/ hexane = 50 %) and concentrated to afford the desired compound (0.282 g, 65.6 %) as a brown solid.

Step 3: Synthesis of compound 197

[0265] Methyl 4-(((2S,6R)-4-(indoline-1-carbonyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.100 g, 0.245 mmol) was dissolved in methanol (2 mL), and then hydroxylamine (0.300 mL, 4.908 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.138 g, 2.454 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure to yield **compound 197** (0.068 g, 67.8 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.67 (d, 2 H, *J* = 8.3 Hz), 7.41 (d, 2 H, *J* = 8.1 Hz), 7.18 (d, 1 H, *J* = 7.3 Hz), 7.10 - 7.08 (m, 1 H), 7.00 (d, 1 H, *J* = 7.8 Hz), 6.87 - 6.85 (m, 1 H), 3.83 - 3.78 (m, 4 H), 3.54 (d, 2 H, *J* = 12.6 Hz), 2.98 (t, 2 H, *J* = 8.2 Hz), 2.73 (t, 2 H, *J* = 11.7 Hz), 2.61 -

2.59 (m, 2 H), 0.92 (d, 6 H, $J = 6.0$ Hz); LRMS (ES) m/z 409.2 ($M^+ + 1$).

Example 67: Synthesis of compound 198

((3R,5S)-N-butyl-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-N-phenylpiperazine-1-carboxamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(butylphenylcarbamoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0266] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(phenylcarbamoyl)piperazin-1-yl)methyl)benzoate (formula 13-3, 0.500 g, 1.311 mmol) and NaH (0.033 g, 1.376 mmol) were dissolved in N,N-dimethylformamide (10 mL) and stirred at room temperature for 1 hour. Then, 1-iodobutane (0.164 mL, 1.442 mmol) was added to the reaction mixture, followed by stirring at the same temperature for 3 hours. Next, water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 50 %) and concentrated to afford the desired compound (0.115 g, 20.1 %) as a pale yellow oil.

Step 2: Synthesis of compound 198

[0267] Methyl 4-(((3R,5S)-4-(butylphenylcarbamoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 20-1, 0.060 g, 0.137 mmol) was dissolved in methanol (2 mL), and then hydroxylamine (0.168 mL, 2.742 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.077 g, 1.371 mmol) were added thereto. The mixture was stirred at room temperature for 20 minutes, and a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure to yield **compound 198** (0.038 g, 63.2 %) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 8.95 (s, 1 H), 7.62 (d, 2 H, $J = 8.2$ Hz), 7.35 - 7.30 (m, 4 H), 7.12 - 7.06 (m, 3 H), 3.63 (s, 2 H), 3.52 - 3.48 (m, 2 H), 3.43 (d, 2 H, $J = 13.1$ Hz), 2.39 - 2.37 (m, 2 H), 2.33 - 2.26 (m, 2 H), 1.43 - 1.37 (m, 2 H), 1.28 - 1.20 (m, 2 H), 0.92 - 0.90 (m, 3 H), 0.89 - 0.87 (m, 6 H); LRMS (ES) m/z 439.3 ($M^+ + 1$).

Example 68: Synthesis of compound 204**4-(((3R,5S)-3,5-dimethyl-4-(4,4,4-trifluorobutyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)****Step 1: Synthesis of methyl****4-(((3R,5S)-3,5-dimethyl-4-(4,4,4-trifluorobutyl)piperazin-1-yl)methyl)benzoate**

[0268] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.300 g, 1.004 mmol) was dissolved in acetonitrile (5 mL), and then 1,1,1-trifluoro-4-iodobutane (0.129 mL, 1.004 mmol) and Cs₂CO₃ (0.318 g, 2.510 mmol) were added thereto. The mixture was heated under reflux for 17 hours, and then cooled to room temperature. The reaction mixture was filtered through a glass filter to remove solids, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 50 %) and concentrated to yield the desired compound (0.115 g, 30.8 %) as a pale yellow oil.

Step 2: Synthesis of compound 204

[0269] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(4,4,4-trifluorobutyl)piperazin-1-yl)methyl)benzoate (formula 1-3, 0.065 g, 0.175 mmol) was dissolved in methanol (2 mL), and then hydroxylamine (0.214 mL, 3.491 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.098 g, 1.745 mmol) were added thereto. The mixture was stirred at room temperature for 40 minutes, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. **Compound 204** (0.023g, 35.3 %) was obtained as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.20 (s, 1 H), 9.00 (s, 1 H), 7.70 (d, 2 H, *J* = 7.2 Hz), 7.34 (d, 2 H, *J* = 7.6 Hz), 3.42 (s, 2 H), 2.62 - 2.59 (m, 6 H), 2.34 - 2.33 (m, 2 H), 2.72 - 1.66 (m, 2 H), 1.25 - 1.24 (m, 2 H), 0.94 (d, 6 H, *J* = 5.1 Hz); LRMS (ES) *m/z* 374.2 (M⁺+1).

Example 69: Synthesis of compound 211

(4-(((3R,5S)-4-(2-fluorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)Step 1: Synthesis of methyl4-(((3R,5S)-4-(2-fluorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0270] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), 1-(bromomethyl)-2-fluorobenzene (0.055 mL, 0.457 mmol) and K_2CO_3 (0.105g, 0.762 mmol) were dissolved in acetonitrile (1 mL) and stirred at room temperature for 7 hours. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.067 g, 47.4 %) as a white oil.

Step 2: Synthesis of compound 211

[0271] Methyl 4-(((3R,5S)-4-(2-fluorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.050 g, 0.135 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.165 mL, 2.699 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.076 g, 1.350 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. **Compound 211** (0.031 g, 61.8 %) was obtained as a yellow solid.

^1H NMR (400 MHz, DMSO- d_6) δ 7.69 (d, 2 H, J = 7.3 Hz), 7.63 - 7.60 (m, 1 H), 7.30 (d, 2 H, J = 7.8 Hz), 3.79 (s, 2 H), 3.43 (s, 2 H), 2.68 - 2.56 (m, 4 H), 1.81 (t, 2 H, J = 10.4 Hz), 0.87 (d, 6 H, J = 6.0 Hz).

Example 70: Synthesis of compound 212(4-(((3R,5S)-4-(2,5-difluorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl**4-(((3R,5S)-4-(2,5-difluorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0272] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), 2-(bromomethyl)-1,4-difluorobenzene (0.059 mL, 0.457 mmol) and K_2CO_3 (0.105 g, 0.762 mmol) were dissolved in acetonitrile (1 mL) and stirred at room temperature for 7 hours. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.057 g, 38.5 %) as a white solid.

Step 2: Synthesis of compound 212

[0273] Methyl 4-(((3R,5S)-4-(2,5-difluorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.050 g, 0.129 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.157 mL, 2.574 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.072 g, 1.287 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. **Compound 212** (0.025 g, 49.9 %) was obtained as a pale yellow solid.

^1H NMR (400 MHz, DMSO- d_6) δ 7.69 (d, 2 H, J = 7.8 Hz), 7.39 - 7.35 (m, 1 H), 7.30 (d, 2 H, J = 7.9 Hz), 7.18 - 7.15 (m, 1 H), 3.70 (s, 2 H), 3.44 (s, 2 H), 2.69 - 2.60 (m, 4 H), 1.83 (t, 2 H, J = 10.4 Hz), 0.84 (d, 6 H, J = 6.0 Hz).

Example 71: Synthesis of compound 213**(4-(((3R,5S)-3,5-dimethyl-4-(2,4,5-trifluorobenzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)**

Step 1: Synthesis of methyl**4-(((3R,5S)-3,5-dimethyl-4-(2,4,5-trifluorobenzyl)piperazin-1-yl)methyl)benzoate**

[0274] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), 1-(bromomethyl)-2,4,5-trifluorobenzene (0.103 g, 0.457 mmol) and K_2CO_3 (0.105 g, 0.762 mmol) were dissolved in acetonitrile (1 mL) and stirred at room temperature for 7 hours. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.071 g, 45.8 %) as a white solid.

Step 2: Synthesis of compound 213

[0275] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(2,4,5-trifluorobenzyl)piperazin-1-yl)methyl)benzoate (formula 1-3, 0.050 g, 0.123 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.150 mL, 2.460 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.069 g, 1.230 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. **Compound 213** (0.024 g, 47.9 %) was obtained as a white solid.

^1H NMR (400 MHz, $DMSO-d_6$) δ 7.64 (d, 2 H, $J = 8.0$ Hz), 7.60 - 7.58 (m, 1 H), 7.48 - 7.46 (m, 1 H), 7.11 (d, 2 H, $J = 8.0$ Hz), 3.37 (s, 2 H), 3.22 (s, 2 H), 2.69 - 2.55 (m, 4 H), 1.79 (t, 2 H, $J = 10.2$ Hz), 0.84 (d, 6 H, $J = 6.1$ Hz).

Example 72: Synthesis of compound 214**4-(((3R,5S)-4-(3,5-bis(trifluoromethyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide****Step 1: Synthesis of methyl**

4-(((3R,5S)-4-(3,5-bis(trifluoromethyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0276] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), 1-(bromomethyl)-3,5-bis(trifluoromethyl)benzene (0.084 ml, 0.457 mmol) and K_2CO_3 (0.105 g, 0.762 mmol) were dissolved in acetonitrile (1 mL) and stirred at room temperature for 7 hours. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = 5 %) and concentrated to afford the desired compound (0.075 g, 40.3 %) as a white oil.

Step 2: Synthesis of compound 214

[0277] Methyl 4-(((3R,5S)-4-(3,5-bis(trifluoromethyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.050 g, 0.102 mmol) was dissolved in methanol (1 mL), and then hydroxylamine (0.125 mL, 2.047 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.057 g, 1.024 mmol) were added thereto. The mixture was stirred at room temperature for 1 hour, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. **Compound 214** (0.021 g, 41.9 %) was obtained as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 8.06 (s, 2 H), 7.91 (s, 2 H), 7.67 (d, 2 H, J = 6.7 Hz), 7.22 (d, 2 H, J = 7.3 Hz), 3.89 (s, 2 H), 3.41 (s, 2 H), 2.70 - 2.55 (m, 4 H), 1.83 (t, 2 H, J = 10.1 Hz), 0.82 (d, 6 H, J = 5.9 Hz).

Example 73: Synthesis of compound 215

4-(((2S,6R)-2,6-dimethyl-4-(2,4,5-trifluorobenzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((2S,6R)-2,6-dimethyl-4-(2,4,5-trifluorobenzyl)piperazin-1-yl)methyl)benzoate

[0278] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol), 1-(bromomethyl)-2,4,5-trifluorobenzene (0.103 g, 0.457 mmol) and K₂CO₃ (0.105 g, 0.762 mmol) were dissolved in acetonitrile (1 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 7 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; 4 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.071 g, 45.8 %) as a white solid.

Step 2: Synthesis of compound 215

[0279] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(2,4,5-trifluorobenzyl)piperazin-1-yl)methyl)benzoate (formula 13-3, 0.050 g, 0.123 mmol), hydroxylamine (0.150 mL, 2.460 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.069 g, 1.230 mmol) were dissolved in methanol (1 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 1 hour. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield **compound 215** (0.024 g, 47.9 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.64 (d, 2 H, *J* = 8.04 Hz), 7.60 - 7.46 (m, 3 H), 7.11 (d, 2 H, *J* = 8.04 Hz), 3.67 (s, 2 H), 3.17 (s, 2 H), 2.69 - 2.61 (m, 2 H), 2.60 - 2.57 (m, 2 H), 1.82 - 1.76 (m, 2 H), 0.83 (d, 6 H, *J* = 6.12 Hz).

Example 74: Synthesis of compound 218**(4-(2-((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)ethyl)-N-hydroxybenzamide)****Step 1: Synthesis of methyl****4-(2-((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)ethyl)benzoate**

[0280] (2S,6R)-1-benzyl-2,6-dimethylpiperazine (formula 8-3, 0.200 g, 0.831 mmol) and

DIPEA (0.363 mL, 2.077 mmol) were dissolved in acetonitrile (5 mL), and methyl 4-(2-bromoethyl)benzoate (formula 8-4, 0.404 g, 1.661 mmol) was added thereto at room temperature. The mixture was stirred at 60 °C for 17 hours, and then water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was concentrated by column chromatography (silicon dioxide; ethyl acetate/hexane = 25 %) and concentrated to afford the desired compound (0.075 g, 24.6 %) as a pale yellow oil.

Step 2: Synthesis of compound 218

[0281] Methyl 4-(2-((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)ethyl)benzoate (formula 8-5, 0.075 g, 0.205 mmol) was dissolved in methanol (3 mL), and then hydroxylamine (0.125 mL, 0.2046 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.266 g, 4.093 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and then the reaction mixture was concentrated under reduced pressure. Saturated sodium hydrogen carbonate was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 218** (0.058 g, 77.1 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.64 (d, 2 H, *J* = 8.2 Hz), 7.35 (d, 2 H, *J* = 7.4 Hz), 7.31 - 7.27 (m, 2 H), 7.17 - 7.16 (m, 1 H), 3.72 (s, 2 H), 2.80 (d, 2 H, *J* = 10.0 Hz), 2.74 - 2.71 (m, 2 H), 2.46 - 2.42 (m, 2 H), 1.82 - 1.80 (m, 2 H), 0.93 (d, 6 H, *J* = 6.1 Hz).

Example 75: Synthesis of compound 219

(4-(1-((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)ethyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl 4-(1-bromoethyl)benzoate

[0282] Methyl 4-(1-hydroxyethyl)benzoate (0.500 g, 2.775 mmol) was dissolved in toluene (10 mL), and PBr₃ (0.079 mL, 0.832 mmol) was added thereto at 0 °C. The mixture was stirred at the same temperature for 1 hour and 20 minutes, and the reaction mixture was concentrated under reduced pressure to yield the desired compound (0.410 g, 60.8 %) as a purple oil.

Step 2: Synthesis of methyl

4-(1-((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)ethyl)benzoate

[0283] (3R,5S)-1-benzyl-3,5-dimethylpiperazine (formula 8-3, 0.200 g, 0.831 mmol), methyl 4-(1-bromoethyl)benzoate (formula 8-4, 0.222 g, 0.914 mmol) and Cs_2CO_3 (0.812 g, 2.492 mmol) were dissolved in N,N-dimethylformamide (4 mL) at room temperature, and the reaction solution was stirred at 50 °C for 17 hours. The reaction mixture was filtered through a glass filter to remove solids, and water was added to the filtrate, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 25 %) and concentrated to afford the desired compound (0.168 g, 55.2 %) as a pale yellow oil.

Step 3: Synthesis of compound 219

[0284] Methyl 4-(1-((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)ethyl)benzoate (formula 8-5, 0.080 g, 0.218 mmol) was dissolved in methanol (3 mL), and then hydroxylamine (0.134 mL, 2.183 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.284 g, 4.366 mmol) were added thereto. The mixture was stirred at room temperature for 30 minutes, and the reaction mixture was concentrated under reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure to yield **compound 219** (0.051 g, 63.6 %) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.10 (s, 1 H), 9.10 (s, 1 H), 7.67 (d, 2 H, J = 6.9 Hz), 7.31 - 7.23 (m, 6 H), 7.16 - 7.14 (m, 1 H), 3.68 (s, 2 H), 2.82 (d, 2 H, J = 11.0 Hz), 2.53 - 2.82 (m, 3 H), 1.74 (t, 1 H, J = 10.2 Hz), 1.64 (t, 1 H, J = 10.5 Hz), 1.24 (d, 3 H, J = 6.7 Hz), 0.90 (d, 3 H, J = 6.0 Hz), 0.86 - 0.84 (m, 1 H), 0.81 (d, 3 H, J = 6.7 Hz).

Example 76: Synthesis of compound 220

(4-(((2S,6R)-2,6-dimethyl-4-(1-phenylethyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of (1-bromoethyl)benzene

[0285] (1-hydroxyethyl)benzene (1.000 g, 8.186 mmol) and PBr_3 (0.233 mL, 2.456 mmol) were dissolved in toluene (10 mL) at 0 °C, and the reaction solution was stirred at the same temperature for 1 hour. A saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic

layer was concentrated under reduced pressure to yield the desired compound (0.900 g, 59.4 %) as a pale brown oil.

Step 2: Synthesis of methyl

4-(((2S,6R)-2,6-dimethyl-4-(1-phenylethyl)piperazin-1-yl)methyl)benzoate

[0286] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.200 g, 0.669 mmol), (1-bromoethyl)benzene (0.136 g, 0.736 mmol) and Cs₂CO₃ (0.654 g, 2.008 mmol) were dissolved in N,N-dimethylformamide (4 mL) at room temperature, and the reaction solution was stirred at 50 °C for 17 hours. Then, water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 25 %) and concentrated to afford the desired compound (0.22 g, 89.7 %) as a colorless oil.

Step 3: Synthesis of compound 220

[0287] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(1-phenylethyl)piperazin-1-yl)methyl)benzoate (formula 13-3, 0.110 g, 0.300 mmol) was dissolved in methanol (3 mL), and then hydroxylamine (0.184 mL, 3.001 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.391 g, 6.003 mmol) were added thereto. The mixture was stirred at room temperature for 20 minutes, and then the reaction mixture was concentrated under reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure to yield **compound 220** (0.063 g, 57.1 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.63 (d, 2 H, *J* = 8.3 Hz), 7.35 - 7.33 (m, 2 H), 7.30 - 7.26 (m, 4 H), 7.24 - 7.21 (m, 1 H), 3.69 (s, 2 H), 2.85 - 2.83 (m, 1 H), 2.55 - 2.50 (m, 3 H), 1.75 - 1.74 (m, 1 H), 1.63 - 1.62 (m, 1 H), 1.25 (d, 3 H, *J* = 6.8 Hz), 0.91 - 0.90 (m, 1 H), 0.88 (d, 3 H, *J* = 4.9 Hz), 0.78 (d, 3 H, *J* = 6.1 Hz).

Example 77: Synthesis of compound 222

(4-(((3R,5S)-4-(2-(3-fluorophenyl)acetyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl**4-(((3R,5S)-4-(2-(3-fluorophenyl)acetyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0288] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), 2-(3-fluorophenyl)acetic acid (0.088 g, 0.572 mmol), HOBt (0.077 g, 0.572 mmol), EDCI (0.110 g, 0.572 mmol) and DIPEA (0.133 mL, 0.762 mmol) were dissolved in methylene chloride (2 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 20 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; 4 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.047 g, 30.9 %) as a pale yellow solid.

Step 2: Synthesis of compound 222

[0289] Methyl 4-(((3R,5S)-4-(2-(3-fluorophenyl)acetyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.040 g, 0.100 mmol), hydroxylamine (0.123 mL, 2.008 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.056 g, 1.004 mmol) were dissolved in methanol (1 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 1 hour. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield **compound 222** (0.019 g, 47.4 %) as an orange solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.64 (d, 2 H, *J* = 8.0 Hz), 7.32 - 7.27 (m, 1 H), 7.24 (d, 2 H, *J* = 8.0 Hz), 7.04 - 7.01 (m, 3 H), 4.35 (brs, 1 H), 4.07 (brs, 1 H), 3.75 - 3.62 (m, 2 H), 3.46 (s, 2 H), 2.63 - 2.52 (m, 2 H), 1.99 - 1.73 (m, 2 H), 1.20 (d, 6 H, *J* = 17.2 Hz).

Example 78: Synthesis of compound 223**(4-(((3R,5S)-3,5-dimethyl-4-(2-(3-(trifluoromethyl)phenyl)acetyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)****Step 1: Synthesis of methyl**

4-(((3R,5S)-3,5-dimethyl-4-(2-(3-(trifluoromethyl)phenyl)acetyl)piperazin-1-yl)methyl)benzoate

[0290] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), 2-(3-(trifluoromethyl)phenyl)acetic acid (0.117 g, 0.572 mmol), HOBt (0.077 g, 0.572 mmol), EDCI (0.110 g, 0.572 mmol) and DIPEA (0.133 mL, 0.762 mmol) were dissolved in methylene chloride (2 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 20 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; 12 g cartridge; methanol/ methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.037 g, 21.6 %) as a colorless oil.

Step 2: Synthesis of compound 223

[0291] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(2-(3-(trifluoromethyl)phenyl)acetyl)piperazin-1-yl)methyl)benzoate (formula 1-3, 0.030 g, 0.067 mmol), hydroxylamine (0.082 mL, 1.338 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.038 g, 0.669 mmol) were dissolved in methanol (1 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 1 hour. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield **compound 223** (0.013 g, 43.2 %) as a pale yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.64 (d, 2 H, *J* = 8.0 Hz), 7.56 - 7.48 (m, 4 H), 7.20 (d, 2 H, *J* = 8.4 Hz), 4.36 (brs, 1 H), 4.12 (brs, 1 H), 3.92 - 3.67 (brs, 1 H), 3.48 (s, 2 H), 2.61 (d, 2 H, *J* = 11.2 Hz), 2.05 - 2.00 (m, 2 H), 1.23 (d, 6 H, *J* = 31.6 Hz).

Example 79: Synthesis of compound 224

(4-(((3R,5S)-4-(2-(3-chlorophenyl)acetyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(2-(3-chlorophenyl)acetyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0292] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), 2-(3-chlorophenyl)acetic acid (0.098 g, 0.572 mmol), HOBt (0.077 g, 0.572 mmol), EDCI (0.110 g, 0.572 mmol) and DIPEA (0.133 mL, 0.762 mmol) were dissolved in methylene chloride (2 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 20 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; 4 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.042 g, 26.6 %) as a colorless oil.

Step 2: Synthesis of compound 224

[0293] Methyl 4-(((3R,5S)-4-(2-(3-chlorophenyl)acetyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.035 g, 0.084 mmol), hydroxylamine (0.103 mL, 1.687 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.047 g, 0.844 mmol) were dissolved in methanol (1 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 1 hour. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield **compound 224** (0.020 g, 57.0 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.62 (d, 2 H, *J* = 7.6 Hz), 7.31 - 7.23 (m, 4 H), 7.15 (d, 2 H, *J* = 6.4 Hz), 4.35 (brs, 1 H), 4.07 (brs, 1 H), 3.76 - 3.47 (m, 2 H), 3.30 (s, 2 H), 2.62 (d, 2 H, *J* = 10.8 Hz), 1.98 (brs, 2 H), 1.23 (d, 6 H, *J* = 25.2 Hz).

Example 80: Synthesis of compound 225**4-(((3R,5S)-4-(3-fluorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide****Step 1: Synthesis of methyl****4-(((3R,5S)-4-(3-fluorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0294] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (compound 1-2, 0.150 g, 0.572 mmol), 3-fluorobenzyl bromide (0.077 mL, 0.629 mmol) and K_2CO_3 (0.119 g, 0.858 mmol) were dissolved in acetonitrile (4 mL) at room temperature, and the reaction solution was stirred at the same temperature for 17 hours. Then, water was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; 4 g cartridge; ethyl acetate/ hexane = from 0 % to 40 %) and concentrated to afford the desired compound (0.110 g, 51.9 %) as a white solid.

Step 2: Synthesis of compound 225

[0295] Methyl 4-(((3R,5S)-4-(3-fluorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (compound 1-3, 0.060 g, 0.162 mmol), hydroxylamine (0.099 mL, 1.620 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.211 g, 3.239 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 1 hour, and then concentrated under reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure to yield **compound 225** (0.044 g, 73.1 %) as a white solid.

^1H NMR (400 MHz, $DMSO-d_6$) δ 7.65 (d, 2 H, J = 8.0 Hz), 7.31 - 7.27 (m, 1 H), 7.22 (d, 2 H, J = 8.0 Hz), 7.17 - 7.13 (m, 2 H), 6.97 - 6.96 (m, 1 H), 3.70 (s, 2 H), 3.43 (s, 2 H), 2.64 (d, 2 H, J = 11.2 Hz), 2.57 - 2.56 (m, 2 H), 1.78 (t, 2 H, J = 10.6 Hz), 0.84 (d, 6 H, J = 6.0 Hz); LRMS (ES) m/z 372.2 ($M^+ + 1$).

Example 81: Synthesis of compound 230

((3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-N-(3-methoxybenzyl)-3,5-dimethylpiperazin-1-carboxamide (Trifluoroacetic acid salt))

Step 1: Synthesis of 4-nitrophenyl 3-methoxybenzyl carbamate

[0296] 3-methoxybenzyl amine (0.100 g, 0.729 mmol) and TEA (0.152 mL, 1.093 mmol) were dissolved in methylene chloride (2 mL), and 4-nitrophenyl chloroformate (0.162 g, 0.802 mmol) was added thereto at 0 °C, followed by stirring at the same temperature for 2 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to solid residue and an aqueous layer, and the

organic layer was concentrated under reduced pressure. The obtained product was used without additional purification (0.200 g, 90.8 %, yellow oil).

Step 2: Synthesis of methyl

4-(((2S,6R)-4-((3-methoxybenzyl)carbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0297] 4-Nitrophenyl 3-methoxybenzyl carbamate (0.130 g, 0.430 mmol), methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.129 g, 0.430 mmol) and TEA (0.179 mL, 1.290 mmol) were dissolved in N,N-dimethylformamide (4 mL) at room temperature, and the reaction solution was stirred at 100 °C for 3 hours. Then, the reaction mixture was concentrated under reduced pressure. The obtained product was used without additional purification (0.180 g, 98.4 %, brown oil).

Step 3: Synthesis of compound 230

[0298] Methyl 4-(((2S,6R)-4-((3-methoxybenzyl)carbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.180 g, 0.423 mmol), hydroxylamine (0.517 mL, 8.460 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.237 g, 4.230 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 17 hours. The concentrate was purified by column chromatography (Waters, C₁₈, 19*100 mm column, 0.1 % trifluoroacetic acid/ acetonitrile = from 5 % to 80 %) and concentrated to afford **compound 230** (0.033g, 18.3 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.11 (brs, 1 H), 8.95 (brs, 1 H), 7.64 (d, 2 H, *J* = 8.4 Hz), 7.39 (d, 2 H, *J* = 8.0 Hz), 7.17 (dd, 1 H, *J* = 7.0, 7.0 Hz), 7.03 (dd, 1 H, *J* = 6.0, 6.0 Hz), 6.75 - 6.72 (m, 2 H), 4.16 (d, 2 H, *J* = 5.6 Hz), 3.80 (d, 2 H, *J* = 12.4 Hz), 3.72 (s, 2 H), 3.68 (s, 3 H), 2.53 (d, 2 H, *J* = 10.4 Hz), 2.42 - 2.38 (m, 2 H), 0.89 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 427.3 (*M*⁺+1).

Example 82: Synthesis of compound 231

((3R,5S)-N-(3-fluorobenzyl)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethylpiperazine-1-carboxamide)

Step 1: Synthesis of 4-nitrophenyl 3-fluorobenzylcarbamate

[0299] (3-fluorophenyl)methylamine (0.200 g, 1.598 mmol) and TEA (0.243 g, 2.397 mmol) were dissolved in methylene chloride (2 mL), and 4-nitrophenyl chloroformate (0.354 g, 1.758 mmol) was added thereto at 0 °C, followed by stirring at the same temperature for 1 hour. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The obtained product was used without additional purification (0.410 g, 88.4 %, yellow solid).

Step 2: Synthesis of methyl

4-(((2S,6R)-4-((3-fluorobenzyl)carbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0300] 4-Nitrophenyl 3-fluorobenzylcarbamate (0.200 g, 0.689 mmol), methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.216 g, 0.724 mmol) and TEA (0.287 mL, 2.067 mmol) were dissolved in N,N-dimethylformamide (3 mL) at room temperature, and the reaction solution was stirred at 100 °C for 2 hours and 30 minutes. Then, the reaction mixture was concentrated under reduced pressure using V10. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 50 %) and concentrated to afford the desired compound (0.178 g, 62.5 %) as a pale brown oil.

Step 3: Synthesis of compound 231

[0301] Methyl 4-(((2S,6R)-4-((3-fluorobenzyl)carbamoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.100 g, 0.242 mmol), hydroxylamine (0.296 mL, 4.837 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.136 g, 2.418 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate (10 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 231** (0.055 g, 54.9 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.64 (d, 2 H, *J* = 8.0 Hz), 7.38 (d, 2 H, *J* = 8.0 Hz), 7.33 - 7.27 (m, 1 H), 7.10 (t, 1 H, *J* = 5.8 Hz), 7.06 - 6.98 (m, 3 H), 4.20 (d, 2 H, *J* = 5.6 Hz), 3.79 (d, 2 H, *J* = 12.8 Hz), 3.72 (s, 2 H), 2.52 (t, 2 H, *J* = 11.6 Hz), 2.42 - 2.38 (m, 2 H), 0.89 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 415.2 (*M*⁺+1).

Example 83: Synthesis of compound 232

((2S,6R)-N-(3-fluorobenzyl)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylpiperazine-1-carboxamide)**Step 1: Synthesis of methyl****4-(((3R,5S)-4-((3-fluorobenzyl)carbamoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0302] 4-Nitrophenyl 3-fluorobenzylcarbamate (0.220 g, 0.758 mmol), methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.209 g, 0.796 mmol) and TEA (0.315 mL, 2.274 mmol) were dissolved in N,N-dimethylformamide (3 mL) at room temperature, and the reaction solution was stirred at 100 °C for 2 hours and 30 minutes. Then, the reaction mixture was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 50 %) and concentrated to afford the desired compound (0.185 g, 59.0 %) as a colorless oil.

Step 2: Synthesis of compound 232

[0303] Methyl 4-(((3R,5S)-4-((3-fluorobenzyl)carbamoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.100 g, 0.242 mmol), hydroxylamine (0.296 mL, 4.837 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.136 g, 2.418 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure to yield **compound 232** (0.026g, 25.9 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.70 (d, 2 H, *J* = 8.0 Hz), 7.48 (d, 2 H, *J* = 8.4 Hz), 7.31 - 7.25 (m, 1 H), 7.06 (d, 1 H, *J* = 7.6 Hz), 6.98 (d, 1 H, *J* = 10.0 Hz), 6.93 - 6.88 (m, 1 H), 4.35 (s, 2 H), 4.07 - 4.04 (m, 2 H), 3.54 (s, 2 H), 2.67 (d, 2 H, *J* = 11.2 Hz), 2.17 (dd, 2 H, *J* = 10.2, 3.6 Hz), 1.31 (d, 6 H, *J* = 6.8 Hz).

Example 84: Synthesis of compound 233**(4-(((2S,6R)-4-(2-(3-chlorophenyl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)**

Step 1: Synthesis of methyl**4-(((2S,6R)-4-(2-(3-chlorophenyl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate**

[0304] 2-(3-chlorophenyl)acetic acid (0.200 g, 0.669 mmol), methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.126 g, 0.736 mmol), EDCI (0.257 g, 1.339 mmol), HOBt (0.205 g, 1.339 mmol) and DIPEA (0.584 mL, 3.347 mmol) were dissolved in methylene chloride (5 mL) at room temperature, and the reaction solution was stirred at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous solution, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 10 % to 70 %) and concentrated to afford the desired compound (0.187 g, 67.3 %) as a colorless oil.

Step 2: Synthesis of compound 233

[0305] Methyl 4-(((2S,6R)-4-(2-(3-chlorophenyl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.100 g, 0.241 mmol), hydroxylamine (50.00 % aqueous solution, 0.295 mL, 4.820 mmol) and potassium hydroxide (0.135 g, 2.410 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous solution, and the organic layer was concentrated under reduced pressure. Diethyl ether (3 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 233** (0.053 g, 52.9 %) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 7.63 (d, 2 H, J = 8.4 Hz), 7.33 (d, 2 H, J = 8.4 Hz), 7.27 - 7.24 (m, 3 H), 7.16 - 7.14 (m, 1 H), 4.10 (d, 1 H, J = 12.4 Hz), 3.81 (d, 1 H, J = 13.2 Hz), 3.76 - 3.65 (m, 4 H), 2.86 - 2.52 (m, 1 H), 2.43 (d, 1 H, J = 12.4 Hz), 2.38 - 2.28 (m, 2 H), 0.90 (t, 6 H, J = 5.4 Hz); LRMS (ES) m/z 416.1 ($M^+ + 1$).

Example 85: Synthesis of compound 234**(4-(((3R,5S)-4-(2-([1,1'-biphenyl]-3-yl)acetyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)**

Step 1: Synthesis of methyl**4-(((3R,5S)-4-(2-([1,1'-biphenyl]-3-yl)acetyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0306] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), 2-([1,1'-biphenyl]-3-yl)acetic acid (0.097 g, 0.457 mmol), HOBt (0.077 g, 0.572 mmol), EDCI (0.110 g, 0.572 mmol) and DIPEA (0.099 g, 0.762 mmol) were dissolved in methylene chloride (2 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 7 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; methanol/ methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.114 g, 65.5 %) as a yellow solid.

Step 2: Synthesis of compound 234

[0307] Methyl 4-(((3R,5S)-4-(2-([1,1'-biphenyl]-3-yl)acetyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-2, 0.050 g, 0.110 mmol), hydroxylamine (0.134 mL, 2.190 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.061 g, 1.095 mmol) were dissolved in methanol (1 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 1 hour. Saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate, and then concentrated under reduced pressure to yield **compound 234** (0.027 g, 53.9 %) as a pale yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.70 (d, 2 H, *J* = 7.6 Hz), 7.68 (d, 2 H, *J* = 8.0 Hz), 7.58 - 7.30 (m, 8 H), 7.21 (m, 1 H), 4.39 (brs, 1 H), 4.14 (brs, 1 H) 3.83 - 3.64 (m, 2 H), 3.48 (s, 2 H), 2.62 (d, 2 H, *J* = 10.8 Hz), 2.29 (brs, 2 H), 1.22 (d, 6 H, *J* = 20 Hz).

Example 86: Synthesis of compound 242**4-(((3R,5S)-4-(3-(furan-2-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide**

Step 1: Synthesis of 3-iodobenzoyl chloride

[0308] 3-iodobenzoic acid (0.200 g, 0.806 mmol) was dissolved in SOCl_2 (1.170 mL, 16.128 mmol) and stirred at 100 °C for 2 hours, and the reaction mixture was concentrated under reduced pressure. The obtained product was used without additional purification (0.215 g, 100.0 %, brown oil).

Step 2: Methyl**4-(((3R,5S)-4-(3-iodobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0309] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.215 g, 0.807 mmol), 3-iodobenzoyl chloride (0.233 mL, 0.887 mmol) and TEA (0.224 mL, 1.613 mmol) were dissolved in methylene chloride (5 mL) at 0 °C, and the reaction solution was stirred at the same temperature for 2 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 30 % to 50 %) and concentrated to afford the desired compound (0.365 g, 91.8 %) as a colorless oil.

Step 3: Methyl**4-(((3R,5S)-4-(3-(furan-2-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0310] 1,2-Dimethoxyethane/water (v/v=3/1) (1 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(3-iodobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-1, 0.346 g, 0.703 mmol), furan-2-ylboronic acid (0.118 g, 1.054 mmol), Pd(dppf)Cl_2 (0.029 g, 0.035 mmol) and Na_2CO_3 (0.223 g, 2.108 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a 1N aqueous solution of hydrochloric acid was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with water, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 10 % to 25 %) and concentrated to afford the desired compound (0.301 g, 99.0 %) as a brown oil.

Step 4: Synthesis of compound 242

[0311] Methyl 4-(((3R,5S)-4-(3-(furan-2-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-2, 0.050 g, 0.116 mmol), hydroxylamine (0.141 mL, 2.312 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.065 g, 1.156 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 242** (0.034 g, 67.6 %) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 7.79 (s, 1 H), 7.78 - 7.70 (m, 3 H), 7.64 (s, 1 H), 7.48 (t, 1 H, J = 7.7 Hz), 7.37 (d, 2 H, J = 8.0 Hz), 7.24 (d, 1 H, J = 7.6 Hz), 7.08 (d, 1 H, J = 3.4 Hz), 6.63 - 6.61 (m, 1 H), 3.53 (s, 2 H), 2.63 (brs, 2 H), 2.18 - 2.14 (m, 2 H), 1.31 (brs, 6 H).

Example 87: Synthesis of compound 243

(4-(((3R,5S)-4-(3-(furan-3-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-(furan-3-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0312] 1,2-Dimethoxyethane/water (v/v=3/1) (1 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(3-iodobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-1, 0.120 g, 0.244 mmol), furan-3-ylboronic acid (0.041 g, 0.366 mmol), Pd(dbpf)Cl₂ (0.008 g, 0.012 mmol) and Na₂CO₃ (0.077 g, 0.731 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a 1N aqueous solution of hydrochloric acid was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with water, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 10 % to 30 %) and concentrated to afford the desired compound (0.050 g, 47.0 %) as a brown solid.

Step 2: Synthesis of compound 243

[0313] 4-(((3R,5S)-4-(3-(furan-3-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

(formula 4-2, 0.050 g, 0.114 mmol), hydroxylamine (0.140 mL, 2.289 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.064 g, 1.144 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 243** (0.029 g, 57.4 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.29 (s, 1 H), 7.76 - 7.70 (m, 3 H), 7.66 (d, 1 H, *J* = 8.0 Hz), 7.46 - 7.38 (m, 3 H), 7.20 (d, 1 H, *J* = 7.6 Hz), 7.05 - 7.04 (m, 1 H), 3.54 (s, 2 H), 2.68 - 2.64 (m, 2 H), 2.19 - 2.15 (m, 2 H), 1.32 (brs, 6 H).

Example 88: Synthesis of compound 244

4-(((3R,5S)-4-(3-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0314] 1,2-Dimethoxyethane/water (v/v=3/1) (1 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(3-iodobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-1, 0.120 g, 0.244 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.077 g, 0.366 mmol), Pd(dbpf)Cl₂ (0.008 g, 0.012 mmol) and Na₂CO₃ (0.077 g, 0.731 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a 1N aqueous solution of hydrochloric acid was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with water, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 10 % to 50 %) and concentrated to afford the desired compound (0.049 g, 44.8 %) as a brown oil.

Step 2: Synthesis of compound 244

[0315] Methyl 4-(((3R,5S)-4-(3-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-2, 0.049 g, 0.113 mmol), hydroxylamine (0.139 mL, 2.266

mmol, 50.00 % aqueous solution) and potassium hydroxide (0.064 g, 1.133 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 244** (0.013 g, 24.7 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.72 (d, 2 H, *J* = 8.0 Hz), 7.50 (d, 1 H, *J* = 7.7 Hz), 7.45 - 7.37 (m, 4 H), 7.22 (d, 1 H, *J* = 7.4 Hz), 6.33 (s, 1 H), 4.23 - 4.22 (m, 2 H), 3.82 (t, 2 H, *J* = 5.3 Hz), 3.53 (s, 2 H), 2.68 - 2.63 (m, 2 H), 2.18 - 2.14 (m, 2 H), 1.30 (brs, 6 H).

Example 89: Synthesis of compound 245

4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-4-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide(Trifluoroacetic acid salt)

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-4-yl)benzoyl)piperazin-1-yl)methyl)benzoate

[0316] 1,2-Dimethoxyethane/water (v/v=3/1) (1 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(3-iodobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-1, 0.200 g, 0.406 mmol), pyridine-4-boronic acid hydrate (0.086 g, 0.609 mmol), Pd(dbpf)Cl₂ (0.013 g, 0.020 mmol) and Na₂CO₃ (0.129 g, 1.219 mmol), and heated by microwave irradiation at 120 °C for 20 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with water, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.167 g, 92.8 %) as a brown oil.

Step 2: Synthesis of compound 245

[0317] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-4-yl)benzoyl)piperazin-1-yl)methyl)benzoate (formula 4-2, 0.105 g, 0.236 mmol), hydroxylamine (0.288 mL, 4.712 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.132 g, 2.356 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, a saturated aqueous solution of sodium hydrogen

carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. Then, the concentrate was purified by column chromatography (Waters, C₁₈, 19*100 mm column, 0.1 % trifluoroacetic acid aqueous solution/acetonitrile = from 5 % to 80 %) and concentrated to afford **compound 245** (0.072 g, 54.6 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.91 (d, 2 H, *J* = 6.6 Hz), 8.24 (d, 2 H, *J* = 6.0 Hz), 8.05 (d, 1 H, *J* = 7.9 Hz), 7.98 (s, 1 H), 7.81 (d, 2 H, *J* = 7.9 Hz), 7.68 (t, 1 H, *J* = 7.7 Hz), 7.61 - 7.56 (m, 3 H), 4.78 (brs, 1 H), 4.24 - 4.00 (m, 3 H), 3.23 - 3.10 (m, 2 H), 1.36 (brs, 6 H).

Example 90: Synthesis of compound 246

4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of

4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)benzoate

[0318] 1,2-Dimethoxyethane/water (v/v=3/1) (1.2 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(3-iodobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-1, 0.100 g, 0.203 mmol), pyridine-3-ylboronic acid (0.050 g, 0.406 mmol), Na₂CO₃ (0.065 g, 0.609 mmol) and Pd(dbpf)Cl₂ (0.007 g, 0.010 mmol), and heated by microwave irradiation at 120 °C for 20 minutes, followed by cooling to room temperature. Then, water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 80 %) and concentrated to afford the desired compound (0.080 g, 88.8 %) as a yellow solid.

Step 2: Synthesis of compound 246

[0319] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)benzoate (formula 4-2, 0.065 g, 0.147 mmol), hydroxylamine (0.090 mL, 1.465 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.191 g, 2.931 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 2 hours, and then concentrated. The concentrate was washed with a saturated aqueous solution of sodium hydrogen carbonate and distilled water, thereby

obtaining **compound 246** (0.035 g, 53.7 %) as a yellow solid.

¹H NMR (400 MHz, CDCl₃): 8.93 (d, 1 H, *J* = 2.3 Hz), 8.60 (m, 1 H), 7.06 (dd, 1 H, *J* = 8.0, 1.6 Hz), 7.82 - 7.77 (m, 1 H), 7.72 - 7.69 (m, 3 H), 7.58 - 7.48 (m, 2 H), 7.39 - 7.35 (m, 3 H), 3.37 - 3.28 (m, 2 H), 2.63 (m, 2 H), 2.19 (dd, 2 H, *J* = 11.4, 4.0 Hz), 1.32 (s, 6 H).

Example 91: Synthesis of compound 247

((4-(((3R,5S)-4-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-(4,4-dimethylcyclohex-1-enyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0320] 1,2-Dimethoxyethane (0.9 mL) / water (0.3 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(3-iodobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-1, 0.100 g, 0.203 mmol), 2-(4,4-dimethylcyclohex-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.096 g, 0.406 mmol), Na₂CO₃ (0.065 g, 0.609 mmol) and Pd(dbpf)Cl₂ (0.007 g, 0.010 mmol), and heated by microwave irradiation at 120 °C for 20 minutes, followed by cooling to room temperature. Then, water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 40 %) and concentrated to afford the desired compound (0.030 g, 31.1 %) as a yellow solid.

Step 2: Synthesis of compound 247

[0321] Methyl 4-(((3R,5S)-4-(3-(4,4-dimethylcyclohex-1-enyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-2, 0.030 g, 0.063 mmol), hydroxylamine (0.039 mL, 0.632 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.082 g, 1.264 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 2 hours. Then, the reaction mixture was concentrated. The concentrate was washed with a saturated aqueous solution of sodium hydrogen carbonate and distilled water, thereby obtaining the desired **compound 247** (0.021 g, 69.9 %) as a yellow solid.

¹H NMR (400 MHz, CDCl₃): 7.71 (d, 1 H, *J* = 8.0 Hz), 7.47 - 7.45 (m, 1 H), 7.38 - 7.32 (m, 4 H),

7.18 (d, 1 H, $J = 7.6$ Hz), 6.16 (s, 1 H), 3.51 (m, 2 H), 2.62 (m, 2 H), 2.38 (m, 2 H), 2.15 (m, 2 H), 1.98 (m, 2 H), 1.50 - 1.46 (m, 2 H), 2.29 (m, 6 H), 0.94 (s, 6 H).

Example 92: Synthesis of compound 248

(4-(((3R,5R)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5R)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0322] Methyl 4-(((3R,5R)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 21-1, 0.050 g, 0.191 mmol), benzyl bromide (0.023 mL, 0.191 mmol) and K_2CO_3 (0.040 g, 0.286 mmol) were dissolved in acetonitrile (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 17 hours. Then, the reaction mixture was filtered through a plastic filter to remove solids, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 30 %) and concentrated to afford the desired compound (0.038 g, 56.6 %) as a colorless oil.

Step 2: Synthesis of compound 248

[0323] Methyl 4-(((3R,5R)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 21-2, 0.038 g, 0.108 mmol), hydroxylamine (0.132 mL, 2.156 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.060 g, 1.078 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure to yield **compound 248** (0.018 g, 47.2 %) as a white solid.

^1H NMR (400 MHz, $DMSO-d_6$) δ 7.71 (d, 2 H, $J = 8.2$ Hz), 7.44 (d, 2 H, $J = 8.2$ Hz), 7.38 (d, 2 H, $J = 7.3$ Hz), 7.29 (dd, 1 H, $J = 7.4, 7.4$ Hz), 7.23 - 7.22 (m, 1 H), 4.02 (d, 1 H, $J = 13.4$ Hz), 3.58 (d, 1 H, $J = 13.5$ Hz), 3.43 - 3.42 (m, 2 H), 2.92 - 2.88 (m, 2 H), 2.49 - 2.47 (m, 2 H), 2.25 - 2.25 (m, 2 H), 1.09 (d, 6 H, $J = 6.4$ Hz); LRMS (ES) m/z 354.2 ($M^+ + 1$).

Example 93: Synthesis of compound 249

4-(((3R,5R)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5R)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0324] Methyl 4-(((3R,5R)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 21-1, 0.050 g, 0.191 mmol) and TEA (0.053 mL, 0.381 mmol) were dissolved in methylene chloride (2 mL), and 2-furoyl chloride (0.019 mL, 0.191 mmol) was added thereto at 0 °C, followed by stirring at the same temperature for 3 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 40 %) and concentrated to afford the desired compound (0.033 g, 48.6 %) as a yellow oil.

Step 2: Synthesis of compound 249

[0325] Methyl 4-(((3R,5R)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 21-3, 0.033 g, 0.093 mmol), hydroxylamine (0.113 mL, 1.852 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.052 g, 0.926 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure to yield **compound 249** (0.019 g, 57.4 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.73 (d, 2 H, *J* = 7.9 Hz), 7.66 (s, 1 H), 7.48 (d, 2 H, *J* = 7.9 Hz), 7.01 (d, 1 H, *J* = 3.3 Hz), 6.58 (s, 1 H), 4.17 - 4.13 (m, 2 H), 3.67 (d, 1 H, *J* = 13.5 Hz), 3.53 (d, 1 H, *J* = 13.8 Hz), 2.68 - 2.65 (m, 2 H), 2.42 - 2.38 (m, 2 H), 1.35 (d, 6 H, *J* = 6.4 Hz); LRMS (ES) *m/z* 358.1 (*M*⁺+1).

Example 94: Synthesis of compound 250

4-(((2S,6R)-4-(2-([1,1'-biphenyl]-3-yl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(2-(3-bromophenyl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0326] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 2.000 g, 6.693 mmol), 2-(3-bromophenyl)acetic acid (1.583 g, 7.363 mmol), EDCI (2.566 g, 13.386 mmol), HOBt (2.050 g, 13.386 mmol) and DIPEA (5.845 mL, 33.466 mmol) were dissolved in methylene chloride (5 mL) at room temperature, and the reaction solution was stirred at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; ethyl acetate/hexane = from 40 % to 70 %) and concentrated to afford the desired compound (2.230 g, 72.5 %) as a colorless oil.

Step 2: Synthesis of methyl

4-(((2S,6R)-4-(2-(3-bromophenyl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0327] 1,2-Dimethoxyethane (2 mL) was added to a mixture of methyl 4-(((2S,6R)-4-(2-(3-bromophenyl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-1, 0.100 g, 0.218 mmol), phenylboronic acid (0.029 g, 0.239 mmol), Pd(PPh₃)₄ (0.013g, 0.011 mmol) and Na₂CO₃ (0.069 g, 0.653 mmol) at room temperature, and the reaction solution was stirred at 100 °C for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 40 %) and concentrated to afford the desired compound (0.043 g, 43.3 %) as a colorless oil.

Step 3: Synthesis of compound 250

[0328] Methyl 4-(((2S,6R)-4-(2-([1,1'-biphenyl]-3-yl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-2, 0.043 g, 0.094 mmol), hydroxylamine (0.115 mL, 1.884 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.053 g, 0.942 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous solution, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, 19*100 mm column, 0.1 % trifluoroacetic acid/acetonitrile = from 5 % to 80 %) and concentrated to afford **compound 250** (0.015 g, 34.8 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.55 - 7.37 (m, 9 H), 7.30 (d, 2 H, *J* = 7.7 Hz), 7.22 (dd, 1 H, *J* = 7.2, 7.2 Hz), 7.12 (d, 2 H, *J* = 7.0 Hz), 4.55 - 4.48 (m, 2 H), 4.38 (d, 1 H, *J* = 14.7 Hz), 4.15 (d, 1 H, *J* = 15.0 Hz), 3.91 (d, 1 H, *J* = 15.0 Hz), 3.68 (d, 1 H, *J* = 6.5 Hz), 3.67 (d, 1 H, *J* = 14.5 Hz), 3.35 - 3.27 (m, 1 H), 2.97 - 2.91 (m, 3 H), 1.54 (d, 3 H, *J* = 5.7 Hz), 1.31 (d, 3 H, *J* = 6.4 Hz).

Example 95: Synthesis of compound 251

4-(((2S,6R)-2,6-dimethyl-4-(2-(3-(pyridin-4-yl)phenyl)acetyl)piperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)

Step 1: Synthesis of methyl

4-(((2S,6R)-2,6-dimethyl-4-(2-(3-(pyridin-4-yl)phenyl)acetyl)piperazin-1-yl)methyl)benzoate

[0329] 1,2-Dimethoxyethane (4 mL) / water (1 mL) were added to a mixture of methyl 4-(((2S,6R)-4-(2-(3-bromophenyl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-1, 0.200 g, 0.435 mmol), pyridin-4-ylboronic acid (0.059 g, 0.479 mmol), Pd(PPh₃)₄ (0.025 g, 0.022 mmol) and Na₂CO₃ (0.138 g, 1.306 mmol) at room temperature and the reaction mixture was heated under reflux for 17 hours, and then cooled to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the

desired compound (0.123 g, 61.7 %) as a yellow oil.

Step 2: Synthesis of compound 251

[0330] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(2-(3-(pyridin-4-yl)phenyl)acetyl)piperazin-1-yl)methyl)benzoate (formula 15-2, 0.100 g, 0.219 mmol), hydroxylamine (0.267 mL, 4.371 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.123 g, 2.186 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous solution, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, 19*100 mm column, 0.1 % trifluoroacetic acid/ acetonitrile = from 5 % to 80 %) and concentrated to afford **compound 251** (0.006 g, 6.0 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.65 (d, 2 H, *J* = 5.9 Hz), 7.69 - 7.64 (m, 5 H), 7.45 (dd, 1 H, *J* = 7.7, 7.7 Hz), 7.34 (d, 3 H, *J* = 8.3 Hz), 4.16 (d, 1 H, *J* = 12.8 Hz), 3.91 (d, 1 H, *J* = 13.1 Hz), 3.82 (d, 2 H, *J* = 8.0 Hz), 3.71 (s, 2 H), 2.90 (dd, 1 H, *J* = 10.4, 13.3 Hz), 2.41 - 2.32 (m, 2 H), 0.96 - 0.85 (m, 6 H).

Example 96: Synthesis of compound 252

4-(((2S,6R)-4-(2-(3-(3,6-dihydro-2H-pyran-4-yl)phenyl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(2-(3-(3,6-dihydro-2H-pyran-4-yl)phenyl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0331] 1,2-Dimethoxyethane (4 mL) / water (1 mL) were added to a mixture of methyl 4-(((2S,6R)-4-(2-(3-bromophenyl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-1, 0.200 g, 0.435 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.101 g, 0.479 mmol), Pd(PPh₃)₄ (0.025 g, 0.022 mmol) and Na₂CO₃ (0.138 g, 1.306 mmol) at room temperature and the reaction mixture was heated under reflux for 17 hours, and then cooled to room temperature. Then, a saturated aqueous solution of sodium

hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 30 % to 100 %) and concentrated to afford the desired compound (0.084 g, 41.7 %) as a white solid.

Step 2: Synthesis of compound 252

[0332] Methyl 4-(((2S,6R)-4-(2-(3-(3,6-dihydro-2H-pyran-4-yl)phenyl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-2, 0.050 g, 0.108 mmol), hydroxylamine (0.132 mL, 2.162 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.061 g, 1.081 mmol) were dissolved in methanol (2 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous solution, and the organic layer was concentrated under reduced pressure to yield **compound 252** (0.016 g, 31.9 %) as a white solid.

¹H NMR (400 MHz, CH₃OD) δ 7.70 - 7.69 (m, 2 H), 7.43 (d, 2 H, *J* = 8.3 Hz), 7.34 (d, 2 H, *J* = 5.8 Hz), 7.30 - 7.28 (m, 1 H), 7.16 - 7.16 (m, 1 H), 6.20 - 6.19 (m, 1 H), 4.32 - 4.30 (m, 3 H), 3.94 (t, 2 H, *J* = 5.5 Hz), 3.86 - 3.77 (m, 5 H), 2.85 (dd, 1 H, *J* = 11.3, 11.3 Hz), 2.59 - 2.56 (m, 1 H), 2.52 - 2.50 (m, 3 H), 2.19 - 2.18 (m, 1 H), 1.06 (d, 3 H, *J* = 6.1 Hz), 0.95 (d, 3 H, *J* = 6.2 Hz); LRMS (ES) *m/z* 464.2 (*M*⁺+1).

Example 97: Synthesis of compound 253

4-(((2S,6R)-4-(2-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-yl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(2-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-yl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0333] 1,2-Dimethoxyethane (4 mL) / water (1 mL) were added to a mixture of methyl 4-(((2S,6R)-4-(2-(3-bromophenyl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula

15-1, 0.150 g, 0.327 mmol), 2-(4,4-dimethylcyclo-1-hexenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.085 g, 0.359 mmol), Pd(PPh₃)₄ (0.019 g, 0.016 mmol) and Na₂CO₃ (0.104 g, 0.980 mmol) at room temperature and the reaction mixture was heated under reflux for 17 hours, and then cooled to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 20 %) and concentrated to afford the desired compound (0.089 g, 55.8 %) as a pale yellow oil.

Step 2: Synthesis of compound 253

[0334] Methyl 4-(((2S,6R)-4-(2-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-yl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-2, 0.050 g, 0.102 mmol), hydroxylamine (0.125 mL, 2.046 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.057 g, 1.023 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous solution, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, 19*100 mm column, 0.1 % trifluoroacetic acid/acetonitrile = from 5 % to 80 %) and concentrated to yield **compound 253** (0.015 g, 29.9 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.65 (d, 2 H, *J* = 8.2 Hz), 7.33 - 7.26 (m, 4 H), 7.23 (dd, 1 H, *J* = 7.6, 7.6 Hz), 7.07 (d, 1 H, *J* = 6.9 Hz), 6.07 (s, 1 H), 4.15 (d, 1 H, *J* = 11.0 Hz), 3.85 (d, 1 H, *J* = 13.2 Hz), 3.76 - 3.65 (m, 4 H), 2.85 (dd, 1 H, *J* = 11.3, 11.3 Hz), 2.47 - 2.44 (m, 1 H), 2.37 (s, 3 H), 2.25 (s, 1 H), 1.98 (s, 1 H), 1.49 (t, 2 H, *J* = 6.3 Hz), 0.94 (s, 9 H), 0.89 (d, 3 H, *J* = 5.8 Hz); LRMS (ES) *m/z* 490.3 (M⁺+1).

Example 98: Synthesis of compound 255

(4-(((3R,5S)-4-(3-(1H-pyrrol-1-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-(1H-pyrrol-1-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0335] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.200 g, 0.762 mmol), 1-(3-(bromomethyl)phenyl)-1H-pyrrole (0.198 g, 0.839 mmol) and K₂ CO₃ (0.211 g, 1.525 mmol) were dissolved in acetonitrile (2 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 8 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.164 g, 51.5 %) as a colorless oil.

Step 2: Synthesis of compound 255

[0336] Methyl 4-(((3R,5S)-4-(3-(1H-pyrrol-1-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.050 g, 0.120 mmol), hydroxylamine (0.146 mL, 2.395 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.067 g, 1.197 mmol) were dissolved in methanol (1 ml) at 25 °C, and the solution was stirred at the same temperature for 1 hour. Then, saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with an anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield **compound 255** (0.024 g, 47.9 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.61 (d, 2 H, *J* = 8.4 Hz), 7.45 - 7.42 (m, 1 H), 7.32 (d, 2 H, *J* = 5.2 Hz), 7.26 (d, 2 H, *J* = 2.4 Hz), 7.22 - 7.21 (m, 1 H), 7.13 - 7.11 (m, 2 H), 6.22 - 6.21 (m, 2 H), 3.80 (s, 2 H), 3.33 (s, 2H), 2.63 - 2.57 (m, 4 H), 1.79 - 1.72 (m, 2 H), 0.85 (d, 6 H, *J* = 16.8 Hz).

Example 99: Synthesis of compound 256**(4-(((2S,6R)-4-(3-(1H-pyrrol-1-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)****Step 1: Synthesis of methyl****4-(((2S,6R)-4-(3-(1H-pyrrol-1-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate**

[0337] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.200 g, 0.762 mmol), 1-(3-(bromomethyl)phenyl)-1H-pyrrole (0.198 g, 0.839 mmol) and K₂CO₃ (0.211 g, 1.525 mmol) were dissolved in acetonitrile (2 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 8 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.177 g, 55.6 %) as a white solid.

Step 2: Synthesis of compound 256

[0338] Methyl 4-(((2S,6R)-4-(3-(1H-pyrrol-1-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.050 g, 0.120 mmol), hydroxylamine (0.146 mL, 2.395 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.067 g, 1.197 mmol) were dissolved in methanol (1 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 1 hour. Then, saturated sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with an anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield **compound 256** (0.031 g, 61.9 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.61 (d, 2 H, *J* = 8.4 Hz), 7.41 - 7.30 (m, 7 H), 7.14 (d, 2 H, *J* = 7.2 Hz), 6.22 - 6.21 (m, 2 H, *J* = 2.4 Hz), 3.70 (s, 2 H), 3.42 (s, 2H), 2.66 (d, 2 H, *J* = 10 Hz), 2.57 - 2.52 (m, 2 H), 1.83 - 1.77 (m, 2 H), 0.85 (d, 6 H, *J* = 10.4 Hz).

Example 100: Synthesis of compound 257

(4-(((2S,6R)-4-(3-(furan-2-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(3-iodobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0339] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 7.000 g,

28.224 mmol), 3-iodobenzoic acid (8.145 g, 31.046 mmol), EDCI (10.821 g, 56.447 mmol), HOBt (7.628 g, 56.447 mmol) and *N,N*-diisopropylethylamine (18.238 g, 141.118 mmol) were dissolved in methylene chloride (150 mL) at room temperature, and the reaction solution was stirred overnight at the same temperature. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous sodium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 30 % to 50 %) and concentrated to afford the desired compound (10.737 g, 77.3 %) as a white solid.

Step 2: Synthesis of methyl

4-(((2S,6R)-4-(3-(furan-2-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0340] 1,2-Dimethoxyethane/water (v/v=3/1) (3 mL) were added to a mixture of methyl 4-(((2S,6R)-4-(3-iodobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-1, 0.400 g, 0.812 mmol), furan-2-ylboronic acid (0.136 g, 1.219 mmol), Pd(dbpf)Cl₂ (0.026 g, 0.041 mmol) and Na₂CO₃ (0.258 g, 2.437 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a 1N aqueous solution of hydrochloric acid was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with water, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/ hexane = from 10 % to 50 %) and concentrated to afford the desired compound (0.030 g, 8.5 %) as a yellow oil.

Step 3: Synthesis of compound 257

[0341] Methyl 4-(((2S,6R)-4-(3-(furan-2-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-2, 0.030 g, 0.069 mmol), hydroxylamine (0.084 mL, 1.378 mmol, 50 % aqueous solution) and potassium hydroxide (0.039 g, 0.689 mmol) were dissolved in methanol (1 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 257** (0.012 g, 41.2 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.79 - 7.79 (m, 2 H), 7.77 - 7.68 (m, 3 H), 7.50 (t, 1 H, *J* = 7.7 Hz), 7.41 (d, 2 H, *J* = 7.9 Hz), 7.29 (d, 1 H, *J* = 7.6 Hz), 7.07 (d, 1 H, *J* = 3.3 Hz), 6.63 - 6.62 (m, 1 H), 4.30 - 4.27 (m, 1 H), 3.78 (s, 2 H), 3.01 - 2.99 (m, 1 H), 2.73 - 2.71 (m, 1 H), 2.56 - 2.51 (m, 3 H), 1.03 (s, 3 H), 0.82 (s, 3 H).

Example 101: Synthesis of compound 258

4-(((2S,6R)-4-(3-(furan-3-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(3-(furan-3-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0342] 1,2-Dimethoxyethane/water (v/v=3/1) (3 mL) were added to a mixture of methyl 4-(((2S,6R)-4-(3-iodobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-1, 0.400 g, 0.812 mmol), furan-3-ylboronic acid (0.136 g, 1.219 mmol), Pd(dbpf)Cl₂ (0.026 g, 0.041 mmol) and Na₂CO₃ (0.258 g, 2.437 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a 1N aqueous solution of hydrochloric acid was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with water, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/ hexane = from 10 % to 50 %) and concentrated to afford the desired compound (0.061 g, 17.4 %) as a yellow oil.

Step 2: Synthesis of compound 258

[0343] Methyl 4-(((2S,6R)-4-(3-(furan-3-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-2, 0.061 g, 0.141 mmol), hydroxylamine (0.173 mL, 2.830 mmol, 50 % aqueous solution) and potassium hydroxide (0.079 g, 1.415 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 258** (0.016 g, 25.9 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.29 (s, 1 H), 7.77 (s, 1 H), 7.72 - 7.68 (m, 3 H), 7.64 (s, 1 H), 7.47 - 7.41 (m, 3 H), 7.25 (d, 1 H, *J* = 7.6 Hz), 7.03 (s, 1 H), 4.31 - 4.28 (m, 1 H), 3.79 (s, 2 H), 3.00 - 2.98 (m, 1 H), 2.71 - 2.68 (m, 1 H), 2.56 - 2.51 (m, 3 H), 1.03 (s, 3 H), 0.82 (s, 3 H).

Example 102: Synthesis of compound 259

4-(((2S,6R)-4-(3-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(3-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0344] 1,2-Dimethoxyethane/water (v/v=3/1) (3 mL) were added to a mixture of methyl 4-(((2S,6R)-4-(3-iodobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-1, 0.400 g, 0.812 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.256 g, 1.219 mmol), Pd(dbpf)Cl₂ (0.026 g, 0.041 mmol) and Na₂CO₃ (0.258 g, 2.437 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 20 % to 65 %) and concentrated to afford the desired compound (0.290 g, 79.6 %) as a brown solid.

Step 2: Synthesis of compound 259

[0345] Methyl 4-(((2S,6R)-4-(3-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-2, 0.060 g, 0.134 mmol), hydroxylamine (0.164 mL, 2.675 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.075 g, 1.338 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 259** (0.010g, 16.6 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.69 (d, 2 H, *J* = 8.0 Hz), 7.54 (d, 1 H, *J* = 7.9 Hz), 7.44 - 7.41 (m, 4 H), 7.28 (d, 1 H, *J* = 7.7 Hz), 6.33 (s, 1 H), 4.24 - 4.23 (m, 3 H), 3.83 (t, 2 H, *J* = 5.4 Hz), 3.78 (s, 2 H), 2.98 - 2.96 (m, 1 H), 2.70 - 2.68 (m, 1 H), 2.55 - 2.51 (m, 3 H), 2.46 (s, 2 H), 1.02 (s, 3 H), 0.82 (s, 3 H).

Example 103: Synthesis of compound 260

4-(((2S,6R)-2,6-dimethyl-4-(3-(pyridin-4-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)**Step 1: Synthesis of methyl****4-(((2S,6R)-2,6-dimethyl-4-(3-(pyridin-4-yl)benzoyl)piperazin-1-yl)methyl)benzoate**

[0346] 1,2-Dimethoxyethane/water (v/v=3/1) (3 mL) were added to a mixture of methyl 4-(((2S,6R)-4-(3-iodobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-1, 0.400 g, 0.812 mmol), pyridine-4-boronic acid hydrate (0.172 g, 1.219 mmol), Pd(dbpf)Cl₂ (0.026 g, 0.041 mmol) and Na₂CO₃ (0.258 g, 2.437 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 50 % to 65 %) and concentrated to afford the desired compound (0.354 g, 98.3 %) as a brown oil.

Step 2: Synthesis of compound 260

[0347] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(3-(pyridin-4-yl)benzoyl)piperazin-1-yl)methyl)benzoate (formula 15-2, 0.060 g, 0.135 mmol), hydroxylamine (0.165 mL, 2.706 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.076 g, 1.353 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 260** (0.003 g, 5.5 %) as a pale brown solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.67 - 8.66 (m, 2 H), 7.91 (d, 1 H, *J* = 7.9 Hz), 7.81 (s, 1 H), 7.77 - 7.75 (m, 2 H), 7.68 (d, 2 H, *J* = 8.2 Hz), 7.61 (t, 1 H, *J* = 7.7 Hz), 7.49 (d, 1 H, *J* = 7.6 Hz), 7.43 - 7.41 (m, 2H), 4.31 - 4.29 (m, 1 H), 3.79 (s, 2 H), 3.02 - 3.02 (m, 1 H), 2.73 - 2.68 (m, 1 H), 2.67 - 2.55 (m, 3 H), 1.04 (s, 3 H), 0.86 (s, 3 H).

Example 104: Synthesis of compound 261**4-(((2S,6R)-2,6-dimethyl-4-(3-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)**

Step 1: Synthesis of methyl**4-(((2S,6R)-2,6-dimethyl-4-(3-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)benzoate**

[0348] 1,2-Dimethoxyethane/water (v/v=3/1) (3 mL) were added to a mixture of methyl 4-(((2S,6R)-4-(3-iodobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-1, 0.328 g, 0.665 mmol), pyridin-3-ylboronic acid (0.090 g, 0.732 mmol), Pd(dbpf)Cl₂ (0.022 g, 0.033 mmol) and Na₂CO₃ (0.155 g, 1.464 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 50 % to 65 %) and concentrated to afford the desired compound (0.244 g, 82.8 %) as a brown solid.

Step 2: Synthesis of compound 261

[0349] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(3-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)benzoate (formula 15-2, 0.060 g, 0.135 mmol), hydroxylamine (0.165 mL, 2.706 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.076 g, 1.353 mmol) were dissolved in methanol (2 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 261** (0.014 g, 23.3 %) as a pale brown solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.91 - 8.90 (m, 1 H), 8.59 - 8.58 (m, 1 H), 8.12 - 8.09 (m, 1 H), 7.81 (d, 1 H, *J* = 7.8 Hz), 7.72 (s, 1 H), 7.67 (d, 2 H, *J* = 8.1 Hz), 7.56 (t, 1 H, *J* = 7.7 Hz), 7.51 - 7.47 (m, 1 H), 7.43 - 7.39 (m, 3 H), 4.29 - 4.26 (m, 1 H), 3.77 (s, 2 H), 3.44 - 3.42 (m, 1 H), 3.01 - 2.99 (m, 1 H), 2.71 - 2.66 (m, 1 H), 2.58 (brs, 2 H), 1.01 (s, 3 H), 0.81 (s, 3 H).

Example 105: Synthesis of compound 262**4-(((2S,6R)-4-(3-(2-fluoropyridin-4-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)**

Step 1: Synthesis of methyl**4-(((2S,6R)-4-(3-(2-fluoropyridin-4-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate**

[0350] 1,2-Dimethoxyethane/water (v/v=3/1) (3 mL) were added to a mixture of methyl 4-(((2S,6R)-4-(3-iodobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-1, 0.400 g, 0.812 mmol), (2-fluoropyridin-4-yl)boronic acid (0.172 g, 1.219 mmol), Pd(dbpf)Cl₂ (0.026 g, 0.041 mmol) and Na₂CO₃ (0.258 g, 2.437 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 10 % to 50 %) and concentrated to afford the desired compound (0.366 g, 97.5 %) as a brown oil.

Step 2: Synthesis of compound 262

[0351] Methyl 4-(((2S,6R)-4-(3-(2-fluoropyridin-4-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-2, 0.060 g, 0.130 mmol), hydroxylamine (0.159 mL, 2.600 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.073 g, 1.300 mmol) were dissolved in methanol (2 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 262** (0.009 g, 14.1 %) as a pale brown solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.77 (d, 1 H, *J* = 8.0 Hz), 7.67 - 7.65 (m, 3 H), 7.54 (t, 1 H, *J* = 7.7 Hz), 7.47 - 7.44 (m, 2 H), 7.38 (d, 2 H, *J* = 8.1 Hz), 6.60 - 6.59 (m, 1 H), 6.51 (dd, 1 H, *J* = 6.8, 1.6 Hz), 4.26 - 4.24 (m, 1 H), 3.77 (s, 2 H), 2.99 - 2.97 (m, 1 H), 2.72 - 2.70 (m, 1 H), 2.66 - 2.54 (m, 3 H), 1.01 (s, 3 H), 0.81 (s, 3 H).

Example 106: Synthesis of compound 263**(4-(((2S,6R)-4-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-carbonyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)**

Step 1: Synthesis of methyl**4-(((2S,6R)-4-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-carbonyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate**

[0352] 1,2-Dimethoxyethane/water (v/v=3/1) (3 mL) were added to a mixture of methyl 4-(((2S,6R)-4-(3-iodobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-1, 0.400 g, 0.812 mmol), 2-(4,4-dimethylcyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.288 g, 1.219 mmol), Pd(dbpf)Cl₂ (0.026 g, 0.041 mmol) and Na₂CO₃ (0.258 g, 2.437 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 10 % to 20 %) and concentrated to afford the desired compound (0.065 g, 16.8 %) as a brown oil.

Step 2: Synthesis of compound 263

[0353] Methyl 4-(((2S,6R)-4-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-carbonyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-2, 0.065 g, 0.137 mmol), hydroxylamine (0.167 mL, 2.735 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.077 g, 1.367 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 263** (0.044 g, 68.3 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.66 (d, 2 H, *J* = 8.1 Hz), 7.49 (d, 1 H, *J* = 8.0 Hz), 7.38 - 7.34 (m, 4 H), 7.21 (d, 1 H, *J* = 7.6 Hz), 6.15 - 6.13 (m, 1 H), 4.24 - 4.22 (m, 1 H), 3.76 (s, 2 H), 2.95 - 2.93 (m, 1 H), 2.67 - 2.50 (m, 4 H), 2.37 (s, 2 H), 1.96 (s, 2 H), 1.47 (t, 2 H, *J* = 6.3 Hz), 1.05 (s, 3 H), 0.92 (s, 6 H), 0.80 (s, 3 H).

Example 107: Synthesis of compound 265**(4-(((3R,5S)-3,5-dimethyl-4-(naphthalen-2-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)**

Step 1: Synthesis of methyl**4-(((3R,5S)-3,5-dimethyl-4-(naphthalene-2-ylmethyl)piperazin-1-yl)methyl)benzoate**

[0354] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.150 g, 0.572 mmol), Cs₂CO₃ (0.279 g, 0.858 mmol) and 2-(bromomethyl)naphthalene (0.126 g, 0.572 mmol) were dissolved in acetonitrile (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 48 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The obtained product was used without additional purification (0.230 g, 99.9 %).

Step 2: Synthesis of compound 265

[0355] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(naphthalene-2-ylmethyl)piperazin-1-yl)methyl)benzoate (formula 1-3, 0.230 g, 0.571 mmol), hydroxylamine (0.699 mL, 11.428 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.321 g, 5.714 mmol) were dissolved in methanol (3 mL) / tetrahydrofuran (1 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure to remove the solvent, a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was crystallized from methanol (5 mL) to yield **compound 265** (0.042 g, 18.2 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.87 - 7.82 (m, 4 H), 7.66 (d, 2 H, *J* = 8.0 Hz), 7.50 (d, 1 H, *J* = 9.0 Hz), 7.47 - 7.44 (m, 2 H), 7.23 (d, 2 H, *J* = 8.0 Hz), 3.88 (s, 2 H), 3.41 (s, 2 H), 2.67 - 2.61 (m, 4 H), 1.84 (t, 2 H, *J* = 10.1 Hz), 0.93 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 404.2 (*M*⁺+1).

Example 108: Synthesis of compound 266**(4-(((3R,5S)-3,5-dimethyl-4-(pyridin-4-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamide(Trifluoroacetic acid salt))****Step 1: Synthesis of methyl**

4-(((3R,5S)-3,5-dimethyl-4-(pyridin-4-ylmethyl)piperazin-1-yl)methyl)benzoate

[0356] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.150 g, 0.572 mmol), Cs₂CO₃ (0.279 g, 0.858 mmol) and 4-(bromomethyl)pyridine (0.098 g, 0.572 mmol) were dissolved in acetonitrile (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 17 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The product was used without additional purification (0.200 g, 99.0 %).

Step 2: Synthesis of compound 266

[0357] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(pyridin-4-ylmethyl)piperazin-1-yl)methyl)benzoate (formula 1-3, 0.200 g, 0.566 mmol), hydroxylamine (0.692 mL, 11.317 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.317 g, 5.658 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, 19*100 mm column, 0.1 % trifluoroacetic acid/acetonitrile = from 5 % to 80 %) and concentrated to afford the desired **compound 266** (0.019 g, 9.5 %) as a white solid.

¹H NMR (400 MHz, CH₃OD) δ 8.77 (d, 2 H, *J* = 6.7 Hz), 8.17 (d, 2 H, *J* = 6.7 Hz), 7.90 (d, 2 H, *J* = 8.3 Hz), 7.67 (d, 2 H, *J* = 8.3 Hz), 4.45 (s, 2 H), 4.18 (s, 2 H), 3.41 (d, 2 H, *J* = 11.4 Hz), 3.03 - 3.00 (m, 4 H), 1.04 (d, 6 H, *J* = 6.0 Hz).

Example 109: Synthesis of compound 267**(4-(((3R,5S)-4-(3-chloro-2-(trifluoromethyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)****Step 1: Synthesis of methyl**

4-(((3R,5S)-4-(3-chloro-2-(trifluoromethyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0358] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.150 g, 0.572 mmol), Cs₂CO₃ (0.279 g, 0.858 mmol) and 1-(bromomethyl)-3-chloro-2-(trifluoromethyl)benzene (0.156 g, 0.572 mmol) were dissolved in acetonitrile (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 17 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 30 %) and concentrated to afford the desired compound (0.203 g, 78.0 %).

Step 2: Synthesis of compound 267

[0359] Methyl 4-(((3R,5S)-4-(3-chloro-2-(trifluoromethyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.100 g, 0.220 mmol), hydroxylamine (0.269 mL, 4.396 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.123 g, 2.198 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure to yield **compound 267** (0.044 g, 43.9 %) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 9.80 (brs, 2 H), 7.82 (s, 1 H), 7.71 - 7.65 (m, 4 H), 7.33 (d, 2 H, *J* = 3.9 Hz), 4.58 (s, 2 H), 3.44 - 3.35 (m, 3 H), 2.67 (d, 2 H, *J* = 10.3 Hz), 2.60 (s, 2 H), 1.82 (t, 2 H, *J* = 9.4 Hz), 0.83 (s, 6 H); LRMS (ES) *m/z* 456.1 (M⁺+1).

Example 110: Synthesis of compound 268**4-(((2S,6R)-2,6-dimethyl-4-(naphthalen-2-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamide****Step 1: Synthesis of methyl****4-(((2S,6R)-2,6-dimethyl-4-(naphthalene-2-ylmethyl)piperazin-1-yl)methyl)benzoate**

[0360] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.150 g, 0.502 mmol), Cs₂CO₃ (0.245 g, 0.753 mmol) and 2-(bromomethyl)naphthalene (0.111 g, 0.502 mmol) were dissolved in acetonitrile (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 17 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The product was used without additional purification (0.200 g, 99.0 %).

Step 2: Synthesis of compound 268

[0361] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(naphthalene-2-ylmethyl)piperazin-1-yl)methyl)benzoate (formula 13-3, 0.200 g, 0.497 mmol), hydroxylamine (0.608 mL, 9.937 mmol) and potassium hydroxide (0.279 g, 4.969 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate (3 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried, and the resulting product was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford **compound 268** (0.075 g, 37.4 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.13 (s, 1 H), 8.99 (s, 1 H), 7.90 - 7.86 (m, 3 H), 7.78 (s, 1 H), 7.67 (d, 2 H, *J* = 7.2 Hz), 7.50 - 7.47 (m, 3 H), 7.42 (d, 2 H, *J* = 7.8 Hz), 3.76 (s, 2 H), 3.57 (s, 2 H), 2.71 (d, 2 H, *J* = 10.6 Hz), 2.60 - 2.56 (m, 2 H), 1.86 (t, 2 H, *J* = 10.5 Hz), 0.88 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 404.2 (M⁺+1).

Example 111: Synthesis of compound 270

(N-hydroxy-4-(((3R,5S)-4-isopentyl-3,5-dimethylpiperazin-1-yl)methyl)benzamide (Trifluoroacetic acid salt))

Step 1: Synthesis of methyl

4-(((3R,5S)-4-isopentyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0362] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.150 g, 0.572 mmol), Cs₂CO₃ (0.279 g, 0.858 mmol) and 1-bromo-3-methylbutane (0.086 mL, 0.720 mmol) were dissolved in N,N-dimethylformamide (100 ml) at room temperature, and the reaction solution was stirred at the same temperature for 17 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The product was used without additional purification (0.190 g, 99.9 %).

Step 2: Synthesis of compound 270

[0363] Methyl 4-(((3R,5S)-4-isopentyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.190 g, 0.571 mmol), hydroxylamine (0.699 mL, 11.429 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.321 g, 5.715 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, 19*100 mm column, 0.1 % trifluoroacetic acid/acetonitrile = from 5 % to 80 %) and concentrated to afford **compound 270** (0.025 g, 13.1 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.23 (brs, 1 H), 9.10 (brs, 1 H), 7.75 (d, 2 H, *J* = 8.2 Hz), 7.42 (d, 2 H, *J* = 8.1 Hz), 3.71 (s, 2 H), 3.45 - 3.45 (m, 2 H), 3.18 - 3.18 (m, 2 H), 3.01 (d, 2 H, *J* = 11.3 Hz), 2.28 (t, 2 H, *J* = 11.3 Hz), 1.67 - 1.60 (m, 1 H), 1.52 - 1.48 (m, 2 H), 1.22 (d, 6 H, *J* = 6.3 Hz), 0.93 (d, 6 H, *J* = 6.6 Hz); LRMS (ES) *m/z* 334.2 (*M*⁺+1).

Example 112: Synthesis of compound 271

(N-hydroxy-4-(((2S,6R)-4-isopentyl-2,6-dimethylpiperazin-1-yl)methyl)benzamide (Trifluoroacetic acid salt))

Step 1: Synthesis of methyl

4-(((2S,6R)-4-isopentyl-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0364] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.150 g, 0.502 mmol), Cs₂CO₃ (0.245 g, 0.753 mmol) and 1-bromo-3-methylbutane (0.060 mL, 0.502 mmol) were dissolved in acetonitrile (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 17 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The product was used without additional purification (0.170 g, 101.9 %).

Step 2: Synthesis of compound 271

[0365] Methyl 4-(((2S,6R)-4-isopentyl-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.170 g, 0.511 mmol), hydroxylamine (0.626 mL, 10.226 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.287 g, 5.113 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the concentrate was purified by column chromatography (Waters, C₁₈, 19*100 mm column, 0.1 % trifluoroacetic acid/acetonitrile = from 5 % to 80 %) and concentrated to afford **compound 271** (0.097 g, 56.9 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.18 (brs, 1 H), 9.00 (brs, 1 H), 7.67 (d, 2 H, *J* = 8.3 Hz), 7.41 (d, 2 H, *J* = 8.2 Hz), 3.74 (s, 2 H), 2.70 (d, 2 H, *J* = 10.8 Hz), 2.56 - 2.53 (m, 2 H), 2.19 (t, 2 H, *J* = 7.6 Hz), 1.70 (t, 2 H, *J* = 10.6 Hz), 1.57 - 1.54 (m, 1 H), 1.32 - 1.26 (m, 2 H), 0.89 (d, 6 H, *J* = 6.2 Hz), 0.86 (d, 6 H, *J* = 6.6 Hz); LRMS (ES) *m/z* 334.2 (M⁺+1).

Example 113: Synthesis of compound 272

(4-(((3R,5S)-3,5-dimethyl-4-(3-methylbut-2-en-1-yl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-methylbut-2-en-1-yl)piperazin-1-yl)methyl)benzoate

[0366] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.150 g, 0.572 mmol), Cs₂CO₃ (0.279 g, 0.858 mmol) and 1-bromo-3-methyl-2-butene (0.067 mL, 0.572 mmol) were dissolved in N,N-dimethylformamide (3 mL) at room temperature, and the reaction solution was stirred at 100 °C for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with

methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous solution, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.123 g, 65.1 %) as crude.

Step 2: Synthesis of compound 272

[0367] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-methylbut-2-en-1-yl)piperazin-1-yl)methyl)benzoate (formula 1-3, 0.070 g, 0.212 mmol), hydroxylamine (0.259 mL, 4.237 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.119 g, 2.118 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure to yield **compound 272** (0.030 g, 42.7 %) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 11.10 (brs, 1 H), 9.00 (brs, 1 H), 7.69 (d, 2 H, J = 8.0 Hz), 7.33 (d, 2 H, J = 8.0 Hz), 5.30 (s, 1 H), 3.40 (s, 2 H), 3.35 (s, 2 H), 3.29 (d, 2 H, J = 6.1 Hz), 2.62 - 2.60 (m, 4 H), 1.74 - 1.72 (m, 2 H), 1.69 (s, 3 H), 1.60 (s, 3 H), 0.92 (d, 6 H, J = 7.0 Hz); LRMS (ES) m/z 332.2 ($M^+ + 1$).

Example 114: Synthesis of compound 273

(N-hydroxy-4-(((2S,6R)-4-isopropyl-2,6-dimethylpiperazin-1-yl)methyl)benzamide (Trifluoroacetic acid salt))

Step 1: Synthesis of methyl

4-(((2S,6R)-4-isopropyl-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0368] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.150 g, 0.502 mmol), Cs_2CO_3 (0.245 g, 0.753 mmol) and 2-iodopropane (0.050 mL, 0.502 mmol) were dissolved in acetonitrile (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 17 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove

solid residue and an aqueous solution, and the organic layer was concentrated under reduced pressure. The product was used without additional purification (0.150 g, 98.2 %).

Step 2: Synthesis of compound 273

[0369] Methyl 4-(((2S,6R)-4-isopropyl-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.150 g, 0.493 mmol), hydroxylamine (0.603 mL, 10.226 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.276 g, 4.927 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the concentrate was purified by column chromatography (Waters, C₁₈, 19*100 mm column, 0.1 % trifluoroacetic acid/acetonitrile = from 5 % to 80 %) and concentrated to afford **compound 273** (0.097 g, 64.5 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.20 (s, 1 H), 9.36 (s, 1 H), 7.72 (d, 2 H, *J* = 8.2 Hz), 7.46 (d, 2 H, *J* = 8.2 Hz), 3.93 (s, 2 H), 3.44 - 3.41 (m, 1 H), 3.35 (d, 2 H, *J* = 11.6 Hz), 2.92 - 2.90 (m, 2 H), 2.77 - 2.74 (m, 2 H), 1.25 (d, 6 H, *J* = 6.6 Hz), 1.08 (d, 6 H, *J* = 4.8 Hz); LRMS (ES) *m/z* 306.2 (*M*⁺+1).

Example 115: Synthesis of compound 274

(4-(((2S,6R)-4-butyl-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt))

Step 1: Synthesis of methyl

4-(((2S,6R)-4-butyl-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0370] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.150 g, 0.502 mmol), Cs₂CO₃ (0.245 g, 0.753 mmol) and 1-iodobutane (0.057 mL, 0.502 mmol) were dissolved in acetonitrile (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 17 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous solution, and the organic layer was concentrated under reduced pressure. The product was used without additional purification (0.160 g, 100.1 %).

Step 2: Synthesis of compound 274

[0371] Methyl 4-(((2S,6R)-4-butyl-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.160 g, 0.502 mmol), hydroxylamine (0.615 mL, 10.049 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.282 g, 5.024 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the concentrate was purified by column chromatography (Waters, C₁₈, 19*100 mm column, 0.1 % trifluoroacetic acid/acetonitrile = from 5 % to 80 %) and concentrated to afford **compound 274** (0.087 g, 54.2 %) as a white solid.

¹H NMR (400 MHz, D₂O) δ 7.66 (d, 2 H, *J* = 8.3 Hz), 7.51 (d, 2 H, *J* = 8.4 Hz), 4.40 (s, 2 H), 3.58 (d, 2 H, *J* = 12.4 Hz), 3.37 - 3.36 (m, 2 H), 3.07 - 2.97 (m, 4 H), 1.57 - 1.54 (m, 2 H), 1.39 (d, 6 H, *J* = 6.3 Hz), 1.26 - 1.20 (m, 2 H), 0.79 (t, 3 H, *J* = 7.4 Hz); LRMS (ES) *m/z* 320.2 (M⁺+1).

Example 116: Synthesis of compound 275

4-(((3R,5S)-4-butyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-butyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0372] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.150 g, 0.502 mmol), Cs₂CO₃ (0.245 g, 0.753 mmol) and 1-iodobutane (0.057 mL, 0.502 mmol) were dissolved in acetonitrile (3 mL), and the reaction mixture was heated under reflux for 17 hours, and then cooled to room temperature. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous solution, and the organic layer was concentrated under reduced pressure. The product was used without additional purification (0.120 g, 98.9 %).

Step 2: Synthesis of compound 275

[0373] Methyl 4-(((3R,5S)-4-butyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.120 g, 0.377 mmol), hydroxylamine (0.461 mL, 7.537 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.211 g, 3.768 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent,

and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, 19*100 mm column, 0.1 % trifluoroacetic acid/acetonitrile = from 5 % to 80 %) and concentrated to afford the desired **compound 275** (0.088 g, 73.1 %) as a white solid.

¹H NMR (400 MHz, D₂O) δ 7.66 (d, 2 H, *J* = 8.3 Hz), 7.47 (d, 2 H, *J* = 8.2 Hz), 4.15 - 4.15 (m, 2 H), 3.57 - 3.56 (m, 2 H), 3.44 (d, 2 H, *J* = 13.2 Hz), 3.22 (t, 2 H, *J* = 8.5 Hz), 2.91 - 2.90 (m, 2 H), 1.58 - 1.54 (m, 2 H), 1.28 (d, 6 H, *J* = 6.4 Hz), 0.82 (t, 3 H, *J* = 7.4 Hz); LRMS (ES) *m/z* 320.2 (*M*⁺+1).

Example 117: Synthesis of compound 276

4-(((2S,6R)-4-(2-(furan-2-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(2-iodobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0374] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 4.000 g, 16.128 mmol), 2-iodobenzoic acid (4.654 g, 17.741 mmol), EDCI (6.183 g, 32.255 mmol), HOBt (4.359 g, 32.255 mmol) and *N,N*-diisopropylethylamine (10.422 g, 80.639 mmol) were dissolved in methylene chloride (100 mL) at room temperature, and the solution was stirred overnight at the same temperature. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 30 % to 50 %) and concentrated to afford the desired compound (7.630 g, 96.1 %) as a white solid.

Step 2: Synthesis of methyl 4-(((2S,6R)-4-(2-(furan-2-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0375] 1,2-Dimethoxyethane/water (v/v=3/1) (3 mL) were added to a mixture of methyl 4-(((2S,6R)-4-(2-iodobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-1, 0.400

g, 0.812 mmol), furan-2-ylboronic acid (0.136 g, 1.219 mmol), Pd(dbpf)Cl₂ (0.026 g, 0.041 mmol) and Na₂CO₃ (0.258 g, 2.437 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/ hexane = from 10 % to 30 %) and concentrated to afford the desired compound (0.211 g, 60.1 %) as a white solid.

Step 3: Synthesis of compound 276

[0376] Methyl 4-(((2S,6R)-4-(2-(furan-2-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-2, 0.060 g, 0.139 mmol), hydroxylamine (0.170 mL, 2.775 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.078 g, 1.387 mmol) were dissolved in methanol (1 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 276** (0.017 g, 27.9 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.80 - 7.65 (m, 4 H), 7.50 - 7.47 (m, 1 H), 7.40 - 7.30 (m, 3 H), 7.26 (t, 1 H, *J* = 6.8 Hz), 6.69 (dd, 1 H, *J* = 27.4, 9.3 Hz), 6.61 - 6.51 (m, 1 H), 4.36 - 4.33 (m, 1 H), 3.76 - 3.61 (m, 2 H), 3.09 - 2.99 (m, 1 H), 2.83 - 2.77 (m, 1 H), 2.69 - 2.55 (m, 3 H), 1.03 (d, 3 H, *J* = 5.9 Hz), 0.70 (m, 3 H).

Example 118: Synthesis of compound 277

(4-(((2S,6R)-4-(2-(furan-3-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(2-(furan-3-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0377] 1,2-Dimethoxyethane/water (v/v=3/1) (3 mL) were added to a mixture of methyl 4-(((2S,6R)-4-(2-iodobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-1, 0.400 g, 0.812 mmol), furan-3-ylboronic acid (0.136 g, 1.219 mmol), Pd(dbpf)Cl₂ (0.026 g, 0.041

mmol) and Na_2CO_3 (0.258 g, 2.437 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/ hexane = from 10 % to 30 %) and concentrated to afford the desired compound (0.186 g, 52.8 %) as a brown solid.

Step 2: Synthesis of compound 277

[0378] Methyl 4-(((2S,6R)-4-(2-(furan-3-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-2, 0.060 g, 0.139 mmol), hydroxylamine (0.170 mL, 2.775 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.078 g, 1.387 mmol) were dissolved in methanol (1 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 277** (0.023 g, 37.6 %) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.82 (s, 1 H), 7.77 - 7.64 (m, 3 H), 7.58 - 7.52 (m, 1 H), 7.46 (t, 1 H, $J = 7.5$ Hz), 7.36 (q, 2 H, $J = 8.1$ Hz), 7.29 - 7.25 (m, 2 H), 6.67 - 6.66 (m, 1 H), 4.31 (d, 1 H, $J = 10.5$ Hz), 3.74 (s, 1 H), 3.62 (q, 2 H, $J = 18.9$ Hz), 2.90 (m, 1 H), 2.76 - 2.68 (m, 1 H), 2.62 - 2.56 (m, 2 H), 1.00 - 0.98 (m, 3 H), 0.66 (m, 3 H).

Example 119: Synthesis of compound 278

4-(((2S,6R)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0379] Methyl 4-(((2S,6R)-4-(2-iodobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-1, 0.400 g, 0.812 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.256 g, 1.219 mmol), $\text{Pd}(\text{dbpf})\text{Cl}_2$ (0.026 g, 0.041 mmol) and Na_2CO_3 (0.258 g, 2.437 mmol) were dissolved in 1,2-dimethoxyethane/water (v/v=3/1) (3 mL) at room

temperature, and the reaction solution was stirred overnight at 100 °C. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 10 % to 50 %) and concentrated to afford the desired compound (0.272 g, 74.6 %) as a brown solid.

Step 2: Synthesis of compound 278

[0380] Methyl 4-(((2S,6R)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-2, 0.060 g, 0.134 mmol), hydroxylamine (0.164 mL, 2.675 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.075 g, 1.338 mmol) were dissolved in methanol (1 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 278** (0.049 g, 81.8 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.68 (d, 2 H, *J* = 8.0 Hz), 7.45 - 7.39 (m, 3 H), 7.31 (t, 2 H, *J* = 7.5 Hz), 7.23 - 7.18 (m, 1 H), 5.83 - 5.76 (m, 1 H), 4.32 - 4.29 (m, 1 H), 4.15 - 4.10 (m, 2 H), 3.78 - 3.73 (m, 4 H), 3.06 (d, 1 H, *J* = 12.6 Hz), 2.78 (q, 1 H, *J* = 10.9 Hz), 2.67 - 2.56 (m, 2 H), 2.24 - 2.10 (m, 1 H), 1.03 - 1.02 (m, 3 H), 0.80 - 0.78 (m, 3 H).

Example 120: Synthesis of compound 279

(4-(((2S,6R)-2,6-dimethyl-4-(2-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-2,6-dimethyl-4-(2-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)benzoate

[0381] Methyl 4-(((2S,6R)-4-(2-iodobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-1, 0.400 g, 0.812 mmol), pyridin-3-ylboronic acid (0.150 g, 1.219 mmol), Pd(dppf)Cl₂ (0.026 g, 0.041 mmol) and Na₂CO₃ (0.258 g, 2.437 mmol) were dissolved in 1,2-dimethoxyethane/water (v/v=3/1) (3 mL) at room temperature, and the reaction solution was stirred overnight at 100 °C. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic

layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 50 % to 60 %) and concentrated to afford the desired compound (0.348 g, 96.7 %) as a brown oil.

Step 2: Synthesis of compound 279

[0382] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(2-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)benzoate (formula 15-2, 0.070 g, 0.158 mmol), hydroxylamine (0.193 mL, 3.156 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.089 g, 1.578 mmol) were dissolved in methanol (1 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 279** (0.062 g, 88.4 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.62 - 8.53 (m, 2 H), 7.82 - 7.76 (m, 1 H), 7.67 (d, 2 H, *J* = 8.0 Hz), 7.60 - 7.43 (m, 4 H), 7.34 (dd, 3 H, *J* = 36.4, 7.5 Hz), 4.20 (d, 1 H, *J* = 12.5 Hz), 3.72 - 3.60 (m, 1 H), 3.55 - 3.41 (m, 1 H), 3.06 - 2.86 (m, 1 H), 2.66 - 2.63 (m, 1 H), 2.28 - 2.22 (m, 1 H), 1.99 (brs, 1 H), 1.06 (brs, 1 H), 0.92 - 0.91 (m, 3 H), 0.68 - 0.62 (m, 3 H).

Example 121: Synthesis of compound 280

4-(((2S,6R)-4-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-carbonyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-carbonyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0383] Methyl 4-(((2S,6R)-4-(2-iodobenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-1, 0.400 g, 0.812 mmol), 2-(4,4-dimethylcyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.288 g, 1.219 mmol), Pd(dbpf)Cl₂ (0.026 g, 0.041 mmol) and Na₂CO₃ (0.258 g, 2.437 mmol) were dissolved in 1,2-dimethoxyethane/water (v/v=3/1) (3 mL) at room temperature, and the reaction solution was stirred overnight at 100 °C. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium

sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 10 % to 20 %) and concentrated to afford the desired compound (0.274 g, 71.1 %) as a brown solid.

Step 2: Synthesis of compound 280

[0384] Methyl 4-(((2S,6R)-4-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-carbonyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 15-2, 0.060 g, 0.135 mmol), hydroxylamine (0.165 mL, 2.706 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.076 g, 1.353 mmol) were dissolved in methanol (1 mL) at room temperature, and the reaction solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 280** (0.049 g, 75.7 %) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 7.69 - 7.67 (m, 2 H), 7.38 - 7.34 (m, 3 H), 7.31 - 7.24 (m, 2 H), 7.16 (t, 1 H, J = 8.7 Hz), 5.56 (s, 1 H), 4.29 (dd, 1 H, J = 31.1, 13.2 Hz), 3.81 - 3.71 (m, 2 H), 3.09 (t, 1 H, J = 14.5 Hz), 2.84 - 2.62 (m, 2 H), 2.46 - 2.33 (m, 3 H), 2.10 (brs, 1 H), 1.88 - 1.73 (m, 2 H), 1.44 - 1.38 (m, 2 H), 1.05 - 1.00 (m, 3 H), 0.95 - 0.89 (m, 6 H), 0.81 - 0.67 (m, 3 H).

Example 122: Synthesis of compound 283

(4-(((3R,5S)-4-(2-(furan-2-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of 2-iodobenzoyl chloride

[0385] 2-Iodobenzoic acid (4.000 g, 16.128 mmol) and SOCl_2 (23.399 mL, 322.555 mmol) were stirred overnight at 100 °C, and then the reaction mixture was concentrated under reduced pressure. The product was used without additional purification (4.295 g, 99.9 %, brown oil).

Step 2: Synthesis of methyl

4-(((3R,5S)-4-(2-iodobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0386] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 4.295 g, 16.119 mmol), 2-iodobenzoyl chloride (4.652 g, 17.731 mmol) and TEA (4.469 mL, 32.237 mmol) were dissolved in methylene chloride (70 mL) at room temperature, and the reaction solution was stirred at the same temperature for 1 hour. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 30 % to 50 %) and concentrated to afford the desired compound (7.120 g, 89.7 %) as a white solid.

Step 3: Synthesis of methyl

4-(((3R,5S)-4-(2-(furan-2-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0387] 1,2-Dimethoxyethane/water (v/v=3/1) (3 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(2-iodobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-1, 0.400 g, 0.812 mmol), furan-2-ylboronic acid (0.136 g, 1.219 mmol), Pd(dbpf)Cl₂ (0.026 g, 0.041 mmol) and Na₂CO₃ (0.258 g, 2.437 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/ hexane = from 0 % to 15 %) and concentrated to afford the desired compound (0.040 g, 11.4 %) as a colorless oil.

Step 4: Synthesis of compound 283

[0388] Methyl 4-(((3R,5S)-4-(2-(furan-2-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-2, 0.040 g, 0.092 mmol), hydroxylamine (0.113 mL, 1.850 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.052 g, 0.925 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 283** (0.016 g, 39.4 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.78 - 7.68 (m, 4 H), 7.46 (t, 1 H, *J* = 7.6 Hz), 7.41 - 7.21 (m, 4 H), 6.73 (dd, 1 H, *J* = 33.6, 3.4 Hz), 6.61 - 6.59 (m, 1 H), 4.70 - 4.65 (m, 1 H), 3.56 - 3.41 (m, 3 H), 2.72 - 2.66 (m, 1 H), 2.41 - 2.33 (m, 1 H), 2.18 - 2.03 (m, 1 H), 1.63 - 1.60 (m, 1 H), 1.33 (t, 3 H, *J* = 9.8 Hz), 1.16 (d, 2 H, *J* = 6.8 Hz), 0.86 (d, 1 H, *J* = 6.8 Hz).

Example 123: Synthesis of compound 284**4-(((3R,5S)-4-(2-(furan-3-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)****Step 1: Synthesis of methyl****4-(((3R,5S)-4-(2-(furan-3-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0389] 1,2-Dimethoxyethane/water (v/v=3/1) (3 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(2-iodobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-1, 0.400 g, 0.812 mmol), furan-3-ylboronic acid (0.136 g, 1.219 mmol), Pd(dbpf)Cl₂ (0.026 g, 0.041 mmol) and Na₂CO₃ (0.258 g, 2.437 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/ hexane = from 0 % to 10 %) and concentrated to afford the desired compound (0.128 g, 36.5 %) as a colorless oil.

Step 2: Synthesis of compound 284

[0390] Methyl 4-(((3R,5S)-4-(2-(furan-3-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-2, 0.128 g, 0.296 mmol), hydroxylamine (0.362 mL, 5.919 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.166 g, 2.959 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 284** (0.038 g, 29.5 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.85 - 7.75 (m, 2 H), 7.68 (d, 2 H, *J* = 8.2 Hz), 7.60 - 7.51 (m, 1 H), 7.46 - 7.35 (m, 2 H), 7.33 - 7.21 (m, 3 H), 6.82 - 6.66 (m, 1 H), 4.69 - 4.54 (m, 1 H), 3.52 - 3.49 (m, 1 H), 3.27 - 3.25 (m, 1 H), 2.70 - 2.56 (m, 1 H), 2.37 - 2.34 (m, 1 H), 2.16 - 2.04 (m, 1 H), 1.86 - 1.82 (m, 1 H), 1.39 - 1.21 (m, 4 H), 1.12 (d, 2 H, *J* = 6.8 Hz), 0.82 (d, 1 H, *J* = 6.8 Hz).

Example 124: Synthesis of compound 285**4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-4-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide****Step 1: Synthesis of methyl****4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-4-yl)benzoyl)piperazin-1-yl)methyl)benzoate**

[0391] 1,2-Dimethoxyethane/water (v/v=3/1) (3 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(2-iodobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-1, 0.400 g, 0.812 mmol), pyridine-4-boronic acid hydrate (0.172 g, 1.219 mmol), Pd(dbpf)Cl₂ (0.026 g, 0.041 mmol) and Na₂CO₃ (0.258 g, 2.437 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 50 % to 60 %) and concentrated to afford the desired compound (0.129 g, 35.9 %) as a pale yellow solid.

Step 2: Synthesis of compound 285

[0392] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-4-yl)benzoyl)piperazin-1-yl)methyl)benzoate (formula 4-2, 0.060 g, 0.135 mmol), hydroxylamine (0.165 mL, 2.706 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.076 g, 1.353 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 285** (0.016 g, 26.9 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.64 (d, 2 H, *J* = 5.8 Hz), 7.67 (d, 2 H, *J* = 8.0 Hz), 7.61 - 7.41 (m, 6 H), 7.30 (d, 1 H, *J* = 8.0 Hz), 4.34 (brs, 1 H), 3.24 - 3.17 (m, 3 H), 2.24 (d, 1 H, *J* = 11.0 Hz), 1.44 - 1.40 (m, 1 H), 1.29 (d, 3 H, *J* = 6.7 Hz), 1.07 (d, 3 H, *J* = 6.6 Hz).

Example 125: Synthesis of compound 286

4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)benzoate

[0393] 1,2-Dimethoxyethane/water (v/v=3/1) (3 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(2-iodobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-1, 0.400 g, 0.812 mmol), pyridin-3-ylboronic acid (0.150 g, 1.219 mmol), Pd(dbpf)Cl₂ (0.026 g, 0.041 mmol) and Na₂CO₃ (0.258 g, 2.437 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = 50 %) and concentrated to afford the desired compound (0.292 g, 81.1 %) as a yellow solid.

Step 2: Synthesis of compound 286

[0394] Methyl ((3R,5S)-3,5-dimethyl-4-(2-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)benzoate (formula 4-2, 0.060 g, 0.135 mmol), hydroxylamine (0.165 mL, 2.706 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.076 g, 1.353 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 286** (0.050 g, 83.8 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.58 - 8.57 (m, 2 H), 7.78 (d, 1 H, *J* = 7.9 Hz), 7.68 (d, 2 H, *J* = 8.1 Hz), 7.57 - 7.43 (m, 5 H), 7.30 (d, 2 H, *J* = 7.9 Hz), 4.31 - 4.29 (m, 1 H), 3.26 - 3.18 (m, 3 H), 2.23 (d, 1 H, *J* = 11.2 Hz), 1.37 - 1.35 (m, 1 H), 1.28 (d, 3 H, *J* = 6.7 Hz), 1.07 (d, 3 H, *J* = 6.7 Hz).

Example 126: Synthesis of compound 288

4-(((3R,5S)-4-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl 4-(((3R,5S)-4-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-carbonyl)-3,5-diethylpiperazin-1-yl)methyl)benzoate

[0395] 1,2-Dimethoxyethane/water (v/v=3/1) (3 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(2-iodobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-1, 0.400 g, 0.812 mmol), 2-(4,4-dimethylcyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.288 g, 1.219 mmol), Pd(dbpf)Cl₂ (0.026 g, 0.041 mmol) and Na₂CO₃ (0.258 g, 2.437 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 0 % to 10 %) and concentrated to afford the desired compound (0.143 g, 37.0 %) as a brown solid.

Step 2: Synthesis of compound 288

[0396] Methyl 4-(((3R,5S)-4-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-carbonyl)-3,5-diethylpiperazin-1-yl)methyl)benzoate (formula 4-3, 0.060 g, 0.126 mmol), hydroxylamine (0.155 mL, 2.528 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.071 g, 1.264 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 288** (0.047 g, 78.0 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.71 (d, 2 H, *J* = 8.0 Hz), 7.36 - 7.26 (m, 4 H), 7.21 - 7.19 (m, 2 H), 5.55 (s, 1 H), 4.48 (brs, 1 H), 3.50 - 3.47 (m, 2 H), 2.69 (d, 1 H, *J* = 11.0 Hz), 2.40 - 2.37 (m, 1 H), 2.12 - 1.98 (m, 3 H), 1.86 - 1.81 (m, 2 H), 1.41 - 1.38 (m, 2 H), 1.34 (d, 3 H, *J* = 6.6 Hz), 1.17 (d, 3 H, *J* = 6.6 Hz), 0.93 - 0.91 (m, 6 H).

Example 127: Synthesis of compound 290

(4-(((3R,5S)-3,5-dimethyl-4-(4-methylbenzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide(Trifluoroacetic acid salt))

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(4-methylbenzoyl)piperazin-1-yl)methyl)benzoate

[0397] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), 4-methylbenzoyl chloride (0.060 mL, 0.457 mmol) and TEA (0.077 g, 0.762 mmol) were dissolved in methylene chloride (1 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 3 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield the desired compound (0.078 g, 53.8 %) as a pale yellow solid.

Step 2: Synthesis of compound 290

[0398] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(4-methylbenzoyl)piperazin-1-yl)methyl)benzoate (formula 1-3, 0.050 g, 0.131 mmol), hydroxylamine (0.161 mL, 2.628 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.074 g, 1.314 mmol) were dissolved in methanol (0.5 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 1 hour. Then, a saturated solution of sodium hydrogen carbonate was added to the reaction solution, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, acetonitrile/0.1 % trifluoroacetic acid aqueous solution = from 5 % to 70 %) and concentrated to afford **compound 290** (0.019 g, 37.9 %) as a white solid.

¹H NMR (400 MHz, D₂O) δ 7.67 (d, 2 H, *J* = 8.4 Hz), 7.53 (d, 2 H, *J* = 8.3 Hz), 7.21 (d, 2 H, *J* = 7.8 Hz), 7.17 (d, 2 H, *J* = 8.2 Hz), 4.38 (s, 2 H), 3.20 (m, 4 H), 2.24 (s, 3 H), 1.29 (brs, 6 H).

Example 128: Synthesis of compound 291**(N-hydroxy-4-(((3R,5S)-4-(4-methoxybenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamide(Trifluoroacetic acid salt))****Step 1: Synthesis of methyl****4-(((3R,5S)-4-(4-methoxybenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0399] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), 4-methoxybenzoyl chloride (0.062 mL, 0.457 mmol) and TEA (0.077 g, 0.762 mmol) were dissolved in methylene chloride (1 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 3 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield the desired compound (0.088 g, 58.2 %) as a pale yellow solid.

Step 2: Synthesis of compound 291

[0400] Methyl 4-(((3R,5S)-4-(4-methoxybenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.050 g, 0.126 mmol), hydroxylamine (0.154 mL, 2.522 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.071 g, 1.261 mmol) were dissolved in methanol (0.5 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 1 hour. Then, a saturated solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, acetonitrile/0.1 % trifluoroacetic acid aqueous solution = from 5 % to 70 %) and concentrated to afford **compound 291** (0.023 g, 45.9 %) as a white solid.

¹H NMR (400 MHz, D₂O) δ 7.67 (d, 2 H, *J* = 8.4 Hz), 7.52 (d, 2 H, *J* = 8.3 Hz), 7.24 (d, 2 H, *J* = 8.8 Hz), 6.93 (d, 2 H, *J* = 8.8 Hz), 4.38 (s, 2 H), 3.73 (s, 3 H), 3.36 - 3.20 (m, 4 H), 1.29 (brs, 6 H).

Example 129: Synthesis of compound 292

4-(((3R,5S)-3,5-dimethyl-4-pivaloylpiperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)

Step 1: Synthesis of methyl 4-(((3R,5S)-3,5-dimethyl-4-pivaloylpiperazin-1-yl)methyl)benzoate

[0401] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), pivaloyl chloride (0.055 g, 0.457 mmol) and TEA (0.077 g, 0.762 mmol) were dissolved in methylene chloride (1 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 3 hours. Then, water was added to the reaction mixture, followed by

extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield the desired compound (0.105 g, 79.5 %) as a yellow oil.

Step 2: Synthesis of compound 292

[0402] Methyl 4-(((3R,5S)-3,5-dimethyl-4-pivaloylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.050 g, 0.144 mmol), hydroxylamine (0.177 mL, 2.886 mmol) and potassium hydroxide (0.081 g, 1.443 mmol) were dissolved in methanol (0.5 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 1 hour. Then, a saturated solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, acetonitrile/0.1 % trifluoroacetic acid aqueous solution = from 5 % to 70 %) and concentrated to afford the desired **compound 292** (0.018 g, 35.9 %) as a white solid.

¹H NMR (400 MHz, D₂O) δ 7.66 (d, 2 H, *J* = 8.3 Hz), 7.52 (d, 2 H, *J* = 8.2 Hz), 4.75 - 4.73 (m, 2 H), 4.35 (s, 2 H), 3.34 (m, 2 H), 3.13 (m, 2 H), 1.31 (brs, 6 H), 1.12 (s, 9 H).

Example 130: Synthesis of compound 293.

(4-(((3R,5S)-3,5-dimethyl-4-propionylpiperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt))

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-propionylpiperazin-1-yl)methyl)benzoate

[0403] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), propionyl chloride (0.042 g, 0.457 mmol) and TEA (0.077 g, 0.762 mmol) were dissolved in methylene chloride (1 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 3 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield the desired compound (0.113 g, 93.1 %) as a yellow oil.

Step 2: Synthesis of compound 293

[0404] Methyl 4-(((3R,5S)-3,5-dimethyl-4-propionylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.050 g, 0.157 mmol), hydroxylamine (0.192 mL, 3.141 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.088 g, 1.570 mmol) were dissolved in methanol (0.5 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 1 hour. Then, a saturated solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, acetonitrile/0.1 % trifluoroacetic acid aqueous solution = from 5 % to 70 %) and concentrated to afford **compound 293** (0.027 g, 53.8 %) as a white solid.

¹H NMR (400 MHz, D₂O) δ 7.66 (d, 2 H, *J* = 7.9 Hz), 7.52 (d, 2 H, *J* = 8.0 Hz), 4.75 - 4.73 (m, 2 H), 4.37 (s, 2 H), 3.40 - 3.37 (m, 2 H), 3.12 - 3.08 (m, 2 H), 2.42 - 2.27 (m, 2 H), 1.31 (brs, 6 H), 0.95 (t, 3 H, *J* = 11.6 Hz).

Example 131: Synthesis of compound 294

(4-(((3R,5S)-4-butyryl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt))

Step 1: Synthesis of methyl

4-(((3R,5S)-4-butyryl-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0405] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), butyryl chloride (0.049 g, 0.457 mmol) and TEA (0.077 g, 0.762 mmol) were dissolved in methylene chloride (1 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 3 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield the desired compound (0.077 g, 60.8 %) as a pale yellow oil.

Step 2: Synthesis of compound 294

[0406] Methyl 4-(((3R,5S)-4-butyryl-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.050 g, 0.150 mmol), hydroxylamine (0.184 mL, 3.008 mmol) and potassium hydroxide (0.084

g, 1.504 mmol) were dissolved in methanol (0.5 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 1 hour. Then, a saturated solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, acetonitrile/0.1 % trifluoroacetic acid aqueous solution = from 5 % to 70 %) and concentrated to afford **compound 294** (0.024 g, 47.9 %) as a white solid.

¹H NMR (400 MHz, D₂O) δ 7.67 (d, 2 H, *J* = 6.5 Hz), 7.52 (d, 2 H, *J* = 6.1 Hz), 4.73 - 4.71 (m, 2 H), 4.35 (s, 2 H), 3.40 - 3.37 (m, 2 H), 3.11 - 3.09 (m, 2 H), 2.35 - 2.23 (m, 2 H), 1.44 (q, 6 H, *J* = 14.8, 7.4 Hz), 1.33 (brs, 3 H), 1.22 (brs, 3 H), 0.77 (t, 3 H, *J* = 7.4 Hz).

Example 132: Synthesis of compound 295

4-(((3R,5S)-4-(cyclopropanecarbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide (Trifluoroacetic acid salt)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(cyclopropanecarbonyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0407] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), cyclopropanecarbonyl chloride (0.042 mL, 0.457 mmol) and TEA (0.077 g, 0.762 mmol) were dissolved in methylene chloride (1 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 3 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield the desired compound (0.105 g, 83.4 %) as a yellow oil.

Step 2: Synthesis of compound 295

[0408] Methyl 4-(((3R,5S)-4-(cyclopropanecarbonyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.050 g, 0.151 mmol), hydroxylamine (0.185 mL, 3.026 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.085 g, 1.513 mmol) were dissolved in methanol (0.5 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 1 hour. Then, a saturated solution of sodium hydrogen carbonate was added

to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, acetonitrile/0.1 % trifluoroacetic acid aqueous solution = from 5 % to 70 %) and concentrated to afford **compound 295** (0.021 g, 41.9 %) as a white solid.

¹H NMR (400 MHz, D₂O) δ 7.66 (d, 2 H, *J* = 8.2 Hz), 7.53 (d, 2 H, *J* = 8.2 Hz), 4.73 - 4.71 (m, 2 H), 4.38 (s, 2 H), 3.43 - 3.40 (m, 2 H), 3.14 - 3.12 (m, 2 H), 1.83 - 1.25 (m, 1 H), 1.28 (brs, 6 H), 0.79 - 0.75 (m, 4 H).

Example 133: Synthesis of compound 296

(N-hydroxy-4-(((3R,5S)-4-isobutyryl-3,5-dimethylpiperazin-1-yl)methyl)benzamide (Trifluoroacetic acid salt))

Step 1: Synthesis of methyl

4-(((3R,5S)-4-isobutyryl-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0409] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), isobutyryl chloride (0.048 mL, 0.457 mmol) and TEA (0.077 g, 0.762 mmol) were dissolved in methylene chloride (1 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 3 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield the desired compound (0.097 g, 76.5 %) as a yellow oil.

Step 2: Synthesis of compound 296

[0410] Methyl 4-(((3R,5S)-4-isobutyryl-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.050 g, 0.150 mmol), hydroxylamine (0.184 mL, 3.008 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.084 g, 1.504 mmol) were dissolved in methanol (0.5 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 1 hour. Then, a saturated solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters,

C₁₈, acetonitrile/0.1 % trifluoroacetic acid aqueous solution = from 5 % to 70 %) and concentrated to afford **compound 296** (0.025 g, 49.9 %) as a white solid.

¹H NMR (400 MHz, D₂O) δ 7.67 (d, 2 H, *J* = 8.2 Hz), 7.52 (d, 2 H, *J* = 8.2 Hz), 4.73 (m, 1 H), 4.49 (m, 1 H), 4.37 (s, 2 H), 3.41 - 3.38 (m, 2 H), 3.13 - 3.09 (m, 2 H), 2.83 - 2.79 (m, 1 H), 1.33 (brs, 3 H), 1.22 (brs, 3 H), 0.95 - 0.93 (m, 6 H).

Example 134: Synthesis of compound 297

4-(((3R,5S)-3,5-dimethyl-4-(3-methylbutanoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide(Trifluoroacetic acid salt)

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-methylbutanoyl)piperazin-1-yl)methyl)benzoate

[0411] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), 3-methylbutanoyl chloride (55 mg, 0.457 mmol) and TEA (0.077 g, 0.762 mmol) were dissolved in methylene chloride (1 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 3 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield the desired compound (0.078 g, 59.1 %) as a yellow oil.

Step 2: Synthesis of compound 297

[0412] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-methylbutanoyl)piperazin-1-yl)methyl)benzoate (formula 1-3, 0.050 g, 0.144 mmol), hydroxylamine (0.177 mL, 2.886 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.081 g, 1.443 mmol) were dissolved in methanol (0.5 ml) at 25 °C, and the reaction solution was stirred at the same temperature for 1 hour. Then, a saturated solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, acetonitrile/0.1 % trifluoroacetic acid aqueous solution = from 5 % to 70 %) and concentrated to afford the desired **compound 297** (0.021 g, 41.9 %) as a white solid.

¹H NMR (400 MHz, D₂O) δ 7.66 (d, 2 H, *J* = 8.3 Hz), 7.52 (d, 2 H, *J* = 8.3 Hz), 4.78 - 4.75 (m, 1

H), 4.44 - 4.43 (m, 1 H), 4.37 (s, 2 H), 3.40 - 3.38 (m, 2 H), 3.10 - 3.09 (m, 2 H), 2.32 - 2.08 (m, 2 H), 1.91 - 1.84 (m, 1 H), 1.32 (brs, 3 H), 1.25 (brs, 1 H), 0.82 - 0.72 (m, 6 H).

Example 135: Synthesis of compound 298

4-(((2S,6R)-2,6-dimethyl-4-(3-(trifluoromethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((2S,6R)-2,6-dimethyl-4-(3-(trifluoromethyl)benzyl)piperazin-1-yl)methyl)benzoate

[0413] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.200 g, 0.762 mmol), 3-(trifluoromethyl)benzaldehyde (0.133 g, 0.762 mmol) and acetic acid (0.022 mL, 0.762 mmol) were dissolved in 1,2-ethylene chloride (4 mL), and stirred at room temperature for 2 hours, and then Na(CN)BH₃ (0.048 g, 0.762 mmol) was added thereto, followed by stirring at the same temperature for 17 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 20 %) and concentrated to afford the desired compound (0.246 g, 76.7 %) as a colorless oil.

Step 2: Synthesis of compound 298

[0414] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(3-(trifluoromethyl)benzyl)piperazin-1-yl)methyl)benzoate (formula 13-3, 0.100 g, 0.238 mmol), hydroxylamine (0.291 mL, 4.757 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.133 g, 2.378 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure to yield **compound 298** (0.061 g, 60.9 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.67 - 7.56 (m, 6 H), 7.28 (d, 2 H, *J* = 8.2 Hz), 3.73 (s, 2 H), 3.50 (s, 2 H), 2.65 - 2.26 (m, 4 H), 1.85 (t, 2 H, *J* = 10.4 Hz), 0.91 (d, 6 H, *J* = 6.1 Hz); LRMS

(ES) m/z 422.1 ($M^+ + 1$).

Example 136: Synthesis of compound 299

4-(((2S,6R)-4-(4-(dimethylamino)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl 4-(((2S,6R)-4-(4-(dimethylamino)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0415] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol), 4-(dimethylamino)benzaldehyde (0.057 g, 0.381 mmol) and acetic acid (0.011 mL, 0.381 mmol) were dissolved in 1,2-ethylene chloride (4 mL), and stirred at room temperature for 2 hours, and then $\text{Na}(\text{CN})\text{BH}_3$ (0.024 g, 0.381 mmol) was added thereto, followed by stirring at the same temperature for 17 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 20 %) and concentrated to afford the desired compound (0.062 g, 41.1 %) as a colorless oil.

Step 2: Synthesis of compound 299

[0416] Methyl 4-(((2S,6R)-4-(4-(dimethylamino)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.062 g, 0.157 mmol), hydroxylamine (0.192 mL, 3.135 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.088 g, 1.567 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate (5 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 299** (0.041 g, 66.0 %) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.65 (d, 2 H, $J = 8.2$ Hz), 7.36 (d, 2 H, $J = 8.1$ Hz), 7.07 (d, 2 H, $J = 8.6$ Hz), 6.67 (d, 2 H, $J = 8.6$ Hz), 3.72 (s, 2 H), 3.27 (s, 2 H), 2.63 (d, 2 H, $J = 10.5$ Hz), 2.55 - 2.51 (m, 2 H), 1.73 (t, 2 H, $J = 10.6$ Hz), 0.87 (d, 6 H, $J = 6.1$ Hz); LRMS (ES) m/z 397.2 ($M^+ + 1$).

Example 137: Synthesis of compound 300

4-(((2S,6R)-2,6-dimethyl-4-(4-(methylsulfonyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide**Step 1: Synthesis of methyl****4-(((2S,6R)-2,6-dimethyl-4-(4-(methylsulfonyl)benzyl)piperazin-1-yl)methyl)benzoate**

[0417] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol), 4-(methylsulfonyl)benzaldehyde (0.070 g, 0.381 mmol) and acetic acid (0.011 mL, 0.381 mmol) were dissolved in 1,2-ethylene chloride (4 mL), and stirred at room temperature for 2 hours, and then Na(CN)BH₃ (0.024 g, 0.381 mmol) was added thereto, followed by stirring at the same temperature for 17 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 10 % to 70 %) and concentrated to afford the desired compound (0.058 g, 35.3 %) as a yellow oil.

Step 2: Synthesis of compound 300

[0418] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(4-(methylsulfonyl)benzyl)piperazin-1-yl)methyl)benzoate (formula 13-3, 0.058 g, 0.135 mmol), hydroxylamine (0.165 mL, 2.694 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.076 g, 1.347 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure to yield **compound 300** (0.015 g, 25.8 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.87 (d, 2 H, *J* = 8.2 Hz), 7.65 (d, 2 H, *J* = 8.1 Hz), 7.57 (d, 2 H, *J* = 8.1 Hz), 7.30 (d, 2 H, *J* = 8.0 Hz), 3.74 (s, 2 H), 3.52 (s, 2 H), 3.21 (s, 3 H), 2.65 (d, 2 H, *J* = 11.8 Hz), 2.60 - 2.56 (m, 2 H), 1.85 (t, 2 H, *J* = 10.4 Hz), 0.93 (d, 6 H, *J* = 6.8 Hz); LRMS (ES) *m/z* 432.2 (*M*⁺+1).

Example 138: Synthesis of compound 301

4-(((2S,6R)-4-(4-(1H-imidazol-1-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(4-(1H-imidazol-1-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0419] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol), 4-(1H-imidazol-1-yl)benzaldehyde (0.066 g, 0.381 mmol) and acetic acid (0.011 mL, 0.381 mmol) were dissolved in 1,2-ethylene chloride (4 mL), and stirred at room temperature for 2 hours, and then Na(CN)BH₃ (0.024 g, 0.381 mmol) was added thereto, followed by stirring at the same temperature for 17 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.065 g, 40.7 %) as a pale yellow oil.

Step 2: Synthesis of compound 301

[0420] Methyl 4-(((2S,6R)-4-(4-(1H-imidazol-1-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.065 g, 0.155 mmol), hydroxylamine (0.190 mL, 3.106 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.087 g, 1.553 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure to yield **compound 301** (0.037 g, 56.8 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.18 (brs, 1 H), 9.00 (brs, 1 H), 8.24 (s, 1 H), 7.74 (s, 1 H), 7.67 (d, 2 H, *J* = 8.0 Hz), 7.60 (d, 2 H, *J* = 8.3 Hz), 7.42 (d, 4 H, *J* = 8.0 Hz), 7.10 (s, 1 H), 3.86 (s, 2 H), 3.46 (s, 2 H), 2.68 (d, 2 H, *J* = 10.6 Hz), 2.60 - 2.58 (m, 2 H), 1.83 (t, 2 H, *J* = 10.6 Hz), 0.89 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 420.2 (M⁺+1).

Example 139: Synthesis of compound 302

4-(((2S,6R)-2,6-dimethyl-4-(4-(thiophen-2-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-2,6-dimethyl-4-(4-(thiophen-2-yl)benzyl)piperazin-1-yl)methyl)benzoate

[0421] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol), 4-(thiophen-2-yl)benzaldehyde (0.072 g, 0.381 mmol) and acetic acid (0.011 mL, 0.381 mmol) were dissolved in 1,2-ethylene chloride (4 mL), and stirred at room temperature for 2 hours, and then Na(CN)BH₃ (0.024 g, 0.381 mmol) was added thereto, followed by stirring at the same temperature for 17 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 20 %) and concentrated to afford the desired compound (0.022 g, 13.3 %) as a pale yellow oil.

Step 2: Synthesis of compound 302

[0422] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(4-(thiophen-2-yl)benzyl)piperazin-1-yl)methyl)benzoate (formula 13-3, 0.022 g, 0.051 mmol), hydroxylamine (0.062 mL, 1.012 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.028 g, 0.506 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure to yield **compound 302** (0.019 g, 86.2 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.65 (d, 2 H, *J* = 8.1 Hz), 7.61 (d, 2 H, *J* = 8.0 Hz), 7.53 (d, 1 H, *J* = 5.0 Hz), 7.49 (d, 1 H, *J* = 3.2 Hz), 7.33 - 7.31 (m, 4 H), 7.13 (dd, 1 H, *J* = 4.4, 4.4 Hz), 3.74 (s, 2 H), 3.41 (s, 2 H), 2.67 (d, 2 H, *J* = 9.5 Hz), 2.56 - 2.51 (m, 2 H), 1.82 (t, 2 H, *J* = 10.6 Hz), 0.90 (d, 6 H, *J* = 6.1 Hz); LRMS (ES) *m/z* 436.2 (M⁺+1).

Example 140: Synthesis of compound 303

4-(((2S,6R)-4-(4-(furan-2-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)**Step 1: Synthesis of methyl****4-(((2S,6R)-4-(4-(furan-2-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate**

[0423] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol), 4-(furan-2-yl)benzaldehyde (0.066 g, 0.381 mmol) and acetic acid (0.011 mL, 0.381 mmol) were dissolved in 1,2-ethylene chloride (4 mL), and stirred at room temperature for 2 hours, and then Na(CN)BH₃ (0.024 g, 0.381 mmol) was added thereto, followed by stirring at the same temperature for 17 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 20 %) and concentrated to afford the desired compound (0.053 g, 33.2 %) as a pale yellow oil.

Step 2: Synthesis of compound 303

[0424] Methyl 4-(((2S,6R)-4-(4-(furan-2-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.053 g, 0.127 mmol), hydroxylamine (0.155 mL, 2.533 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.071 g, 1.266 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate (5 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 303** (0.045 g, 84.7 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.74 (s, 1 H), 7.73 - 7.63 (m, 4 H), 7.33 (d, 2 H, *J* = 8.2 Hz), 7.26 (d, 2 H, *J* = 8.1 Hz), 6.91 (d, 1 H, *J* = 3.1 Hz), 6.59 (dd, 1 H, *J* = 3.4, 1.8 Hz), 3.72 (s, 2 H), 3.41 (s, 2 H), 2.65 (d, 2 H, *J* = 10.8 Hz), 2.56 - 2.55 (m, 2 H), 1.81 - 1.79 (m, 2 H), 0.91 (d, 6 H, *J* = 6.1 Hz); LRMS (ES) *m/z* 420.2 (*M*⁺+1).

Example 141: Synthesis of compound 304

4-(((2S,6R)-4-(4-(4H-1,2,4-triazol-4-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(4-(4H-1,2,4-triazol-4-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0425] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol), 4-(4H-1,2,4-triazol-4-yl)benzaldehyde (0.066 g, 0.381 mmol) and acetic acid (0.011 mL, 0.381 mmol) were dissolved in 1,2-ethylene chloride (4 mL), and stirred at room temperature for 2 hours, and then Na(CN)BH₃ (0.024 g, 0.381 mmol) was added thereto, followed by stirring at the same temperature for 17 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.064 g, 40.0 %) as a pale yellow oil.

Step 2: Synthesis of compound 304

[0426] Methyl 4-(((2S,6R)-4-(4-(4H-1,2,4-triazol-4-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-3, 0.064 g, 0.153 mmol), hydroxylamine (0.187 mL, 3.051 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.086 g, 1.526 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure to yield **compound 304** (0.016 g, 24.9 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.18 (brs, 1 H), 9.28 (s, 1 H), 9.00 (brs, 1 H), 8.23 (s, 1 H), 7.81 (d, 2 H, *J* = 8.5 Hz), 7.67 (d, 2 H, *J* = 8.2 Hz), 7.47 (d, 2 H, *J* = 8.5 Hz), 7.41 (d, 2 H, *J* = 8.4 Hz), 3.75 (s, 2 H), 3.47 (s, 2 H), 2.68 (d, 2 H, *J* = 10.2 Hz), 2.61 - 2.26 (m, 2 H), 1.84 (t, 2 H, *J* = 10.6 Hz), 0.89 (d, 6 H, *J* = 6.1 Hz); LRMS (ES) *m/z* 421.2 (M⁺+1).

Example 142: Synthesis of compound 305

4-(((2S,6R)-2,6-dimethyl-4-(2-(2-methyl-1H-imidazol-1-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-2,6-dimethyl-4-(2-(2-methyl-1H-imidazol-1-yl)benzyl)piperazin-1-yl)methyl)benzoate

[0427] Methyl 4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 13-2, 0.100 g, 0.381 mmol), 2-(2-methyl-1H-imidazol-1-yl)benzaldehyde (0.071 g, 0.381 mmol) and acetic acid (0.011 mL, 0.381 mmol) were dissolved in 1,2-ethylene chloride (4 mL), and stirred at room temperature for 2 hours, and then Na(CN)BH₃ (0.024 g, 0.381 mmol) was added thereto, followed by stirring at the same temperature for 17 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.066 g, 40.0 %) as a pale yellow oil.

Step 2: Synthesis of compound 305

[0428] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(2-(2-methyl-1H-imidazol-1-yl)benzyl)piperazin-1-yl)methyl)benzoate (formula 13-3, 0.066 g, 0.153 mmol), hydroxylamine (0.187 mL, 3.052 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.086 g, 1.526 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate (5 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 305** (0.036 g, 54.4 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.66 (d, 2 H, *J* = 8.2 Hz), 7.56 (dd, 1 H, *J* = 7.6, 1.5 Hz), 7.49 (ddd, 1 H, *J* = 7.5, 7.5, 1.4 Hz), 7.43 (dt, 1 H, *J* = 7.5, 7.5, 1.7 Hz), 7.37 (d, 2 H, *J* = 8.2 Hz), 7.31 (dd, 1 H, *J* = 7.7, 1.2 Hz), 7.15 (d, 1 H, *J* = 1.3 Hz), 6.91 (d, 1 H, *J* = 1.2 Hz), 3.75 (s, 2 H), 3.12 - 3.04 (m, 2 H), 2.48 - 2.46 (m, 4 H), 2.05 (s, 3 H), 1.68 (t, 2 H, *J* = 10.7 Hz), 0.85 (d, 6 H, *J* = 7.0 Hz); LRMS (ES) *m/z* 434.2 (M⁺+1).

Example 143: Synthesis of compound 309

4-(((3R,5S)-4-(4-(furan-3-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(4-(furan-3-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0429] 1,2-Dimethoxyethane (1 ml) / water (0.5 ml) were added to a mixture of methyl 4-(((3R,5S)-4-(4-iodobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-1, 0.100 g, 0.209 mmol), furan-3-ylboronic acid (0.028 g, 0.251 mmol), Pd(dbpf)Cl₂ (0.007 g, 0.010 mmol) and Na₂CO₃ (0.066 g, 0.627 mmol) at room temperature, and heated by microwaves at 120 °C for 20 minutes. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.052 g, 59.4 %) as a pale brown solid.

Step 2: Synthesis of compound 309

[0430] Methyl 4-(((3R,5S)-4-(4-(furan-3-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-2, 0.030 g, 0.072 mmol), hydroxylamine (0.088 mL, 1.434 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.040 g, 0.717 mmol) were dissolved in methanol (0.5 mL) at room temperature, and the mixture was stirred at the same temperature for 1 hour. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield **compound 309** (0.021 g, 69.8 %) as a pale orange solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.15 (s, 1 H), 7.73 (s, 1 H), 7.65 (d, 2 H, *J* = 8.1 Hz), 7.55 (d, 2 H, *J* = 8.1 Hz), 7.31 - 7.27 (m, 4 H), 3.72 (s, 1 H), 3.39 (s, 2 H), 2.67 - 2.64 (m, 2 H), 2.58 - 2.56 (m, 2 H), 1.83 - 1.73 (m, 2 H), 0.90 (s, 3 H), 0.88 (s, 3 H).

Example 144: Synthesis of compound 321

((2S,6R)-N-(3-(1H-pyrrol-1-yl)phenyl)-4-(4-((E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)benzyl)-2,6-dimethylpiperazine-1-carboxamide)

Step 1: Synthesis of (E)-methyl**3-(4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)phenyl)acrylate**

[0431] (2S,6R)-2,6-dimethylpiperazine (0.500 g, 4.379 mmol), (E)-methyl 3-(4-(bromomethyl)phenyl)acrylate (formula 8-4, 1.173 g, 4.598 mmol) and Cs_2CO_3 (2.140 g, 6.568 mmol) were dissolved in acetonitrile (10 mL) at room temperature, and the reaction solution was stirred at the same temperature for 5 hours. Then, the reaction mixture was filtered through a glass filter to remove solids, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; methanol/methylene chloride = from 0 % to 15 %) and concentrated to afford the desired compound (1.090 g, 86.3 %) as an orange solid.

Step 2: Synthesis of (E)-methyl**3-(4-(((3R,5S)-4-((3-(1H-pyrrol-1-yl)phenyl)carbamoyl)-3,5-dimethylpiperazin-1-yl)methyl)phenyl)acrylate**

[0432] (E)-methyl 3-(4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 9-1, 0.050 g, 0.173 mmol) and TEA (0.036 mL, 0.260 mmol) were dissolved in methylene chloride (2 mL), and 1-(3-isocyanatophenyl)-1H-pyrrole (0.034 g, 0.182 mmol) was added thereto at 0 °C, followed by stirring at the same temperature for 1 hour and 40 minutes. Then, the reaction mixture was filtered through a celite pad to remove solids, and water was added to the filtrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 40 %) and concentrated to afford the desired compound (0.050 g, 61.0 %) as a white solid.

Step 3: Synthesis of compound 321

[0433] (E)-methyl 3-(4-(((3R,5S)-4-((3-(1H-pyrrol-1-yl)phenyl)carbamoyl)-3,5-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 9-2, 0.050 g, 0.106 mmol), hydroxylamine (0.129 mL, 2.116 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.059 g, 1.058 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction

mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure to yield **compound 321** (0.048 g, 95.8 %) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 9.90 (brs, 1 H), 8.41 (s, 1 H), 7.73 - 7.72 (m, 1 H), 7.52 (d, 1 H, $J = 7.7$ Hz), 7.42 - 7.28 (m, 6 H), 7.24 (dd, 2 H, $J = 2.1, 2.1$ Hz), 7.12 (dd, 1 H, $J = 7.9, 1.3$ Hz), 6.45 (d, 1 H, $J = 15.9$ Hz), 6.26 (dd, 1 H, $J = 2.1, 2.1$ Hz), 4.24 (t, 2 H, $J = 5.0$ Hz), 3.53 (s, 2 H), 2.69 (d, 2 H, $J = 11.1$ Hz), 2.14 (d, 2 H, $J = 7.4$ Hz), 1.31 (d, 6 H, $J = 6.6$ Hz); LRMS (ES) m/z 474.2 ($M^+ + 1$).

Example 145: Synthesis of compound 322

((E)-3-(4-(((3R,5S)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide)

Step 1: Synthesis of (E)-methyl

3-(4-(((3R,5S)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)phenyl)acrylate

[0434] (E)-methyl 3-(4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 9-1, 0.050 g, 0.173 mmol) and TEA (0.036 mL, 0.260 mmol) were dissolved in methylene chloride (2 mL), and furan-2-carbonyl chloride (0.018 mL, 0.182 mmol) was added thereto at 0 °C, followed by stirring at the same temperature for 1 hour and 30 minutes. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 20 %) and concentrated to afford the desired compound (0.053 g, 79.9 %) as a colorless oil.

Step 2: Synthesis of compound 322

[0435] (E)-methyl 3-(4-(((3R,5S)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 9-2, 0.053 g, 0.139 mmol), hydroxylamine (0.170 mL, 2.772 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.078 g, 1.386 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced

pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure to yield **compound 322** (0.027 g, 50.8 %) as a pale yellow solid.

^1H NMR (400 MHz, DMSO- d_6) δ 9.50 (brs, 1 H), 7.82 (s, 1 H), 7.46 (d, 2 H, J = 7.8 Hz), 7.34 (d, 2 H, J = 7.8 Hz), 7.10 (d, 1 H, J = 15.7 Hz), 6.95 (s, 1 H), 6.61 (d, 1 H, J = 1.5 Hz), 6.39 (d, 1 H, J = 15.8 Hz), 4.49 - 4.48 (m, 2 H), 3.50 (s, 2 H), 2.70 (d, 2 H, J = 11.0 Hz), 2.12 (d, 2 H, J = 7.2 Hz), 1.37 (d, 6 H, J = 6.2 Hz); LRMS (ES) m/z 384.1 (M^+ +1).

Example 146: Synthesis of compound 323

((E)-3-(4-(((3R,5S)-3,5-dimethyl-4-(2-phenylacetyl)piperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide)

Step 1: Synthesis of ((E)-methyl

3-(4-(((3R,5S)-3,5-dimethyl-4-(2-phenylacetyl)piperazin-1-yl)methyl)phenyl)acrylate

[0436] (E)-methyl 3-(4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 9-1, 0.050 g, 0.173 mmol) and TEA (0.036 mL, 0.260 mmol) were dissolved in methylene chloride (2 mL), and 2-phenylacetyl chloride (0.024 mL, 0.182 mmol) was added thereto at 0 °C, followed by stirring at the same temperature for 2 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 30 %) and concentrated to afford the desired compound (0.037 g, 52.5 %) as a colorless oil.

Step 2: Synthesis of compound 323

[0437] (E)-methyl 3-(4-(((3R,5S)-3,5-dimethyl-4-(2-phenylacetyl)piperazin-1-yl)methyl)phenyl)acrylate (formula 9-2, 0.037 g, 0.091 mmol), hydroxylamine (0.111 mL, 1.820 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.051 g, 0.910 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen

carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure to yield **compound 323** (0.021 g, 56.6 %) as a pale yellow solid.

^1H NMR (400 MHz, D_2O) δ 9.90 (brs, 1 H), 7.48 (d, 2 H, $J = 8.0$ Hz), 7.35 (d, 2 H, $J = 8.1$ Hz), 7.32 - 7.28 (m, 2 H), 7.23 - 7.17 (m, 4 H), 6.41 (d, 1 H, $J = 15.8$ Hz), 4.42 (s, 1 H), 4.11 (s, 1 H), 3.77 (d, 1 H, $J = 13.8$ Hz), 3.62 (d, 1 H, $J = 15.9$ Hz), 3.48 (s, 2 H), 2.68 - 2.62 (m, 2 H), 2.01 (d, 2 H, $J = 8.0$ Hz), 0.88 - 0.85 (m, 6 H); LRMS (ES) m/z 408.2 ($\text{M}^+ + 1$).

Example 147: Synthesis of compound 326

4-(((3R,5S)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0438] 1,2-Dimethoxyethane/water (v/v=3/1) (3 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(2-iodobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-1, 0.400 g, 0.812 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.256 g, 1.219 mmol), $\text{Pd}(\text{dbpf})\text{Cl}_2$ (0.026 g, 0.041 mmol) and Na_2CO_3 (0.258 g, 2.437 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 0 % to 20 %) and concentrated to afford the desired compound (0.098 g, 26.8 %) as a brown oil.

Step 2: Synthesis of compound 326

[0439] Methyl 4-(((3R,5S)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-2, 0.098 g, 0.218 mmol), hydroxylamine (0.267 mL, 4.370 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.123 g, 2.185 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the

same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 326** (0.010 g, 9.7 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.69 (d, 2 H, *J* = 8.1 Hz), 7.41 - 7.23 (m, 6 H), 5.81 (s, 1 H), 4.49 (br, 1 H), 4.15 - 4.14 (m, 2 H), 3.78 (t, 2 H, *J* = 5.4 Hz), 3.49 (s, 2 H), 2.71 - 2.68 (m, 2 H), 2.15 - 2.02 (m, 3 H), 1.34 (d, 3 H, *J* = 6.7 Hz), 1.13 (d, 3 H, *J* = 6.7 Hz).

Example 148: Synthesis of compound 327

(4-(((3R,5S)-4-(2-(furan-2-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(2-(furan-2-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0440] 1,2-Dimethoxyethane/water (v/v=3/1) (2 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(2-iodobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-1, 0.250 g, 0.523 mmol), furan-2-ylboronic acid (0.088 g, 0.784 mmol), Pd(dbpf)Cl₂ (0.017 g, 0.026 mmol) and Na₂CO₃ (0.166 g, 1.568 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/ hexane = from 0 % to 10 %) and concentrated to afford the desired compound (0.066 g, 30.0 %) as a brown oil.

Step 2: Synthesis of compound 327

[0441] Methyl 4-(((3R,5S)-4-(2-(furan-2-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-2, 0.066 g, 0.157 mmol), hydroxylamine (0.192 mL, 3.140 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.088 g, 1.570 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 327** (0.044 g, 66.5 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.95 (d, 1 H, *J* = 7.7 Hz), 7.80 (s, 1 H), 7.70 (d, 2 H, *J* = 8.1 Hz), 7.56 - 7.54 (m, 1 H), 7.33 - 7.23 (m, 4 H), 6.71 (d, 1 H, *J* = 3.3 Hz), 6.64 - 6.62 (m, 1 H), 3.79 (s, 2 H), 2.69 - 2.60 (m, 4 H), 1.85 (t, 2 H, *J* = 10.4 Hz), 0.76 (d, 6 H, *J* = 6.0 Hz).

Example 149: Synthesis of compound 328

4-(((3R,5S)-4-(2-(furan-3-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(2-(furan-3-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0442] 1,2-Dimethoxyethane/water (v/v=3/1) (2 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(2-iodobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-1, 0.250 g, 0.523 mmol), furan-3-ylboronic acid (0.088 g, 0.784 mmol), Pd(dbpf)Cl₂ (0.017 g, 0.026 mmol) and Na₂CO₃ (0.166 g, 1.568 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/ hexane = from 0 % to 5 %) and concentrated to afford the desired compound (0.020 g, 9.3 %) as a brown oil.

Step 2: Synthesis of compound 328

[0443] Methyl 4-(((3R,5S)-4-(2-(furan-3-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-2, 0.020 g, 0.049 mmol), hydroxylamine (0.060 mL, 0.975 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.027 g, 0.487 mmol) were dissolved in methanol (1 mL) at room temperature, and the reaction solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 328** (0.010 g, 50.9 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.85 - 7.84 (m, 2 H), 7.76 - 7.76 (m, 1 H), 7.69 (d, 2 H, *J* = 8.1 Hz), 7.28 (t, 4 H, *J* = 8.0 Hz), 7.19 (t, 1 H, *J* = 7.5 Hz), 6.76 - 6.75 (m, 1 H), 3.69 (s, 2 H), 2.65 (d, 2 H, *J* = 10.3 Hz), 2.58 - 2.55 (m, 2 H), 1.84 (t, 2 H, *J* = 10.5 Hz), 0.76 (d, 1 H, *J* = 6.1 Hz).

Example 150: Synthesis of compound 329**4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide****Step 1: Synthesis of methyl****4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-4-yl)benzyl)piperazin-1-yl)methyl)benzoate**

[0444] 1,2-Dimethoxyethane/water (v/v=3/1) (2 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(2-iodobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-1, 0.250 g, 0.523 mmol), pyridine-4-boronic acid hydrate (0.110 g, 0.784 mmol), Pd(dbpf)Cl₂ (0.017 g, 0.026 mmol) and Na₂CO₃ (0.166 g, 1.568 mmol) at room temperature, and the reaction solution was stirred overnight at 100 °C. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 20 % to 60 %) and concentrated to afford the desired compound (0.139 g, 62.1 %) as a white solid.

Step 2: Synthesis of compound 329

[0445] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-4-yl)benzyl)piperazin-1-yl)methyl)benzoate (formula 2-2, 0.088 g, 0.204 mmol), hydroxylamine (0.250 mL, 4.083 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.115 g, 2.042 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 329** (0.076 g, 86.1 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.65 - 8.63 (m, 2 H), 7.85 (d, 1 H, *J* = 7.7 Hz), 7.69 (d, 2 H, *J* = 8.2 Hz), 7.43 - 7.38 (m, 3 H), 7.32 - 7.27 (m, 3 H), 7.18 - 7.16 (m, 1 H), 3.58 (s, 2 H), 2.58 (d, 2 H, *J* = 10.2 Hz), 2.44 - 2.43 (m, 2 H), 1.82 (t, 2 H, *J* = 10.4 Hz), 0.75 (d, 6 H, *J* = 6.2 Hz).

Example 151: Synthesis of compound 330

4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)benzoate

[0446] 1,2-Dimethoxyethane/water (v/v=3/1) (2 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(2-iodobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-1, 0.250 g, 0.523 mmol), pyridin-3-ylboronic acid (0.096 g, 0.784 mmol), Pd(dbpf)Cl₂ (0.017 g, 0.026 mmol) and Na₂CO₃ (0.166 g, 1.568 mmol) at room temperature, and the reaction solution was stirred overnight at 100 °C. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction solution, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 20 % to 60 %) and concentrated to afford the desired compound (0.083 g, 36.8 %) as a yellow oil.

Step 2: Synthesis of compound 330

[0447] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)benzoate (formula 2-2, 0.083 g, 0.192 mmol), hydroxylamine (0.235 mL, 3.841 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.108 g, 1.921 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 1 hour. Then, the reaction solution was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried. The resulting material was purified by column chromatography (Waters, C₁₈, C₁₉*100 column, 0.1 % trifluoroacetic acid aqueous solution/acetonitrile = from 5 % to 80 %), after which the compound was passed through a cartridge (PL-HCO₃ MP resin, methanol), and then concentrated to afford **compound 330** (0.012 g, 14.5 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.61 - 8.59 (m, 1 H), 8.55 (d, 1 H, *J* = 2.1 Hz), 7.82 (dd, 2 H, *J* = 13.4, 4.8 Hz), 7.68 (d, 2 H, *J* = 8.1 Hz), 7.50 - 7.47 (m, 1 H), 7.40 (t, 1 H, *J* = 7.0 Hz), 7.38 - 7.26 (m, 3 H), 7.18 - 7.16 (m, 1 H), 3.56 (s, 2 H), 2.58 (d, 2 H, *J* = 10.0 Hz), 2.46 - 2.43 (m, 2 H), 1.82 (t, 2 H, *J* = 10.4 Hz), 0.75 (d, 6 H, *J* = 6.2 Hz).

Example 152: Synthesis of compound 331

4-(((3R,5S)-4-((4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)-3,5-di

methylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-((4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)-3,5-di
methylpiperazin-1-yl)methyl)benzoate

[0448] 1,2-Dimethoxyethane/water (v/v=3/1) (2 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(2-iodobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-1, 0.250 g, 0.523 mmol), 2-(4,4-dimethylcyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.185 g, 0.784 mmol), Pd(dbpf)Cl₂ (0.017 g, 0.026 mmol) and Na₂CO₃ (0.166 g, 1.568 mmol) at room temperature, and the reaction solution was heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction solution, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 0 % to 5 %) and concentrated to afford the desired compound (0.044 g, 18.4 %) as a white solid.

Step 2: Synthesis of compound 331

[0449] Methyl 4-(((3R,5S)-4-((4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)-3,5-di methylpiperazin-1-yl)methyl)benzoate (formula 2-2, 0.044 g, 0.096 mmol), hydroxylamine (0.118 mL, 1.928 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.054 g, 0.964 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 331** (0.038g, 85.9 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.67 (d, 3 H, *J* = 8.1 Hz), 7.22 - 7.20 (m, 3 H), 7.10 (t, 1 H, *J* = 7.2 Hz), 5.40 (s, 1 H), 3.60 (s, 2 H), 2.64 (d, 2 H, *J* = 10.4 Hz), 2.16 (s, 2 H), 1.94 (s, 2 H), 1.82 (t, 2 H, *J* = 10.5 Hz), 1.47 (t, 2 H, *J* = 6.2 Hz), 1.00 (s, 6 H), 0.78 (d, 6 H, *J* = 6.1 Hz).

Example 153: Synthesis of compound 332

4-(((3R,5S)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl

yl)benzoate

[0450] 1,2-Dimethoxyethane/water (v/v=3/1) (2 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(2-iodobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-1, 0.250 g, 0.523 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.165 g, 0.784 mmol), Pd(dbpf)Cl₂ (0.017 g, 0.026 mmol) and Na₂CO₃ (0.166 g, 1.568 mmol) at 100 °C, and the reaction solution was stirred overnight at the same temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/ hexane = from 0 % to 20 %) and concentrated to afford the desired compound (0.108 g, 47.6 %) as a pale brown solid.

Step 2: Synthesis of compound 332

[0451] Methyl 4-(((3R,5S)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-2, 0.108 g, 0.249 mmol), hydroxylamine (0.304 mL, 4.970 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.139 g, 2.485 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried. The resulting material was purified by column chromatography (Waters, C₁₈, C₁₉*100 column, 0.1 % trifluoroacetic acid aqueous solution/acetonitrile = from 5 % to 80 %), after which the compound was passed through a cartridge (PL-HCO₃ MP resin, methanol), and then concentrated to afford **compound 332** (0.017g, 15.3 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.73 - 7.68 (m, 3 H), 7.29 - 7.20 (m, 3 H), 7.14 (t, 1 H, *J* = 6.9 Hz), 7.04 - 7.02 (m, 1 H), 5.60 (s, 1 H), 4.19 - 4.19 (m, 2 H), 3.82 (t, 2 H, *J* = 5.3 Hz), 3.64 (s, 2 H), 2.66 - 2.57 (m, 4 H), 2.26 (s, 2 H), 1.84 (t, 2 H, *J* = 10.3 Hz), 0.79 - 0.78 (m, 6 H).

Example 154: Synthesis of compound 340

(4-(((3R,5S)-4-(4-(furan-2-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(4-bromobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0452] 4-Bromobenzoyl chloride (1.000 g, 4.557 mmol), methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 1.315 g, 5.012 mmol) and TEA (1.263 mL, 9.113 mmol) were dissolved in methylene chloride (20 mL) at room temperature, and the reaction solution was stirred at the same temperature for 2 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; ethyl acetate/hexane = from 30 % to 50 %) and concentrated to afford the desired compound (2.007 g, 98.9 %) as a white solid.

Step 2: Synthesis of methyl

4-(((3R,5S)-4-(4-(furan-2-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0453] 1,2-Dimethoxyethane/water (v/v=3/1) (4 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(4-bromobenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-1, 0.500 g, 1.123 mmol), furan-2-ylboronic acid (0.138 g, 1.235 mmol), Pd(dbpf)Cl₂ (0.037g, 0.056mmol) and Na₂CO₃ (0.262g, 2.470 mmol), and heated by microwave irradiation at 120 °C for 30 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by

column chromatography (silicon dioxide; ethyl acetate/ hexane = from 0 % to 20 %) and concentrated to afford the desired compound (0.163 g, 33.5 %) as a white solid.

Step 3: Synthesis of compound 340

[0454] Methyl 4-(((3R,5S)-4-(4-(furan-2-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 4-2, 0.100 g, 0.231 mmol), hydroxylamine (0.283 mL, 4.624 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.130 g, 2.312 mmol) were dissolved in methanol (4 mL) at room temperature, and the reaction solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 340** (0.049g, 48.7 %) as a pale yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.85 (d, 1 H, *J* = 7.7 Hz), 7.76 - 7.71 (m, 4 H), 7.40 - 7.36 (m, 3 H), 7.24 (d, 1 H, *J* = 7.9 Hz), 7.01 (d, 1 H, *J* = 3.0 Hz), 6.60 - 6.59 (m, 1 H), 3.51 - 3.47 (m, 2 H), 2.62 - 2.60 (m, 2 H), 2.15 - 2.09 (m, 2 H), 1.27 (brs, 6 H).

Example 155: Synthesis of compound 342

4-(((3R,5S)-4-(3-(furan-2-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-(furan-2-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0455] 1,2-Dimethoxyethane (4 mL) / water (1 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(3-iodobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-1, 0.100 g, 0.209 mmol), furan-2-ylboronic acid (0.047 g, 0.418 mmol), Pd(dppf)₂Cl₂ (0.007 g, 0.010 mmol) and Na₂CO₃ (0.044 g, 0.418 mmol), and heated by microwave irradiation at 120 °C for 20 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, 19*100 mm column, 0.1 % trifluoroacetic acid/ acetonitrile = from 5 % to 80 %) and concentrated. The resulting material

was dissolved in a solvent, and the compound was passed through a cartridge (PL-HCO₃ MP resin, methanol only), and then concentrated to afford the desired compound (0.064 g, 73.2 %) as a brown oil.

Step 2: Synthesis of compound 342

[0456] Methyl 4-(((3R,5S)-4-(3-(furan-2-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (compound 2-2, 0.064 g, 0.153 mmol), hydroxylamine (0.094 mL, 1.529 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.172 g, 3.058 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure to yield **compound 342** (0.031 g, 48.3 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.10 (brs, 1 H), 9.00 (brs, 1 H), 7.75 (d, 1 H, *J* = 1.3 Hz), 7.69 (d, 2 H, *J* = 7.8 Hz), 7.66 (s, 1 H), 7.52 (d, 1 H, *J* = 7.5 Hz), 7.35 - 7.31 (m, 3 H), 7.28 (d, 1 H, *J* = 7.5 Hz), 6.90 (d, 1 H, *J* = 3.0 Hz), 6.58 (dd, 1 H, *J* = 3.4, 1.8 Hz), 3.75 (s, 2 H), 3.44 (s, 2 H), 2.66 - 2.57 (m, 4 H), 1.83 (t, 2 H, *J* = 10.5 Hz), 0.91 (d, 6 H, *J* = 6.1 Hz); LRMS (ES) *m/z* 420.2 (*M*⁺+1).

Example 156: Synthesis of compound 343

(4-(((3R,5S)-4-(3-(furan-3-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-(furan-2-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0457] 1,2-Dimethoxyethane (4 mL) / water (1 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(3-iodobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-1, 0.100 g, 0.209 mmol), furan-3-ylboronic acid (0.047 g, 0.418 mmol), Pd(dppf)₂Cl₂ (0.007 g, 0.010 mmol) and Na₂CO₃ (0.044 g, 0.418 mmol), and heated by microwave irradiation at 120 °C for 20 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of

sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, 19*100 mm column, 0.1 % trifluoroacetic acid/ acetonitrile = from 5 % to 80 %) and concentrated. The resulting material was dissolved in a solvent, and the compound was passed through a cartridge (PL-HCO₃ MP resin, methanol only), and then concentrated to afford the desired compound (0.061 g, 69.7 %) as a brown oil.

Step 2: Synthesis of compound 343

[0458] Methyl 4-(((3R,5S)-4-(3-(furan-3-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-2, 0.061 g, 0.146 mmol), hydroxylamine (0.089 mL, 1.457 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.164 g, 2.915 mmol) were dissolved in methanol (2 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 100 %) and concentrated to afford **compound 343** (0.008 g, 13.1 %) as a white solid.

¹H NMR (400 MHz, CH₃OD) δ 7.89 - 7.89 (m, 1 H), 7.72 (d, 2 H, *J* = 8.2 Hz), 7.57 (dd, 1 H, *J* = 1.6, 1.6 Hz), 7.54 (s, 1 H), 7.44 (d, 3 H, *J* = 7.9 Hz), 7.33 - 7.30 (m, 2 H), 6.80 - 6.79 (m, 1 H), 3.95 (s, 2 H), 3.54 (s, 2 H), 2.77 - 2.17 (m, 4 H), 1.97 (t, 2 H, *J* = 10.8 Hz), 1.13 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 420.2 (*M*⁺+1).

Example 157: Synthesis of compound 344

(4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)benzoate

[0459] 1,2-Dimethoxyethane (4 mL) / water (1 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(3-iodobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-1, 0.100 g, 0.209 mmol), pyridin-3-ylboronic acid (0.051 g, 0.418 mmol), Pd(dbpf)₂ Cl₂ (0.007g, 0.010 mmol) and Na₂CO₃ (0.044 g, 0.418 mmol), and heated by microwave irradiation at 120 °C for 20 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, 19*100 mm column, 0.1 % trifluoroacetic acid/acetonitrile = from 5 % to 80 %) and concentrated. The resulting material was dissolved in a solvent, and the compound was passed through a cartridge (PL-HCO₃ MP resin, methanol only), and then concentrated to afford the desired compound (0.085 g, 94.7 %) as a colorless oil.

Step 2: Synthesis of compound 344

[0460] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)benzoate (formula 2-2, 0.085 g, 0.198 mmol), hydroxylamine (0.121 mL, 1.979 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.222 g, 3.958 mmol) were dissolved in methanol (3 mL) at room temperature, and the reaction solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter equipped with an anhydrous sodium sulfate cartridge to remove solid residue and an aqueous layer, and the filtrate was concentrated under reduced pressure to yield **compound 344** (0.055 g, 64.6 %) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 8.86 (d, 1 H, *J* = 1.9 Hz), 8.58 (d, 1 H, *J* = 3.4 Hz), 8.04 (d, 1 H, *J* = 7.8 Hz), 7.68 (d, 3 H, *J* = 8.1 Hz), 7.54 - 7.48 (m, 2 H), 7.43 (d, 2 H, *J* = 4.8 Hz), 7.26 (d, 2 H, *J* = 8.0 Hz), 3.81 (s, 2 H), 3.41 (s, 2 H), 2.66 (d, 2 H, *J* = 11.0 Hz), 2.63 - 2.59 (m, 2 H), 1.82 (t, 2 H, *J* = 10.2 Hz), 0.93 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 431.2 (M⁺+1).

Example 158: Synthesis of compound 345

(4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-4-yl)benzyl)piperazin-1-yl)methyl)benzoate

[0461] 1,2-Dimethoxyethane (4 mL) / water (1 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(3-iodobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-1, 0.100 g, 0.209 mmol), pyridin-4-ylboronic acid (0.051 g, 0.418 mmol), Pd(dbpf)₂ Cl₂ (0.007 g, 0.010 mmol) and Na₂CO₃ (0.044 g, 0.418 mmol), and heated by microwave irradiation at 120 °C for 20 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, 19*100 mm column, 0.1 % trifluoroacetic acid/acetonitrile = from 5 % to 80 %) and concentrated. The resulting material was dissolved in a solvent, and the compound was passed through a cartridge (PL-HCO₃ MP resin, methanol only), and then concentrated to afford the desired compound (0.088 g, 98.0 %) as a colorless oil.

Step 2: Synthesis of compound 345

[0462] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-4-yl)benzyl)piperazin-1-yl)methyl)benzoate (formula 4-2, 0.040 g, 0.093 mmol), hydroxylamine (0.031 g, 0.931 mmol) and potassium hydroxide (0.105 g, 1.862 mmol) were mixed in methanol (3 mL) at room temperature, and the mixture was stirred at the same temperature for 30 minutes. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and was then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford **compound 345** (0.005 g, 12.5 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.64 (d, 2 H, *J* = 5.2 Hz), 7.74 (s, 1 H), 7.62 - 7.61 (m, 5 H), 7.47 - 7.45 (m, 2 H), 7.25 (d, 2 H, *J* = 7.8 Hz), 3.82 (s, 2 H), 3.41 (s, 2 H), 2.68 - 2.61 (m, 4 H), 1.83 (t, 2 H, *J* = 9.9 Hz), 0.92 (d, 6 H, *J* = 5.8 Hz); LRMS (ES) *m/z* 431.2 (M⁺+1).

Example 159: Synthesis of compound 346**(4-(((3R,5S)-4-(3-(3,6-dihydro-2H-pyran-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)****Step 1: Synthesis of methyl**

4-(((3R,5S)-4-(3-(3,6-dihydro-2H-pyran-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0463] 1,2-Dimethoxyethane (4 mL) / water (1 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(3-iodobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-1, 0.100 g, 0.209 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.088 g, 0.418 mmol), Pd(dbpf)₂Cl₂ (0.007 g, 0.010 mmol) and Na₂CO₃ (0.044 g, 0.418 mmol), and heated by microwave irradiation at 120 °C for 20 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, 19*100 mm column, 0.1 % trifluoroacetic acid/acetonitrile = from 5 % to 80 %) and concentrated. The resulting material was dissolved in a solvent, and the compound was passed through a cartridge (PL-HCO₃ MP resin, methanol only), and then concentrated to afford the desired compound (0.068 g, 74.9 %) as a pale brown oil.

Step 2: Synthesis of compound 346

[0464] Methyl 4-(((3R,5S)-4-(3-(3,6-dihydro-2H-pyran-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-2, 0.068 g, 0.156 mmol), hydroxylamine (0.096 mL, 1.565 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.176 g, 3.130 mmol) were mixed in methanol (3 mL) at room temperature, and the mixture was stirred at the same temperature for 30 minutes. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and was then concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, 19*100 mm column, 0.1 % trifluoroacetic acid/acetonitrile = from 5 % to 80 %) and concentrated. The resulting material was dissolved in a solvent, and the compound was passed through a cartridge (PL-HCO₃ MP resin, 100 % methanol), and then concentrated to afford **compound 346** (0.005 g, 7.3 %) as an apricot solid.

¹H NMR (400 MHz, CH₃OD) δ 7.72 (d, 2 H, *J* = 8.2 Hz), 7.42 (d, 3 H, *J* = 8.4 Hz), 7.31 - 7.28 (m, 3 H), 6.17 (t, 1 H, *J* = 1.5 Hz), 4.32 - 4.30 (m, 2 H), 3.95 - 3.92 (m, 4 H), 3.52 (s, 2 H), 2.75 - 2.69 (m, 4 H), 2.39 - 2.52 (m, 2 H), 1.94 (t, 2 H, *J* = 11.2 Hz), 1.11 (d, 6 H, *J* = 6.1 Hz); LRMS (ES) *m/z* 436.2 (M⁺+1).

Example 160: Synthesis of compound 347

4-(((3R,5S)-4-((4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-yl)methyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-4-((4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-yl)methyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0465] 1,2-Dimethoxyethane (4 mL) / water (1 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(3-iodobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-1, 0.100 g, 0.209 mmol), 2-(4,4-dimethylcyclo-1-hexenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.099 g, 0.418 mmol), Pd(dbpf)₂Cl₂ (0.007 g, 0.010 mmol) and Na₂CO₃ (0.044 g, 0.418 mmol), and heated by microwave irradiation at 120 °C for 20 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and the organic layer was concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈, 19*100 mm column, 0.1 % trifluoroacetic acid/acetonitrile = from 5 % to 80 %) and concentrated. The resulting material was dissolved in a solvent, and the compound was passed through a cartridge (PL-HCO₃ MP resin, methanol only), and then concentrated to afford the desired compound (0.064 g, 66.5 %) as a brown oil.

Step 2: Synthesis of compound 347

[0466] Methyl 4-(((3R,5S)-4-((4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-yl)methyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-2, 0.064 g, 0.139 mmol), hydroxylamine (0.085 mL, 1.389 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.156 g, 2.779 mmol) were mixed in methanol (3 mL) at room temperature, and the mixture was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 347** (0.020 g, 31.2 %) as an orange solid.

¹H NMR (400 MHz, CH₃OD) δ 7.72 (d, 2 H, *J* = 8.1 Hz), 7.43 (d, 2 H, *J* = 8.0 Hz), 7.40 (s, 1 H), 7.28 - 7.23 (m, 3 H), 6.06 (s, 1 H), 3.93 (s, 2 H), 3.52 (s, 2 H), 2.76 - 2.69 (m, 4 H), 2.45 - 2.45

(m, 2 H), 2.03 - 2.02 (m, 2 H), 1.95 (t, 2 H, $J = 10.6$ Hz), 1.57 (t, 2 H, $J = 6.4$ Hz), 1.13 (d, 6 H, $J = 6.0$ Hz), 1.00 (s, 6 H); LRMS (ES) m/z 462.3 ($M^+ + 1$).

Example 161: Synthesis of compound 348

(4-(((2S,6R)-4-(2-(furan-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(2-(furan-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0467] 1,2-Dimethoxyethane (4 mL) / water (1 mL) were added to a mixture of methyl 4-(((2S,6R)-4-(2-iodobenzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 14-1, 0.100 g, 0.209 mmol), furan-3-ylboronic acid (0.047 g, 0.418 mmol), $\text{Pd}(\text{dbpf})_2 \text{Cl}_2$ (0.007g, 0.010 mmol) and Na_2CO_3 (0.044 g, 0.418 mmol), and heated by microwave irradiation at 120 °C for 20 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and was then concentrated under reduced pressure. The product was used without additional purification (0.090 g, 102.9 %, crude).

Step 2: Synthesis of compound 348

[0468] Methyl 4-(((2S,6R)-4-(2-(furan-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 14-2, 0.090 g, 0.215 mmol), hydroxylamine (0.132 mL, 2.150 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.241 g, 4.301 mmol) were mixed in methanol (3 mL) at room temperature, and the mixture was stirred at the same temperature for 30 minutes. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/ methylene chloride = from 0 % to 15 %) and concentrated to afford **compound 348** (0.023 g, 25.5 %) as a pale orange solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.13 (s, 1 H), 8.98 (s, 1 H), 8.99 (d, 1 H, $J = 1.6$ Hz), 7.98 - 7.98 (m, 1 H), 7.76 (dd, 1 H, $J = 1.7, 1.7$ Hz), 7.67 (d, 2 H, $J = 8.6$ Hz), 7.44 - 7.39 (m, 4 H),

7.33 - 7.29 (m, 2 H), 6.84 (dd, 1 H, $J = 1.8, 0.7$ Hz), 3.75 (s, 2 H), 3.37 (s, 2 H), 2.68 (d, 2 H, $J = 10.7$ Hz), 1.85 - 1.84 (m, 2 H), 0.89 (d, 6 H, $J = 6.1$ Hz).

Example 162: Synthesis of compound 349

4-(((2S,6R)-2,6-dimethyl-4-(2-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((2S,6R)-2,6-dimethyl-4-(2-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)benzoate

[0469] 1,2-Dimethoxyethane (4 mL)/water (1 mL) were added to a mixture of methyl 4-(((2S,6R)-4-(2-iodobenzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 14-1, 0.100 g, 0.209 mmol), pyridin-3-ylboronic acid (0.051 g, 0.418 mmol), $\text{Pd}(\text{dbpf})_2 \text{Cl}_2$ (0.007 g, 0.010 mmol) and Na_2CO_3 (0.044 g, 0.418 mmol), and heated by microwave irradiation at 120 °C for 20 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and was then concentrated under reduced pressure. The product was used without additional purification (0.090 g, 100.2 %).

Step 2: Synthesis of compound 349

[0470] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(2-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)benzoate (formula 14-2, 0.090 g, 0.210 mmol), hydroxylamine (0.128 mL, 2.095 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.235 g, 4.190 mmol) were mixed in methanol (3 mL) at room temperature, and the mixture was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, and the precipitated solid was filtered and dried to yield **compound 349** (0.041 g, 45.5 %) as an apricot solid..

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.60 - 8.56 (m, 2 H), 7.86 (d, 1 H, $J = 7.6$ Hz), 7.65 (d, 2 H, $J = 7.6$ Hz), 7.49 - 7.38 (m, 4 H), 7.35 (d, 2 H, $J = 7.9$ Hz), 7.28 (d, 1 H, $J = 6.5$ Hz), 3.70 (s, 2 H), 3.30 (s, 2 H), 2.50 - 2.48 (m, 4 H), 1.72 (t, 2 H, $J = 10.2$ Hz), 0.83 (d, 6 H, $J = 5.9$ Hz); LRMS (ES) m/z 431.2 ($\text{M}^+ + 1$).

Example 163: Synthesis of compound 350**4-(((2S,6R)-2,6-dimethyl-4-(2-(pyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)****Step 1: Synthesis of methyl****4-(((2S,6R)-2,6-dimethyl-4-(2-(pyridine-4-yl)benzyl)piperazin-1-yl)methyl)benzoate**

[0471] 1,2-Dimethoxyethane (3 mL) / water (1 mL) were added to a mixture of methyl 4-(((2S,6R)-4-(2-iodobenzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 14-1, 0.100 g, 0.209 mmol), pyridin-4-ylboronic acid (0.051 g, 0.418 mmol), Pd(dbpf)₂ Cl₂ (0.007 g, 0.010 mmol) and Na₂CO₃ (0.044 g, 0.418 mmol), and heated by microwave irradiation at 120 °C for 20 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was passed through a plastic filter to remove solid residue and an aqueous layer, and was then concentrated under reduced pressure. The product was used without additional purification (0.090 g, 100.2 %).

Step 2: Synthesis of compound 350

[0472] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(2-(pyridine-4-yl)benzyl)piperazin-1-yl)methyl)benzoate (formula 14-2, 0.090 g, 0.210 mmol), hydroxylamine (0.128 mL, 2.095 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.235 g, 4.190 mmol) were mixed in methanol (3 mL) at room temperature, and the mixture was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 15 %) and concentrated to afford **compound 350** (0.026 g, 28.8 %) as a pale orange solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.52 (d, 2 H, *J* = 6.1 Hz), 7.70 (d, 2 H, *J* = 8.2 Hz), 7.49 (d, 2 H, *J* = 6.4 Hz), 7.50 - 7.47 (m, 5 H), 7.42 - 7.40 (m, 2 H), 7.29 - 7.27 (m, 1 H), 3.85 (s, 2 H), 3.42 (s, 2 H), 2.56 (d, 2 H, *J* = 10.6 Hz), 2.47 - 2.46 (m, 2 H), 1.79 (t, 2 H, *J* = 10.7 Hz), 0.97 (d, 6 H, *J* = 6.2 Hz).

Example 164: Synthesis of compound 351**4-(((2S,6R)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide****Step 1: Synthesis of methyl****4-(((2S,6R)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate**

[0473] 1,2-Dimethoxyethane (3 mL) / water (1 mL) were added to a mixture of methyl 4-(((2S,6R)-4-(2-iodobenzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 14-1, 0.100 g, 0.209 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.088 g, 0.418 mmol), Pd(dbpf)₂Cl₂ (0.007 g, 0.010 mmol) and Na₂CO₃ (0.044 g, 0.418 mmol), and heated by microwave irradiation at 120 °C for 20 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 60 %) and concentrated to afford the desired compound (0.017 g, 18.7 %) as a pale yellow oil.

Step 2: Synthesis of compound 351

[0474] Methyl 4-(((2S,6R)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 14-2, 0.017 g, 0.039 mmol), hydroxylamine (0.024 mL, 0.391 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.044 g, 0.782 mmol) were mixed in methanol (1 mL) at room temperature, and the mixture was stirred at the same temperature for 30 minutes. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter equipped with an anhydrous sodium sulfate cartridge to remove solid residue and an aqueous layer, and was then concentrated under reduced pressure to yield **compound 351** (0.012 g, 70.4 %) as a white solid.

¹H-NMR (400 MHz, CD₃OD) δ 7.71 (d, 2 H, *J* = 8.3 Hz), 7.49 (d, 2 H, *J* = 8.3 Hz), 7.38 - 7.37 (m, 1 H), 7.24 - 7.22 (m, 2 H), 7.12 - 7.11 (m, 1 H), 5.61 (s, 1 H), 4.26 - 4.24 (m, 2 H), 3.90 - 3.87 (m, 4 H), 3.48 (s, 2 H), 2.70 (d, 2 H, *J* = 11.0 Hz), 2.69 - 2.64 (m, 2 H), 2.36 - 2.35 (m, 2

H), 1.90 (t, 2 H, $J = 10.9$ Hz), 1.03 (d, 6 H, $J = 6.1$ Hz); LRMS (ES) m/z 436.2 ($M^+ + 1$).

Example 165: Synthesis of compound 352

4-(((2S,6R)-4-((4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((2S,6R)-4-((4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0475] 1,2-Dimethoxyethane (3 mL) / water (1 mL) were added to a mixture of methyl 4-(((2S,6R)-4-(2-iodobenzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 14-1, 0.100 g, 0.209 mmol), 2-(4,4-dimethylcyclo-1-hexenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.099 g, 0.418 mmol), $\text{Pd}(\text{dbpf})_2\text{Cl}_2$ (0.007 g, 0.010 mmol) and Na_2CO_3 (0.044 g, 0.418 mmol), and heated by microwave irradiation at 120 °C for 20 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 10 %) and concentrated to afford the desired compound (0.013 g, 13.5 %) as a pale yellow oil.

Step 2: Synthesis of compound 352

[0476] Methyl 4-(((2S,6R)-4-((4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 14-2, 0.013 g, 0.028 mmol), hydroxylamine (50.00 % aqueous solution, 0.017 mL, 0.282 mmol) and potassium hydroxide (0.032 g, 0.564 mmol) were mixed in methanol (1 mL) at room temperature, and the mixture was stirred at the same temperature for 30 minutes. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by PTLC (silicon dioxide; 100 % ethyl acetate) and concentrated to afford **compound 352** (0.007 g, 53.7 %) as an orange solid.

$^1\text{H-NMR}$ (400 MHz, CD_3OD) δ 7.71 (d, 2 H, $J = 7.1$ Hz), 7.49 (d, 2 H, $J = 6.9$ Hz), 7.37 - 7.36

(m, 1 H), 7.20 - 7.18 (m, 2 H), 7.07 - 7.04 (m, 1 H), 5.43 (s, 1 H), 3.91 (s, 2 H), 3.48 (s, 2 H), 2.72 - 2.66 (m, 4 H), 2.24 (s, 2 H), 1.96 (s, 2 H), 1.88 (t, 2 H, $J = 10.4$ Hz), 1.50 (t, 2 H, $J = 6.2$ Hz), 1.03 (d, 12 H, $J = 3.9$ Hz); LRMS (ES) m/z 462.2 ($M^+ + 1$).

Example 166: Synthesis of compound 354

(4-(((3R,5S)-3,5-dimethyl-4-(oxazol-4-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of oxazol-4-ylmethyl methanesulfonate

[0477] Oxazol-4-ylmethanol (0.300 g, 3.028 mmol) and TEA (0.633 mL, 4.541 mmol) were mixed in methylene chloride (5 mL) at 0 °C, and MsCl (0.258 mL, 3.330 mmol) was added to the mixture, followed by stirring at the same temperature. Water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 50 %) and concentrated to afford the desired compound (0.119 g, 22.2 %) as an orange oil.

Step 2: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(oxazol-4-ylmethyl)piperazin-1-yl)methyl)benzoate

[0478] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.150 g, 0.572 mmol), oxazol-4-ylmethyl methanesulfonate (0.111 g, 0.629 mmol) and Cs_2CO_3 (0.279 g, 0.858 mmol) were added to N,N-dimethylformamide (3 mL) at 80 °C, and the mixture was stirred at the same temperature for 17 hours. Then, the reaction mixture was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 15 %) and concentrated to afford the desired compound (0.054 g, 27.5 %) as a pale yellow oil.

Step 3: Synthesis of compound 354

[0479] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(oxazol-4-ylmethyl)piperazin-1-yl)methyl)benzoate (formula 1-3, 0.054 g, 0.157 mmol), hydroxylamine (0.096 mL, 1.572 mmol, 50.00 % aqueous

solution) and potassium hydroxide (0.176 g, 3.145 mmol) were mixed in methanol (1 mL) at room temperature, and the mixture was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter equipped with an anhydrous sodium sulfate cartridge to remove solid residue and an aqueous layer, and was then concentrated under reduced pressure to afford **compound 354** (0.003 g, 5.5 %) as a yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.16 (s, 1 H), 7.92 (s, 1 H), 7.72 (d, 2 H, *J* = 8.1 Hz), 7.41 (d, 2 H, *J* = 8.0 Hz), 3.98 (s, 2 H), 3.51 (s, 2 H), 2.73 (d, 2 H, *J* = 11.8 Hz), 2.70 - 2.66 (m, 2 H), 1.93 (t, 2 H, *J* = 10.8 Hz), 1.19 (d, 6 H, *J* = 6.1 Hz); LRMS (ES) *m/z* 345.2 (*M*⁺+1).

Example 167: Synthesis of compound 355

4-(((3R,5S)-3,5-dimethyl-4-(pyrimidin-5-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(pyrimidin-5-ylmethyl)piperazin-1-yl)methyl)benzoate

[0480] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.200 g, 0.762 mmol), 5-(chloromethyl)pyrimidine (0.108 g, 0.839 mmol) and Cs₂CO₃ (0.373 g, 1.144 mmol) were added to N,N-dimethylformamide (3 mL) at room temperature, and the mixture was stirred at 120 °C for 48 hours. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and water was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 15 %) and concentrated to afford the desired compound (0.027 g, 10.0 %) as a yellow solid.

Step 2: Synthesis of compound 355

[0481] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(pyrimidin-5-ylmethyl)piperazin-1-yl)methyl)benzoate (formula 1-3, 0.027 g, 0.076 mmol), hydroxylamine (0.047 mL, 0.762 mmol, 50.00 % aqueous

solution) and potassium hydroxide (0.085 g, 1.523 mmol) were mixed in methanol (1 mL) at room temperature, and the mixture was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter equipped with an anhydrous sodium sulfate cartridge to remove solid residue and an aqueous layer, and was then concentrated under reduced pressure to afford **compound 355** (0.003 g, 11.1 %) as a pale yellow solid.

^1H NMR (400 MHz, CH_3OD) δ 9.03 (s, 1 H), 8.83 (s, 1 H), 7.74 (d, 2 H, $J = 8.3$ Hz), 7.46 (d, 2 H, $J = 8.3$ Hz), 3.92 (s, 2 H), 3.56 (s, 2 H), 2.78 (d, 2 H, $J = 10.7$ Hz), 2.72 - 2.68 (m, 2 H), 1.97 (t, 2 H, $J = 10.8$ Hz), 0.93 (d, 6 H, $J = 6.6$ Hz); LRMS (ES) m/z 356.1 ($\text{M}^+ + 1$).

Example 168: Synthesis of compound 356

4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0482] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.500 g, 1.906 mmol), 3-(bromomethyl)benzaldehyde (0.417 g, 2.096 mmol) and Cs_2CO_3 (0.931 g, 2.859 mmol) were mixed in acetonitrile (20 mL) at room temperature, and the mixture was stirred at the same temperature for 17 hours. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and water was added to the resulting concentrate, followed by extraction with ethyl acetate. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; 12 g cartridge; ethyl acetate/hexane = from 0 % to 60 %) and concentrated to afford the desired compound (0.530 g, 73.1 %) as a pale brown oil.

Step 2: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)benzoate

[0483] Methyl 4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.200 g, 0.526 mmol), morpholine (0.050 mL, 0.578 mmol) and acetic acid (0.015 mL, 0.526 mmol) were mixed in tetrahydrofuran (5 mL) at room temperature and the mixture was stirred. Then, $\text{Na}(\text{CN})\text{BH}_3$ (0.033 g, 0.526 mmol) was added to the mixture, followed by stirring at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; 4 g cartridge; ethyl acetate/hexane = from 20 % to 100 %) and concentrated to afford the desired compound (0.109 g, 45.9 %) as a colorless oil.

Step 3: Synthesis of compound 356

[0484] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)benzoate (formula 5-2, 0.050 g, 0.111 mmol), hydroxylamine (0.135 mL, 2.214 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.072 g, 1.107 mmol) were mixed in methanol (2 mL) at room temperature, and the mixture was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter equipped with an anhydrous sodium sulfate cartridge to remove solid residue and an aqueous layer, and was then concentrated under reduced pressure to afford **compound 356** (0.034 g, 67.9 %) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.66 (d, 2 H, $J = 8.0$ Hz), 7.27 - 7.22 (m, 5 H), 7.10 (s, 1 H), 3.71 (s, 2 H), 3.55 (s, 4 H), 3.44 (s, 2 H), 3.39 (s, 2 H), 2.63 (d, 2 H, $J = 10.5$ Hz), 2.57 - 2.55 (m, 2 H), 2.32 (s, 4 H), 1.78 (t, 2 H, $J = 10.5$ Hz), 0.89 (d, 6 H, $J = 6.0$ Hz); LRMS (ES) m/z 453.2 ($\text{M}^+ + 1$).

Example 169: Synthesis of compound 376

(4-(((3R,5S)-3,5-dimethyl-4-(4-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(4-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0485] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.200 g, 0.762 mmol), 4-(bromomethyl)benzaldehyde (0.167 g, 0.839 mmol) and Cs_2CO_3 (0.373 g, 1.144 mmol) were mixed in acetonitrile (5 mL) at room temperature, and the mixture was stirred at the same temperature for 17 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 5 % to 70 %) and concentrated to afford the desired compound (0.131 g, 45.2 %) as a pale yellow oil.

Step 2: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(4-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)benzoate

[0486] Methyl 4-(((3R,5S)-4-(4-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.131 g, 0.344 mmol) and morpholine (0.033 g, 0.379 mmol) were mixed in methylene chloride (4 mL) at room temperature, and the mixture was stirred for 30 minutes. Then, $\text{Na}(\text{OAc})_3\text{BH}$ (0.109g, 0.516 mmol) was added thereto, followed by stirring at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.134 g, 86.2 %) as a pale yellow oil.

Step 3: Synthesis of compound 376

[0487] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(4-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)benzoate (formula 5-2, 0.134 g, 0.297 mmol), hydroxylamine (0.181 mL, 2.967 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.386 g, 5.934 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 376** (0.030 g, 22.3 %) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.18 (brs, 1 H), 9.04 (brs, 1 H), 7.70 (d, 2 H, $J = 8.2$ Hz), 7.35

(d, 2 H, $J = 8.1$ Hz), 7.28 (d, 2 H, $J = 8.0$ Hz), 7.21 (d, 2 H, $J = 8.0$ Hz), 3.71 (s, 2 H), 3.56 (t, 4 H, $J = 4.4$ Hz), 3.43 (s, 2 H), 3.41 (s, 2 H), 2.63 (d, 2 H, $J = 10.4$ Hz), 2.58 - 2.53 (m, 2 H), 2.32 (s, 4 H), 1.80 (t, 2 H, $J = 10.4$ Hz), 0.90 (d, 6 H, $J = 6.1$ Hz); LRMS (ES) m/z 453.2 ($M^+ + 1$).

Example 170: Synthesis of compound 380

(4-(((3R,5S)-4-(3-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of tert-butyl

4-((3-(hydroxymethyl)phenoxy)methyl)piperidine-1-carboxylate

[0488] 3-(hydroxymethyl)phenol (0.500 g, 4.028 mmol), tert-butyl 4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate (formula 12-1, 1.300 g, 4.430 mmol), Cs_2CO_3 (1.968 g, 6.042 mmol) and NaI (0.030 g, 0.201 mmol) were mixed in acetonitrile (50 mL) at room temperature, and the mixture was heated under reflux for 5 hours, and then cooled to room temperature. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of NaCl, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; ethyl acetate/hexane = from 10 % to 60 %) and concentrated to afford the desired compound (0.790 g, 61.0 %) as a colorless oil.

Step 2: Synthesis of tert-butyl

4-((3-(hydroxymethyl)phenoxy)methyl)piperidine-1-carboxylate

[0489] Tert-butyl 4-((3-(hydroxymethyl)phenoxy)methyl)piperidine-1-carboxylate (formula 12-2, 0.500 g, 1.556 mmol) and TEA (0.434 mL, 3.111 mmol) were mixed in methylene chloride (50 mL) at 0 °C, and MsCl (0.132 mL, 1.711 mmol) was added to the mixture. Next, the mixture was stirred at the same temperature for 1 hour, and then stirred at room temperature for 1 hour. Water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 40 %) and

concentrated to afford the desired compound (0.204 g, 38.6 %) as a colorless oil.

Step 3: Synthesis of tert-butyl

4-(((3-(((2S,6R)-4-(4-(methoxycarbonyl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenoxy)methyl)piperidine-1-carboxylate

[0490] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.150 g, 0.572 mmol), tert-butyl 4-((3-(chloromethyl)phenoxy)methyl)piperidine-1-carboxylate (formula 12-3, 0.194 g, 0.572 mmol) and Cs_2CO_3 (0.279g, 0.858 mmol) were mixed in acetonitrile (10 mL) at room temperature, and the mixture was heated under reflux for 5 hours, and then cooled to room temperature. Water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 10 % to 70 %) and concentrated to afford the desired compound (0.181 g, 56.0 %) as a pale yellow oil.

Step 4: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-(piperidin-4-ylmethoxy)benzyl)piperazin-1-yl)methyl)benzoate

[0491] Tert-butyl 4-(((3-(((2S,6R)-4-(4-(methoxycarbonyl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenoxy)methyl)piperidine-1-carboxylate (formula 12-4, 0.180 g, 0.318 mmol) was added to 1,4-dioxane (5 mL) at room temperature, and HCl (4.00 M 1,4-dioxane solution, 0.795 mL, 3.182 mmol) was added to the mixture, which was then stirred at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The product was used without additional purification (0.141 g, 95.2 %, pale yellow oil).

Step 5: Synthesis of ethyl

4-(((3R,5S)-4-(3-((1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)methoxy)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0492] Ethanol (4 mL) were added to mixture of methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-(piperidin-4-ylmethoxy)benzyl)piperazin-1-yl)methyl)benzoate (formula 12-5, 0.150 g, 0.322 mmol), 2,2-dimethyloxirane (0.044 mL, 0.483 mmol) and K_2CO_3 (0.089 g, 0.644 mmol), and heated by microwave irradiation at 110 °C for 20 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.091 g, 52.5 %) as a colorless oil.

Step 6: Synthesis of ethyl

4-(((3R,5S)-4-(3-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0493] Ethyl 4-(((3R,5S)-4-(3-((1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)methoxy)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 12-6, 0.090 g, 0.163 mmol) was dissolved in methylene chloride (5 mL), and DAST (0.029 g, 0.179 mmol) was added thereto at 0 °C. The mixture was stirred at the same temperature for 30 minutes, and then stirred at room temperature for 1 hour. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 8 g cartridge; ethyl acetate/hexane = from 0 % to 50 %) and concentrated to afford the desired compound (0.088 g, 97.4 %) as a pale brown oil.

Step 7: Synthesis of compound 380

[0494] Ethyl 4-(((3R,5S)-4-(3-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 12-7, 0.088 g, 0.159 mmol), hydroxylamine (0.097 mL, 1.589 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.207 g, 3.178 mmol) were dissolved in methanol (10 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 380**

(0.027 g, 31.4 %) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 7.70 (d, 2 H, J = 8.1 Hz), 7.34 (d, 2 H, J = 8.1 Hz), 7.18 (dd, 1 H, J = 8.0, 8.0 Hz), 6.91 - 6.89 (m, 2 H), 6.73 (d, 1 H, J = 8.5 Hz), 3.78 (d, 2 H, J = 5.4 Hz), 3.68 (s, 2 H), 3.51 (s, 2 H), 2.91 (d, 2 H, J = 11.3 Hz), 2.64 (d, 2 H, J = 10.8 Hz), 2.58 - 2.56 (m, 2 H), 2.41 (d, 2 H, J = 22.9 Hz), 2.07 (t, 2 H, J = 10.8 Hz), 1.81 (t, 2 H, J = 10.6 Hz), 1.71 (d, 3 H, J = 11.5 Hz), 1.33 (s, 3 H), 1.28 - 1.24 (m, 5 H), 0.89 (d, 6 H, J = 6.0 Hz); LRMS (ES) m/z 541.3 ($M^+ + 1$).

Example 171: Synthesis of compound 382

4-(((3R,5S)-3,5-dimethyl-4-(3-(piperidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-(piperidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)benzoate

[0495] Methyl 4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.150 g, 0.394 mmol) and piperidine (0.038 mL, 0.434 mmol) were dissolved in methylene chloride (10 mL), and the solution was stirred at room temperature for 30 minutes. $\text{Na}(\text{OAc})_3\text{BH}$ (0.125 g, 0.591 mmol) was added to the reaction solution, followed by stirring at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.095 g, 53.6 %) as a pale yellow oil.

Step 2: Synthesis of compound 382

[0496] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-(piperidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)benzoate (formula 5-2, 0.044 g, 0.098 mmol), hydroxylamine (0.060 mL, 0.979 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.127 g, 1.957 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen

carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 382** (0.037g, 83.9 %) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 7.68 (d, 2 H, J = 8.2 Hz), 7.30 - 7.28 (m, 3 H), 7.22 - 7.20 (m, 2 H), 7.08 (d, 1 H, J = 6.2 Hz), 3.72 (s, 2 H), 3.41 (s, 2 H), 3.40 (s, 2 H), 2.65 - 2.62 (m, 2 H), 2.58 - 2.53 (m, 2 H), 2.29 (s, 4 H), 1.80 (t, 2 H, J = 10.7 Hz), 1.49 - 1.46 (m, 4 H), 1.40 - 1.38 (m, 2 H), 0.90 (d, 6 H, J = 6.1 Hz); LRMS (ES) m/z 451.2 ($M^+ + 1$).

Example 172: Synthesis of compound 383

4-(((3R,5S)-4-(3-(((R)-3-fluoropyrrolidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-(((R)-3-fluoropyrrolidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0497] Methyl 4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.150 g, 0.394 mmol) and (R)-3-fluoropyrrolidine hydrochloride (0.054 g, 0.434 mmol) were dissolved in methylene chloride (10 mL), and the solution was stirred at room temperature for 30 minutes. $\text{Na}(\text{OAc})_3\text{BH}$ (0.125 g, 0.591 mmol) was added to the reaction solution, which was then stirred at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.120 g, 67.1 %) as a pale yellow oil.

Step 2: Synthesis of compound 383

[0498] Methyl 4-(((3R,5S)-4-(3-(((R)-3-fluoropyrrolidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-2, 0.060 g, 0.132 mmol), hydroxylamine (0.081 mL, 1.323 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.172 g, 2.646

mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 383** (0.048 g, 79.8 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.58 (brs, 1 H), 7.67 (d, 2 H, *J* = 8.0 Hz), 7.28 - 7.17 (m, 5 H), 7.11 (s, 1 H), 5.18 (d, 1 H, *J* = 55.7 Hz), 3.72 (s, 2 H), 3.39 (s, 2 H), 2.80 - 2.71 (m, 2 H), 2.64 (d, 2 H, *J* = 10.5 Hz), 2.60 - 2.55 (m, 2 H), 2.31 - 2.27 (m, 1 H), 2.17 - 1.89 (m, 2 H), 1.79 (t, 2 H, *J* = 10.4 Hz), 0.89 (d, 6 H, *J* = 5.9 Hz).

Example 173: Synthesis of compound 384

4-(((3R,5S)-4-(3-((3,3-difluoroazetidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-((3,3-difluoroazetidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0499] Methyl 4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.150 g, 0.394 mmol) and 3,3-difluoroazetidine hydrochloride (0.056 g, 0.434 mmol) were dissolved in methylene chloride (4 mL), and the solution was stirred at room temperature for 30 minutes. Na(OAc)₃BH (0.125 g, 0.591 mmol) was added to the reaction solution, which was then stirred at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.131 g, 72.6 %) as a pale yellow oil.

Step 2: Synthesis of compound 384

[0500] Methyl 4-(((3R,5S)-4-(3-((3,3-difluoroazetidin-1-yl)methyl)benzyl)-3,5-

dimethylpiperazin-1-yl)methyl)benzoate (formula 5-2, 0.058 g, 0.127 mmol), hydroxylamine (0.078 mL, 1.268 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.165 g, 2.535 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with ethyl acetate. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 384** (0.037 g, 63.7 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.69 (d, 2 H, *J* = 8.2 Hz), 7.32 (d, 2 H, *J* = 8.2 Hz), 7.27 - 7.24 (m, 3 H), 7.11 - 7.10 (m, 1 H), 3.72 (s, 2 H), 3.70 (s, 2 H), 3.58 (t, 4 H, *J* = 12.5 Hz), 3.43 (s, 2 H), 2.65 - 2.63 (m, 2 H), 2.59 - 2.53 (m, 2 H), 1.81 (t, 2 H, *J* = 10.6 Hz), 0.89 (d, 6 H, *J* = 6.1 Hz); LRMS (ES) *m/z* 459.2 (*M*⁺+1).

Example 174: Synthesis of compound 385

4-(((3R,5S)-4-(3-((4-benzylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-((4-benzylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0501] Methyl 4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.150 g, 0.394 mmol) and 1-benzylpiperazine (0.076 g, 0.434 mmol) were dissolved in methylene chloride (4 mL), and the solution was stirred at room temperature for 30 minutes. Na(OAc)₃BH (0.125 g, 0.591 mmol) was added to the reaction solution, which was then stirred at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.158 g, 74.1 %) as a pale yellow oil.

Step 2: Synthesis of compound 385

[0502] Methyl 4-(((3R,5S)-4-(3-((4-benzylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl) methyl)benzoate (formula 5-2, 0.095 g, 0.176 mmol), hydroxylamine (0.107 mL, 1.757 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.229 g, 3.514 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 385** (0.084 g, 88.3 %) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 7.67 (d, 2 H, J = 8.2 Hz), 7.33 - 7.22 (m, 10 H), 7.09 - 7.07 (m, 1 H), 3.71 (s, 2 H), 3.45 (s, 2 H), 3.44 (s, 2 H), 3.40 (s, 2 H), 2.65 - 2.62 (m, 2 H), 2.56 - 2.52 (m, 2 H), 2.37 - 2.34 (m, 8 H), 1.79 (t, 2 H, J = 10.5 Hz), 0.89 (d, 6 H, J = 5.9 Hz); LRMS (ES) m/z 542.3 ($M^+ + 1$).

Example 175: Synthesis of compound 386

(N-hydroxy-4-(((3R,5S)-4-(3-((4-(2-hydroxy-2-methylpropyl)piperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamide)

Step 1: Synthesis of tert-butyl

4-(3-(((2S,6R)-4-(4-(methoxycarbonyl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzyl)piperazine-1-carboxylate

[0503] Methyl 4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.500 g, 1.314 mmol) and tert-butyl piperazine-1-carboxylate (0.269 g, 1.446 mmol) were dissolved in methylene chloride (10 mL), and the solution was stirred at room temperature for 30 minutes. $\text{Na}(\text{OAc})_3\text{BH}$ (0.418 g, 1.971 mmol) was added to the reaction solution, which was then stirred at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.303 g, 41.9 %) as a yellow oil.

Step 2: Synthesis of methyl**4-(((3R,5S)-3,5-dimethyl-4-(3-(piperazin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)benzoate**

[0504] Tert-butyl 4-(3-(((2S,6R)-4-(4-(methoxycarbonyl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzyl)piperazine-1-carboxylate (formula 7-1, 0.303 g, 0.550 mmol) was dissolved in 1,4-dioxane (5 mL) at room temperature, and HCl (4.00 M 1,4-dioxane solution, 1.375 mL, 5.502 mmol) was added to the solution, which was then stirred at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The product was used without additional purification (0.235 g, 94.8 %, yellow oil).

Step 3: Synthesis of ethyl**4-(((3R,5S)-4-(3-((4-(2-hydroxy-2-methylpropyl)piperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0505] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-(piperazin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)benzoate (formula 7-2, 0.190 g, 0.422 mmol), isobutylene oxide (0.380 mL, 4.216 mmol) and K₂CO₃ (0.583 g, 4.216 mmol) were added to ethanol (5 mL), and heated by microwave irradiation at 110 °C for 20 minutes, followed by cooling to room temperature to terminate the reaction. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then filtered and concentrated under reduced pressure. The product was used without additional purification (0.196 g, 84.2 %, yellow oil).

Step 4: Synthesis of compound 386

[0506] Ethyl 4-(((3R,5S)-4-(3-((4-(2-hydroxy-2-methylpropyl)piperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 7-3, 0.050 g, 0.093 mmol), hydroxylamine (0.057 mL, 0.932 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.121 g, 1.863 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under

reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 386** (0.032 g, 65.6 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.17 (brs, 1 H) 9.01 (brs, 1 H) 7.70 (d, 2 H, *J* = 8.0 Hz), 7.34 (d, 2 H, *J* = 7.8 Hz), 7.27 (s, 1 H), 7.23 - 7.21 (m, 1 H), 7.09 (d, 1 H, *J* = 6.6 Hz), 4.06 (brs, 1 H) 3.72 (s, 2 H), 3.43 (s, 2 H), 3.42 (s, 2 H), 2.65 - 2.62 (m, 2 H), 2.55 - 2.54 (m, 2 H).

Example 176: Synthesis of compound 387

4-(((3R,5S)-4-(3-((4-(2-fluoro-2-methylpropyl)piperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of ethyl

4-(((3R,5S)-4-(3-((4-(2-hydroxy-2-methylpropyl)piperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0507] Ethyl 4-(((3R,5S)-4-(3-((4-(2-hydroxy-2-methylpropyl)piperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 7-3, 0.150 g, 0.287 mmol) was dissolved in methylene chloride (5 mL), and DAST (0.042 mL, 0.316 mmol) was added thereto at 0 °C. The mixture was stirred at the same temperature for 30 minutes, and then stirred at room temperature for 1 hour. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.098 g, 63.4 %) as a yellow oil.

Step 2: Synthesis of compound 387

[0508] Ethyl 4-(((3R,5S)-4-(3-((4-(2-hydroxy-2-methylpropyl)piperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 7-4, 0.098 g, 0.177 mmol), hydroxylamine (0.108 mL, 1.770 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.230 g, 3.540 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under

reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the reasulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter equipped with an anhydrous sodium sulfate cartridge to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 387** (0.089 g, 93.0 %) as an apricot solid.

^1H NMR (400 MHz, DMSO- d_6) δ 7.68 (d, 2 H, J = 7.9 Hz), 7.29 (d, 3 H, J = 7.7 Hz), 7.23 - 7.21 (m, 2 H), 7.09 - 7.08 (m, 1 H), 3.72 (s, 2 H), 3.43 (s, 2 H), 3.41 (s, 2 H), 2.65 - 2.62 (m, 2 H), 2.56 - 2.54 (m, 2 H), 2.47 - 2.43 (m, 4 H), 2.40 (d, 2 H, J = 23.3 Hz), 2.35 - 2.33 (m, 4 H), 1.80 (t, 2 H, J = 10.4 Hz), 1.32 (s, 3 H), 1.26 (s, 3 H), 0.90 (d, 6 H, J = 6.0 Hz); LRMS (ES) m/z 526.3 ($M^+ + 1$).

Example 177: Synthesis of compound 388

4-(((3R,5S)-4-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of tert-butyl

4-((4-(hydroxymethyl)phenoxy)methyl)piperidine-1-carboxylate

[0509] 4-(hydroxymethyl)phenol (0.500 g, 4.028 mmol), tert-butyl 4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate (formula 12-1, 1.300 g, 4.430 mmol), Cs_2CO_3 (1.968 g, 6.042 mmol) and NaI (0.030 g, 0.201 mmol) were mixed in acetonitrile (20 mL) at room temperature, and the mixture was heated under reflux for 17 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 50 %) and concentrated to afford the desired compound (0.552 g, 42.6 %) as a colorless oil.

Step 2: Synthesis of tert-butyl

4-((4-(chloromethyl)phenoxy)methyl)piperidine-1-carboxylate

[0510] Tert-butyl 4-((4-(hydroxymethyl)phenoxy)methyl)piperidine-1-carboxylate (formula 12-2,

0.500 g, 1.556 mmol) and TEA (0.434 mL, 3.111 mmol) were dissolved in methylene chloride (30 mL) at 0 °C, and methanesulfonyl chloride (0.132 mL, 1.711 mmol) was added to the solution, followed by stirring at the same temperature for 2 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 40 %) and concentrated to afford the desired compound (0.136 g, 25.7 %) as a white solid.

Step 3: Synthesis of tert-butyl

4-(((4-(((2S,6R)-4-(4-(methoxycarbonyl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenoxy)methyl)piperidine-1-carboxylate

[0511] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), tert-butyl 4-((4-(chloromethyl)phenoxy)methyl)piperidine-1-carboxylate (formula 12-3, 0.130 g, 0.381 mmol), Cs₂CO₃ (0.186 g, 0.572 mmol) and NaI (0.003 g, 0.019 mmol) were mixed in acetonitrile (5 mL) at room temperature, and the mixture was heated under reflux for 3 hours, and then cooled to room temperature. Then, water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 10 % to 60 %) and concentrated to afford the desired compound (0.130 g, 60.3 %) as a yellow oil.

Step 4: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(4-(piperidin-4-ylmethoxy)benzyl)piperazin-1-yl)methyl)benzoate (hydrochloride salt)

[0512] Tert-butyl 4-((4-(((2S,6R)-4-(4-(methoxycarbonyl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenoxy)methyl)piperidine-1-carboxylate (formula 12-4, 0.150 g, 0.265 mmol) was dissolved in 1,4-dioxane (5 mL) at room temperature, and HCl (4.00 M solution in 1,4-dioxane, 1.326 mL, 5.303 mmol) was added to the solution, followed by stirring at the same temperature for 17 hours. The precipitated solid was washed with diethyl ether and dried to yield the desired compound (0.126 g, 94.6 %) as a white solid.

Step 5: Synthesis of ethyl

4-(((3R,5S)-4-(4-((1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)methoxy)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0513] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(4-(piperidin-4-ylmethoxy)benzyl)piperazin-1-yl)methyl)benzoate hydrochloride (formula 12-5, 0.102 g, 0.203 mmol), 1,1-dimethyloxirane (0.073 g, 1.016 mmol) and K₂CO₃ (0.281 g, 2.032 mmol) were added to ethanol (3 mL), and heated by microwave irradiation at 110 °C for 20 minutes, followed by cooling to room temperature. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The product was used without additional purification (0.102 g, 93.4 %, pale yellow oil).

Step 6: Synthesis of ethyl

4-(((3R,5S)-4-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0514] Ethyl 4-(((3R,5S)-4-(4-((1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)methoxy)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 12-6, 0.102 g, 0.185 mmol) was dissolved in methylene chloride (5 mL), and DAST (0.027 mL, 0.203 mmol) was added thereto at 0 °C. The mixture was stirred at the same temperature for 30 minutes, and then stirred at room temperature for 1 hour. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The product was used without additional purification (0.083 g, 81.1 %, pale brown oil).

Step 7: Synthesis of compound 388

[0515] Ethyl 4-(((3R,5S)-4-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 12-7, 0.083 g, 0.150 mmol), hydroxylamine (0.092 mL, 1.499 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.195 g, 2.998 mmol) were dissolved in methanol (5 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene

chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 388** (0.073 g, 90.1 %) as an apricot solid.

^1H NMR (400 MHz, DMSO- d_6) δ 7.68 (d, 2 H, J = 8.2 Hz), 7.29 (d, 2 H, J = 8.1 Hz), 7.21 (d, 2 H, J = 8.6 Hz), 6.84 (d, 2 H, J = 8.6 Hz), 3.77 (d, 2 H, J = 5.9 Hz), 3.68 (s, 2 H), 3.40 (s, 2 H), 2.91 (d, 2 H, J = 11.5 Hz), 2.62 (d, 2 H, J = 9.8 Hz), 2.55 - 2.53 (m, 2 H), 2.41 (d, 2 H, J = 22.9 Hz), 2.08 (t, 2 H, J = 10.8 Hz), 1.81 - 1.69 (m, 6 H), 1.33 (s, 3 H), 1.29 (s, 4 H), 0.92 (d, 6 H, J = 6.1 Hz); LRMS (ES) m/z 541.3 (M^+ +1).

Example 178: Synthesis of compound 396

(4-(((2S,6R)-4-(3-(furan-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(3-(furan-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0516] 1,2-Dimethoxyethane (1 ml) / water (0.5 ml) were added to a mixture of methyl 4-(((2S,6R)-4-(3-iodobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 14-1, 0.100 g, 0.209 mmol), furan-3-ylboronic acid (0.028 g, 0.251 mmol), Pd(dbpf)Cl₂ (0.007 g, 0.010 mmol) and Na₂CO₃ (0.066 g, 0.627 mmol), and the solution was heated by microwaves at 120 °C for 20 minutes, and then filtered through celite and concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.051 g, 58.3 %) as a white solid.

Step 2: Synthesis of compound 396

[0517] Methyl 4-(((2S,6R)-4-(3-(furan-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 14-2, 0.030 g, 0.072 mmol), hydroxylamine (0.088 mL, 1.434 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.040 g, 0.717 mmol) were mixed in methanol (0.5 mL) at room temperature, and the mixture was stirred at the same temperature for 1 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to

yield **compound 396** (0.020 g, 66.5 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.18 (s, 1 H), 7.73 (s, 1 H), 7.64 (d, 2 H, *J* = 8.0 Hz), 7.49 - 7.47 (m, 2 H), 7.34 - 7.18 (m, 4 H), 6.94 (d, 1 H, *J* = 0.96 Hz), 3.72 (s, 2 H), 3.41 (s, 2 H), 2.68 - 2.65 (m, 2 H), 2.55 - 2.51 (m, 2 H), 1.84 - 1.79 (m, 2 H), 0.91 (s, 3H), 0.89 (s, 3 H).

Example 179: Synthesis of compound 400

4-(((2S,6R)-4-((4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-4-yl)methyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-((4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-4-yl)methyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0518] 1,2-Dimethoxyethane (1 ml)/water (0.5 ml) were added to a mixture of methyl 4-(((2S,6R)-4-(4-iodobenzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 14-1, 0.100 g, 0.209 mmol), (4,4-dimethylcyclohex-1-en-1-yl)boronic acid (0.038 g, 0.251 mmol), Pd(dbpf)Cl₂ (0.007 g, 0.010 mmol) and Na₂CO₃ (0.066 g, 0.627 mmol), and the solution was heated by microwaves at 120 °C for 20 minutes, after which it was filtered through celite, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.05 g, 51.9 %) as a pale brown solid.

Step 2: Synthesis of compound 400

[0519] Methyl 4-(((2S,6R)-4-((4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-4-yl)methyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 14-3, 0.030 g, 0.065 mmol), hydroxylamine (0.080 mL, 1.303 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.037 g, 0.651 mmol) were mixed in methanol (0.5 mL) at room temperature, and the mixture was stirred at the same temperature for 1 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield **compound 400** (0.023 g, 76.5 %) as a pale yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.64 (d, 2 H, *J* = 7.9 Hz), 7.36 (d, 2 H, *J* = 8.1 Hz), 7.24 - 7.20

(m, 4 H), 6.09 (brs, 1 H), 3.71 (s, 2 H), 2.64 - 2.51 (m, 4 H), 2.37 (brs, 2 H), 1.97 (brs, 2 H), 1.80 - 1.75 (m, 2 H), 1.49 - 1.46 (m, 2 H), 0.93 - 0.89 (m, 12 H).

Example 180: Synthesis of compound 401

4-(((2S,6R)-4-(4-(3,6-dihydro-2H-pyran-4-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(4-(3,6-dihydro-2H-pyran-4-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0520] 1,2-Dimethoxyethane (1 ml) / water (0.5 ml) were added to a mixture of methyl 4-(((2S,6R)-4-(4-iodobenzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 14-1, 0.100 g, 0.209 mmol), (3,6-dihydro-2H-pyran-4-yl)boronic acid (0.032 g, 0.251 mmol), Pd(dbpf)Cl₂ (0.007 g, 0.010 mmol) and Na₂CO₃ (0.066 g, 0.627 mmol), and then heated by microwaves at 120 °C for 20 minutes. The reaction solution was filtered through celite, and the filtrate was concentrate under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; methanol/ methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.029 g, 31.9 %) as a pale brown solid.

Step 2: Synthesis of compound 401

[0521] Methyl 4-(((2S,6R)-4-(4-(3,6-dihydro-2H-pyran-4-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 14-2, 0.025 g, 0.058 mmol), hydroxylamine (0.070 mL, 1.151 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.032 g, 0.575 mmol) were mixed in methanol (0.5 mL) at room temperature, and the mixture was stirred at the same temperature for 1 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure to yield **compound 401** (0.011 g, 43.9 %) as a pale yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.66 (d, 2 H, *J* = 8.12 Hz), 7.40 - 7.36 (m, 4 H), 7.25 (d, 2 H, *J* = 8.12 Hz), 6.23 (brs, 1 H), 4.21 (s, 2 H), 3.81 (t, 2 H, *J* = 5.3 Hz), 3.73 (s, 2 H), 3.39 (s, 2 H), 2.66 - 2.54 (m, 4 H), 2.47 - 2.43 (m, 2 H), 1.82 - 1.76 (m, 2 H), 0.88 (s, 3H), 0.87 (s, 3 H).

Example 181: Synthesis of compound 402

4-(((3R,5S)-3,5-dimethyl-4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of (3R,5S)-tert-butyl

4-(furan-2-carbonyl)-3,5-dimethylpiperazine-1-carboxylate

[0522] (3R,5S)-tert-butyl 3,5-dimethylpiperazine-1-carboxylic acid (formula 8-1, 0.500 g, 2.333 mmol), furan-2-carbonyl chloride (0.276 mL, 2.800 mmol) and TEA (0.976 mL, 7.000 mmol) were dissolved in methylene chloride (10 mL) at 0 °C, and the solution was stirred at the same temperature for 1 hour. Then, water was added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; ethyl acetate/hexane = from 0 % to 30 %) and concentrated to afford the desired compound (0.620 g, 86.2 %) as a colorless oil.

Step 2: Synthesis of (3R,5S)-tert-butyl

3,5-dimethyl-4-(tetrahydrofuran-2-carbonyl)piperazine-1-carboxylate

[0523] (3R,5S)-tert-butyl 4-(furan-2-carbonyl)-3,5-dimethylpiperazine-1-carboxylate (formula 11-1, 0.100 g, 0.324 mmol) was dissolved in ethanol/water (8:1) (2 mL) at room temperature, and Pd/C (0.010 g) was slowly added thereto. Then, a hydrogen balloon was placed over the solution, followed by stirring at the same temperature for 2 hours. The reaction mixture was filtered through a celite pad to remove solids, and the filtrate was concentrated under reduced pressure to remove the solvent. The product was used without additional purification (0.100 g, 98.7 %, colorless oil).

Step 3: Synthesis of

((2S,6R)-2,6-dimethylpiperazin-1-yl)(tetrahydrofuran-2-yl)methanone (hydrochloride salt)

[0524] (3R,5S)-tert-butyl 3,5-dimethyl-4-(tetrahydrofuran-2-carbonyl)piperazine-1-carboxylate (formula 11-2, 0.540 g, 1.729 mmol) and HCl (4.00 M 1,4-dioxane solution, 8.643 mL, 34.571 mmol) were dissolved in 1,4-dioxane (20 mL) at room temperature, and the solution was stirred at the same temperature for 17 hours. The reaction mixture was concentrated under reduced pressure to remove the solvent, and the product was used without additional purification (0.400 g, 109.0 %, colorless oil).

Step 4: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methyl)benzoate

[0525] ((2S,6R)-2,6-dimethylpiperazin-1-yl)(tetrahydrofuran-2-yl)methanone hydrochloride (formula 11-3, 0.400 g, 1.608 mmol), methyl 4-(bromomethyl)benzoate (formula 1-1, 0.368 g, 1.608 mmol) and Cs₂CO₃ (1.572 g, 4.824 mmol) were dissolved in acetonitrile (15 mL) at room temperature, and the solution was stirred at the same temperature for 17 hours. The reaction mixture was filtered through a glass filter to remove solids, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; ethyl acetate/hexane = from 0 % to 40 %) and concentrated to afford the desired compound (0.196 g, 33.8 %) as a colorless oil.

Step 5: Synthesis of compound 402

[0526] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methyl)benzoate (0.140 g, 0.388 mmol), hydroxylamine (0.238 mL, 3.884 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.436 g, 7.768 mmol) were dissolved in methanol (4 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 402** (0.067 g, 47.7 %) as an apricot solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.10 (brs, 1 H) 9.00 (brs, 1 H) 7.73 (d, 2 H, *J* = 8.1 Hz), 7.43 (d, 2 H, *J* = 8.0 Hz), 4.63 - 4.56 (m, 1 H), 4.37 - 4.35 (m, 2 H), 3.75 - 3.72 (m, 2 H), 3.35 (s, 2 H), 2.65 - 2.62 (m, 2 H), 2.11 - 2.09 (m, 3 H), 1.88 - 1.80 (m, 3 H), 1.35 - 1.21 (m, 6 H), 1.35 - 1.21 (m, 6 H); LRMS (ES) *m/z* 362.1 (*M*⁺+1).

Example 182: Synthesis of compound 403

4-(((3R,5S)-3,5-dimethyl-4-(1H-pyrazole-3-carbonyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)**Step 1: Synthesis of methyl****4-(((3R,5S)-3,5-dimethyl-4-(1H-pyrazole-3-carbonyl)piperazin-1-yl)methyl)benzoate**

[0527] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), 1H-pyrazole-3-carboxylic acid (0.047 g, 0.419 mmol), HATU (0.290 g, 0.762 mmol) and DIPEA (0.333 mL, 1.906 mmol) were dissolved in N,N-dimethylformamide (3 mL) at room temperature, and the solution was stirred at the same temperature for 17 hours. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The product was used without additional purification (0.150 g, 110.4 %, yellow oil).

Step 2: Synthesis of compound 403

[0528] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(1H-pyrazole-3-carbonyl)piperazin-1-yl)methyl)benzoate (formula 1-3, 0.150 g, 0.421 mmol), hydroxylamine (0.257 mL, 4.209 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.472 g, 8.417 mmol) were dissolved in methanol (4 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) and methylene chloride (10 mL) were added to the concentrate, followed by stirring. The precipitated solid was filtered, washed with water, and dried to yield **compound 403** (0.046 g, 30.6 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 13.12 (brs, 1 H), 11.19 (brs, 1 H), 3.02 (brs 1 H), 7.79 (s, 1 H), 7.73 (d, 2 H, *J* = 8.2 Hz), 7.45 (d, 2 H, *J* = 8.3 Hz), 6.54 (d, 1 H, *J* = 2.0 Hz), 4.69 (brs, 1 H), 3.55 (s, 2 H), 2.68 - 2.65 (m, 2 H), 2.16 - 2.12 (m, 2 H), 1.35 (d, 6 H, *J* = 6.7 Hz); LRMS (ES) *m/z* 358.2 (*M*⁺+1).

Example 183: Synthesis of compound 404

4-(((3R,5S)-3,5-dimethyl-4-(pyrazine-2-carbonyl)piperazin-1-yl)methyl)-N-hydroxybenzamide**Step 1: Synthesis of methyl****4-(((3R,5S)-3,5-dimethyl-4-(pyrazine-2-carbonyl)piperazin-1-yl)methyl)benzoate**

[0529] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol), pyrazine-2-carboxylic acid (0.052 g, 0.419 mmol), HATU (0.290 g, 0.762 mmol) and DIPEA (0.333 mL, 1.906 mmol) were dissolved in N,N-dimethylformamide (3 mL) at room temperature, and the solution was stirred at the same temperature for 17 hours. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The product was used without additional purification (0.150 g, 106.8 %, brown oil).

Step 2: Synthesis of compound 404

[0530] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(pyrazine-2-carbonyl)piperazin-1-yl)methyl)benzoate (formula 1-3, 0.150 g, 0.408 mmol), hydroxylamine (0.250 mL, 4.082 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.458 g, 8.165 mmol) were dissolved in methanol (4 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈; 0.1 % trifluoroacetic acid aqueous solution/acetonitrile = from 5 % to 80 %), after which it was passed through a SPE cartridge (PL-HCO₃ MP SPE) and concentrated to afford **compound 404** (0.043 g, 28.6 %) as a white solid.

¹H-NMR (400 MHz, CD₃OD) δ 8.85 (d, 1 H, *J* = 1.5 Hz), 8.75 (d, 1 H, *J* = 2.5 Hz), 8.65 (dd, 1 H, *J* = 2.6, 1.6 Hz), 7.82 (d, 2 H, *J* = 8.2 Hz), 7.60 (d, 2 H, *J* = 8.2 Hz), 4.10 (brs, 2 H), 3.18 (brs, 2 H), 2.85 (brs, 2 H), 1.52 (d, 6 H, *J* = 7.1 Hz); LRMS (ES) *m/z* 370.1 (*M*⁺+1).

Example 184: Synthesis of compound 405

(N-hydroxy-4-(((3R,5S)-4-isonicotinoyl-3,5-dimethylpiperazin-1-yl)methyl)benzamide)**Step 1: Synthesis of methyl****4-(((3R,5S)-4-isonicotinoyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0531] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.100 g, 0.381 mmol) and TEA (0.159 mL, 1.144 mmol) were dissolved in methylene chloride (4 mL) at room temperature, and isonicotinoyl chloride (0.081 g, 0.572 mmol) was added to the solution, followed by stirring at the same temperature for 1 hour. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The product was used without additional purification (0.150 g, 107.1 %, pale yellow oil).

Step 2: Synthesis of compound 405

[0532] Methyl 4-(((3R,5S)-4-isonicotinoyl-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-3, 0.150 g, 0.408 mmol), hydroxylamine (0.250 mL, 4.082 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.458 g, 8.165 mmol) were dissolved in methanol (4 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈; 0.1 % trifluoroacetic acid aqueous solution/acetonitrile = from 5 % to 80 %), after which it was passed through a SPE cartridge (PL-HCO₃ MP SPE) and concentrated to afford **compound 405** (0.043 g, 28.6 %) as a white solid.

¹H NMR (400 MHz, CD₃OD) δ 8.73 (d, 2 H, *J* = 6.2 Hz), 7.79 (d, 2 H, *J* = 8.2 Hz), 7.60 - 7.55 (m, 4 H), 3.89 (brs, 2 H), 2.96 (brs, 2 H), 2.61 (brs, 2 H), 1.45 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 369.1 (*M*⁺+1).

Example 185: Synthesis of compound 411

4-(((3R,5S)-4-(4-(((R)-3-fluoropyrrolidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)**Step 1: Synthesis of methyl****4-(((3R,5S)-4-(4-(((R)-3-fluoropyrrolidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0533] Methyl 4-(((3R,5S)-4-(4-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.100 g, 0.263 mmol) was dissolved in methylene chloride (1 mL) at room temperature, and (R)-3-fluoropyrrolidine (0.036 g, 0.289 mmol) was added to the mixture, followed by stirring for 30 minutes. Na(OAc)₃BH (0.061 g, 0.289 mmol) was added to the mixture, which was then stirred overnight at the same temperature. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/ methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.059 g, 49.7 %) as a pale brown solid.

Step 2: Synthesis of compound 411

[0534] Methyl 4-(((3R,5S)-4-(4-(((R)-3-fluoropyrrolidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-2, 0.059 g, 0.130 mmol), hydroxylamine (0.159 mL, 2.601 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.073 g, 1.301 mmol) were dissolved in methanol (1 mL) at room temperature, and the solution was stirred at the same temperature for 2 hours. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (10 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered, washed with water, and dried to yield **compound 411** (0.011 g, 17.8 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.67 (d, 1 H, *J* = 11.2 Hz), 7.43 - 7.20 (m, 6 H), 5.25 - 5.11 (m, 1 H), 3.72 (s, 2 H), 3.55 (s, 2 H), 3.43 (s, 2 H), 2.81 - 2.53 (m, 7 H), 2.35 - 2.08 (m, 2 H), 1.90 - 1.78 (m, 3 H), 0.91 - 0.89 (m, 6 H).

Example 186: Synthesis of compound 412**4-(((3R,5S)-4-(4-((3,3-difluoroazetidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-**

yl)methyl)-N-hydroxybenzamide)Step 1: Synthesis of methyl4-(((3R,5S)-4-(4-((3,3-difluoroazetidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0535] Methyl 4-(((3R,5S)-4-(4-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.100 g, 0.263 mmol) was dissolved in methylene chloride (1 mL) at room temperature, and 3,3-difluoroazetidine (0.037 g, 0.289 mmol) was added to the mixture, followed by stirring for 30 minutes. Na(OAc)₃BH (0.061 g, 0.289 mmol) was added to the reaction mixture, which was stirred overnight at the same temperature. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/ methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.073 g, 60.6 %) as a white solid.

[0536] Step 2: Synthesis of compound 412

[0537] Methyl 4-(((3R,5S)-4-(4-((3,3-difluoroazetidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-2, 0.073 g, 0.160 mmol), hydroxylamine (0.195 mL, 3.191 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.090 g, 1.595 mmol) were dissolved in methanol (1 mL) at room temperature, and the solution was stirred at the same temperature for 2 hours. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (10 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered, washed with water, and dried to yield **compound 412** (0.014 g, 18.9 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.69 (d, 2 H, *J* = 8.2 Hz), 7.30 - 7.19 (m, 6 H), 3.71 - 3.67 (m, 4 H), 3.59 - 3.52 (m, 5 H), 3.41 (m, 1 H), 2.64 - 2.62 (m, 4 H), 1.80 (t, 2 H, *J* = 10.4 Hz), 0.90 - 0.88 (m, 6 H).

Example 187: Synthesis of compound 413(4-(((3R,5S)-4-(4-(4-benzylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl**4-(((3R,5S)-4-(4-((4-benzylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0538] Methyl 4-(((3R,5S)-4-(4-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.100 g, 0.263 mmol) was dissolved in methylene chloride (1 mL), and 1-benzylpiperazine (0.049 mL, 0.289 mmol) was added to the mixture, followed by stirring for 30 minutes. Na(OAc)₃BH (0.061 g, 0.289 mmol) was added to the reaction mixture, which was then stirred overnight at the same temperature. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.074 g, 51.8 %) as a white solid.

Step 2: Synthesis of compound 413

[0539] Methyl 4-(((3R,5S)-4-(4-((4-benzylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-2, 0.074 g, 0.137 mmol), hydroxylamine (0.168 mL, 2.742 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.077 g, 1.371 mmol) were dissolved in methanol (1 mL) at room temperature, and the solution was stirred at the same temperature for 2 hours. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (10 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered, washed with water, and dried to yield **compound 413** (0.053 g, 71.1 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.67 (d, 2 H, *J* = 8.0 Hz), 7.32 - 7.14 (m, 11 H), 3.70 (s, 2 H), 3.44 (m, 6 H), 3.22 (m, 2 H), 2.68 - 2.64 (m, 4 H), 2.35 (m, 6 H), 1.78 (t, 2 H, *J* = 10.4 Hz), 0.90 - 0.88 (m, 6 H).

Example 188: Synthesis of compound 423**4-(((3R,5S)-3,5-dimethyl-4-(3-(pyrrolidin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide****Step 1: Synthesis of 3-(chloromethyl)benzoyl chloride**

[0540] 3-(bromomethyl)benzoic acid (4.301 g, 20.000 mmol) and SOCl_2 (43.793 mL, 600.000 mmol) were mixed at 50 °C, and the mixture was stirred overnight at the same temperature, followed by cooling to room temperature to terminate the reaction. The reaction mixture was concentrated under reduced pressure to remove the solvent, and the product was used without additional purification (3.778 g, 99.9 %, brown liquid).

Step 2 : Synthesis of methyl

4-(((3R,5S)-4-(3-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0541] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 2.622 g, 9.993 mmol), 3-(chloromethyl)benzoyl chloride (formula 6-1, 3.778 g, 19.986 mmol) and TEA (2.770 mL, 19.986 mmol) were dissolved in methylene chloride (40 mL) at room temperature, and the solution was stirred at the same temperature for 3 hours. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; 100 % methylene chloride) and concentrated to afford the desired compound (2.047 g, 49.4 %) as a brown liquid.

Step 3: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)benzoate

[0542] Methyl 4-(((3R,5S)-4-(3-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 6-2, 0.178 g, 0.388 mmol), pyrrolidine (0.032 mL, 0.388 mmol) and TEA (0.108 mL, 0.777 mmol) were dissolved in methylene chloride (2 mL) at room temperature, and the solution was stirred overnight at the same temperature. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.155 g, 88.8 %) as a pale yellow liquid.

Step 4: Synthesis of compound 423

[0543] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)benzoate (formula 6-3, 0.155 g, 0.345 mmol), hydroxylamine (0.422 mL, 6.895 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.193 g, 3.448 mmol) were dissolved in methanol (1.5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford **compound 423** (0.070 g, 44.9 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.2 (brs, 1 H), 9.03 (brs, 1 H), 7.72 (d, 2 H, *J* = 8.6 Hz), 7.43 (d, 2 H, *J* = 8.2 Hz), 7.38 - 7.32 (m, 2 H), 7.24 (s, 1 H), 7.20 - 7.17 (m, 2 H), 4.06 (brs, 2 H), 3.58 - 3.54 (m, 4 H), 2.68 - 2.61 (m, 2 H), 2.40 (s, 4 H), 2.16 - 2.12 (m, 2 H), 1.69 - 1.67 (m, 4 H), 1.21 - 1.28 (m, 6 H).

Example 189: Synthesis of compound 424

4-(((3R,5S)-3,5-dimethyl-4-(3-(piperidin-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-(piperidin-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)benzoate

[0544] Methyl 4-(((3R,5S)-4-(3-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 6-2, 0.165 g, 0.359 mmol), piperidine (0.036 mL, 0.359 mmol) and Cs₂CO₃ (0.142 g, 0.431 mmol) were dissolved in acetonitrile (1.5 mL) at room temperature, and the solution was stirred overnight at the same temperature. Then, water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene

chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.127 g, 76.0 %) as a colorless liquid.

Step 2: Synthesis of compound 424

[0545] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-(piperidin-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)benzoate (formula 6-3, 0.127 g, 0.273 mmol), hydroxylamine (0.334 mL, 5.461 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.153 g, 2.731 mmol) were dissolved in methanol (1.5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure to yield **compound 424** (0.101 g, 79.4 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.72 (d, 2 H, *J* = 8.2 Hz), 7.43 (d, 2 H, *J* = 8.1 Hz), 7.38 - 7.30 (m, 2 H), 7.23 (s, 1 H), 7.20 - 7.18 (m, 1 H), 3.54 (s, 2 H), 3.44 (s, 2 H), 2.63 - 2.61 (m, 2 H), 2.30 (m, 4 H), 2.16 - 2.12 (m, 2 H), 1.49 - 1.46 (m, 4 H), 1.38 - 1.37 (m, 2 H), 1.29 (s, 6 H).

Example 190: Synthesis of compound 425

4-(((3R,5S)-4-(3-((diethylamino)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-((diethylamino)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0546] Methyl 4-(((3R,5S)-4-(3-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 6-2, 0.165 g, 0.359 mmol), diethylamine hydrochloride (0.039 g, 0.359 mmol) and Cs₂CO₃ (0.142 g, 0.431 mmol) were dissolved in acetonitrile (1.5 mL) at room temperature, and the solution was stirred overnight at the same temperature. Then, water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.115 g, 71.1 %) as a colorless liquid.

Step 2: Synthesis of compound 425

[0547] Methyl 4-(((3R,5S)-4-(3-((diethylamino)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 6-3, 0.115 g, 0.255 mmol), hydroxylamine (0.312 mL, 5.106 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.143 g, 2.553 mmol) were dissolved in methanol (1.5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford **compound 425** (0.061 g, 53.1 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.2 (brs, 1 H), 9.03 (brs, 1 H), 7.72 (d, 2 H, *J* = 8.2 Hz), 7.43 (d, 2 H, *J* = 8.2 Hz), 7.36 - 7.34 (m, 2 H), 7.25 (s, 1 H), 7.18 - 7.16 (m, 1 H), 3.54 (s, 4 H), 2.63 - 2.61 (m, 2 H), 2.46 - 2.41 (m, 4 H), 2.16 - 2.12 (m, 2 H), 1.29 (m, 6 H), 0.98 - 0.94 (m, 6 H).

Example 191: Synthesis of compound 426**(4-(((3R,5S)-4-(3-((diethylamino)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)****Step 1: Synthesis of methyl****4-(((3R,5S)-4-(3-((diethylamino)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0548] Methyl 4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.200 g, 0.526 mmol) and diethylamine hydrochloride (0.086 g, 0.788 mmol) were dissolved in methylene chloride (10 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.223 g, 1.051 mmol) was added to the solution, followed by stirring at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride

= from 0 % to 10 %) and concentrated to afford the desired compound (0.026 g, 11.3 %) as a pale yellow oil.

Step 2: Synthesis of compound 426

[0549] Methyl 4-(((3R,5S)-4-(3-((diethylamino)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-2, 0.026 g, 0.059 mmol), hydroxylamine (0.073 mL, 1.188 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.033 g, 0.594 mmol) were dissolved in methanol (4 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction solution was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 426** (0.019 g, 72.9 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 1.10 (brs, 1 H), 9.00 (brs, 1 H), 7.69 (d, 2 H, *J* = 8.3 Hz), 7.33 (d, 2 H, *J* = 8.1 Hz), 7.29 (s, 1 H), 7.24 - 7.18 (m, 2 H), 7.12 - 7.10 (m, 1 H), 3.72 (s, 2 H), 3.50 (s, 2 H), 3.43 (s, 2 H), 2.68 - 2.54 (m, 4 H), 2.43 (q, 4 H, *J* = 7.1 Hz), 1.80 (t, 2 H, *J* = 10.5 Hz), 0.96 (t, 6 H, *J* = 7.1 Hz), 0.90 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 439.3 (*M*⁺+1).

Example 192: Synthesis of compound 427

4-(((3R,5S)-3,5-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)benzoate

[0550] Methyl 4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.200 g, 0.526 mmol) and pyrrolidine (0.066 mL, 0.788 mmol) were dissolved in methylene chloride (4 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.223 g, 1.051 mmol) was added to the solution, followed by stirring at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then

concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.161 g, 70.3 %) as a colorless oil.

Step 2: Synthesis of compound 427

[0551] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)benzoate (formula 5-2, 0.086 g, 0.197 mmol), hydroxylamine (0.242 mL, 3.949 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.111 g, 1.974 mmol) were dissolved in methanol (4 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 427** (0.033 g, 38.3 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 11.10 (brs, 1 H), 9.00 (brs, 1 H), 7.70 (d, 2 H, J = 8.2 Hz), 7.35 (d, 2 H, J = 8.1 Hz), 7.26 (s, 1 H), 7.22 - 7.21 (m, 2 H), 7.11 - 7.09 (m, 1 H), 3.72 (s, 2 H), 3.54 (s, 2 H), 3.44 (s, 2 H), 2.65 - 2.55 (m, 4 H), 2.40 (s, 4 H), 1.81 (t, 2 H, J = 10.5 Hz), 1.69 (s, 4 H), 0.90 (d, 6 H, J = 6.1 Hz); LRMS (ES) m/z 437.3 (M⁺+1).

Example 193: Synthesis of compound 428

4-(((3R,5S)-3,5-dimethyl-4-(3-((4-methylpiperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-((4-methylpiperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)benzoate

[0552] Methyl 4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.200 g, 0.526 mmol) and 1-methylpiperazine (0.088 mL, 0.788 mmol) were dissolved in methylene chloride (4 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.223 g, 1.051 mmol) was added to the solution, followed by stirring at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen

carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.152 g, 62.2 %) as a pale yellow oil.

Step 2: Synthesis of compound 428

[0553] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-((4-methylpiperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)benzoate (formula 5-2, 0.075 g, 0.161 mmol), hydroxylamine (0.197 mL, 3.228 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.091 g, 1.614 mmol) were dissolved in methanol (4 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 428** (0.031 g, 41.2 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.69 (d, 2 H, *J* = 8.2 Hz), 7.30 (d, 2 H, *J* = 8.1 Hz), 7.27 (s, 1 H), 7.23 - 7.21 (m, 2 H), 7.09 - 7.08 (m, 1 H), 3.72 (s, 2 H), 3.43 (s, 2 H), 3.42 (s, 2 H), 2.63 (d, 2 H, *J* = 10.2 Hz), 2.58 - 2.51 (m, 2 H), 2.36 - 2.33 (m, 8 H), 1.80 (t, 2 H, *J* = 10.5 Hz), 0.90 (d, 6 H, *J* = 6.1 Hz).

Example 194: Synthesis of compound 429

4-(((3R,5S)-4-(3-((4-ethylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-((4-ethylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)ethyl)benzoate

[0554] Methyl 4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.200 g, 0.526 mmol) and 1-ethylpiperazine (0.100 mL, 0.788 mmol) were dissolved in methylene chloride (4 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.223 g, 1.051 mmol) was added to the solution, followed by stirring at the

same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.099 g, 39.3 %) as a pale yellow oil.

Step 2: Synthesis of compound 429

[0555] Methyl 4-(((3R,5S)-4-(3-((4-ethylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-2, 0.055 g, 0.115 mmol), hydroxylamine (0.141 mL, 2.298 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.064 g, 1.149 mmol) were dissolved in methanol (4 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 429** (0.031 g, 56.2 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 11.10 (brs, 1 H), 9.00 (brs, 1 H), 7.70 (d, 2 H, *J* = 8.3 Hz), 7.34 (d, 2 H, *J* = 8.2 Hz), 7.27 (s, 1 H), 7.23 - 7.21 (m, 2 H), 7.09 - 7.08 (m, 1 H), 3.72 (s, 2 H), 3.43 (s, 4 H), 2.63 (d, 2 H, *J* = 10.2 Hz), 2.59 - 2.51 (m, 2 H), 2.36 - 2.33 (m, 8 H), 2.28 (q, 2 H, *J* = 7.2 Hz), 1.81 (t, 2 H, *J* = 10.5 Hz), 0.97 (t, 3 H, *J* = 7.2 Hz), 0.90 (d, 6 H, *J* = 6.1 Hz).

Example 195: Synthesis of compound 430

(N-hydroxy-4-(((3R,5S)-4-(3-((4-isopropylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-((4-isopropylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0556] Methyl 4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.200 g, 0.526 mmol) and 1-isopropylpiperazine (0.113 mL, 0.788 mmol) were dissolved in methylene chloride (4 mL), and the solution was stirred at room temperature for 1

hour. Na(OAc)₃BH (0.223 g, 1.051 mmol) was added to the solution, followed by stirring at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.225 g, 86.9 %) as a pale brown oil.

Step 2: Synthesis of compound 430

[0557] Methyl 4-(((3R,5S)-4-(3-((4-isopropylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-2, 0.100 g, 0.203 mmol), hydroxylamine (0.248 mL, 4.059 mmol, 50.00 % aqueous solution) and potassium chloride (0.114 g, 2.030 mmol) were dissolved in methanol (4 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 430** (0.055 g, 54.9 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 11.10 (brs, 1 H), 9.00 (brs, 1 H), 7.70 (d, 2 H, *J* = 8.0 Hz), 7.35 (d, 2 H, *J* = 8.0 Hz), 7.09 - 7.08 (m, 2 H), 3.72 (s, 2 H), 3.43 (s, 2 H), 3.42 (s, 2 H), 2.65 - 2.62 (m, 2 H), 2.59 - 2.51 (m, 3 H), 2.41 - 2.34 (m, 8 H), 1.81 (t, 2 H, *J* = 10.3 Hz), 0.94 (d, 6 H, *J* = 6.5 Hz), 0.90 (d, 6 H, *J* = 6.0 Hz).

Example 196: Synthesis of compound 431

4-(((3R,5S)-4-(3-((4-acetylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-((4-acetylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0558] Methyl 4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.200 g, 0.526 mmol) and 1-acetylpiperazine (0.101 g, 0.788 mmol) were

dissolved in methylene chloride (4 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.223 g, 1.051 mmol) was added to the reaction solution, followed by stirring at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.253 g, 97.7 %) as a pale brown oil.

Step 2: Synthesis of compound 431

[0559] Methyl 4-(((3R,5S)-4-(3-((4-acetylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-2, 0.070 g, 0.142 mmol), hydroxylamine (0.174 mL, 2.842 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.080 g, 1.421 mmol) were dissolved in methanol (4 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 431** (0.067 g, 95.5 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.69 (d, 2 H, *J* = 8.1 Hz), 7.32 (d, 2 H, *J* = 8.1 Hz), 7.28 (s, 1 H), 7.25 - 7.23 (m, 2 H), 7.12 - 7.11 (m, 1 H), 3.73 (s, 2 H), 3.43 - 3.39 (m, 6 H), 2.64 (d, 2 H, *J* = 10.1 Hz), 2.59 - 2.53 (m, 2 H), 2.34 (t, 2 H, *J* = 4.8 Hz), 2.28 (t, 2 H, *J* = 5.0 Hz), 0.90 (d, 6 H, *J* = 6.1 Hz).

Example 197: Synthesis of compound 432

(4-(((3R,5S)-3,5-dimethyl-4-(3-((4-methylpiperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-((4-methylpiperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)benzoate

[0560] Methyl 4-(((3R,5S)-4-(3-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 6-2, 0.200 g, 0.482 mmol), 1-methylpiperazine (0.059 mL, 0.530 mmol) and Cs_2CO_3 (0.188 g, 0.578 mmol) were dissolved in acetonitrile (2 mL) at room temperature, and the solution was stirred overnight at the same temperature. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.163 g, 70.5 %) as a pale yellow liquid.

Step 2: Synthesis of compound 432

[0561] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-((4-methylpiperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)benzoate (formula 6-3, 0.163 g, 0.340 mmol), hydroxylamine (0.416 mL, 6.794 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.191 g, 3.397 mmol) were dissolved in methanol (1.5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure to yield **compound 432** (0.095 g, 58.1 %) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.72 (d, 2 H, $J = 8.2$ Hz), 7.43 (d, 2 H, $J = 8.2$ Hz), 7.38 - 7.30 (m, 2 H), 7.23 - 7.18 (m, 2 H), 3.54 - 3.47 (m, 6 H), 2.67 - 2.61 (m, 2 H), 2.33 (m, 8 H), 2.16 - 2.13 (m, 5 H), 1.28 - 1.23 (m, 6 H).

Example 198: Synthesis of compound 433

4-(((3R,5S)-4-(3-((4-ethylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-((4-ethylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0562] Methyl 4-(((3R,5S)-4-(3-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-

yl)methyl)benzoate (formula 6-2, 0.200 g, 0.482 mmol), 1-ethylpiperazine (0.067 mL, 0.530 mmol) and Cs₂CO₃ (0.188 g, 0.578 mmol) were dissolved in acetonitrile (2 mL) at room temperature, and the solution was stirred overnight at the same temperature. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.165 g, 69.4 %) as a pale yellow liquid.

Step 2: Synthesis of compound 433

[0563] Methyl 4-(((3R,5S)-4-(3-((4-ethylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl) methyl)benzoate (formula 6-3, 0.165 g, 0.334 mmol), hydroxylamine (50.00 % aqueous solution, 0.409 mL, 6.686 mmol) and potassium hydroxide (0.188 g, 3.343 mmol) were dissolved in methanol (1.5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure to yield **compound 433** (0.116 g, 70.0 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.2 (brs, 1 H), 9.03 (brs, 1 H), 7.89 (d, 2 H, *J* = 7.8 Hz), 7.72 (d, 2 H, *J* = 8.2 Hz), 7.44 - 7.30 (m, 2 H), 7.23 (s, 1 H), 7.20 - 7.19 (m, 1 H), 4.51 (s, 4 H), 2.67 - 2.61 (m, 2 H), 2.34 - 2.25 (m, 8 H), 2.14 (dd, 2 H, *J* = 11.3, 4.1 Hz), 1.28 - 1.23 (m, 6 H), 0.98 - 0.85 (m, 3 H).

Example 199: Synthesis of compound 434

(N-hydroxy-4-(((3R,5S)-4-(3-((4-isopropylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-((4-isopropylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0564] Methyl 4-(((3R,5S)-4-(3-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-

yl)methyl)benzoate (formula 6-2, 0.200 g, 0.482 mmol), 1-isopropylpiperazine (0.076 mL, 0.530 mmol) and Cs_2CO_3 (0.188 g, 0.578 mmol) were dissolved in acetonitrile (2 mL) at room temperature, and the solution was stirred overnight at the same temperature. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.170 g, 69.5 %) as a pale yellow liquid.

Step 2: Synthesis of compound 434

[0565] Methyl 4-(((3R,5S)-4-(3-((4-isopropylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 6-3, 0.170 g, 0.335 mmol), hydroxylamine (0.410 mL, 6.699 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.188 g, 3.349 mmol) were dissolved in methanol (1.5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure to yield **compound 434** (0.128 g, 75.5 %) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.2 (brs, 1 H), 9.02 (brs, 1 H), 7.72 (d, 2 H, $J = 8.2$ Hz), 7.43 (d, 2 H, $J = 8.2$ Hz), 7.39 - 7.30 (m, 2 H), 7.23 - 7.19 (s, 2 H), 3.54 (s, 2 H), 3.47 (s, 2 H), 2.67 - 2.60 (m, 3 H), 2.43 - 2.33 (m, 9 H), 2.15 (dd, 1 H, $J = 11.3, 4.0$ Hz), 1.29 - 1.18 (m, 6 H), 0.96 - 0.94 (m, 6 H).

Example 200: Synthesis of compound 435

4-(((3R,5S)-4-(3-((4-acetylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-((4-acetylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0566] Methyl 4-(((3R,5S)-4-(3-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-

yl)methyl)benzoate (formula 6-2, 0.200 g, 0.482 mmol), 1-acetylpiperazine (0.068 g, 0.530 mmol) and Cs_2CO_3 (0.188 g, 0.578 mmol) were dissolved in acetonitrile (2 mL), and the solution was stirred overnight at the same temperature. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/ methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.186 g, 76.2 %) as a pale yellow liquid.

Step 2: Synthesis of compound 435

[0567] Methyl 4-(((3R,5S)-4-(3-((4-acetylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl) methyl)benzoate (formula 6-3, 0.186 g, 0.367 mmol), hydroxylamine (0.449 mL, 7.346 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.206 g, 3.673 mmol) were dissolved in methanol (1.5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure to yield **compound 435** (0.121 g, 64.7 %) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.2 (brs, 1 H), 9.04 (brs, 1 H), 7.72 (d, 2 H, $J = 8.1$ Hz), 7.42 - 7.33 (m, 4 H), 7.25 - 7.20 (s, 2 H), 4.52 (brs, 2 H), 3.53 - 3.52 (m, 4 H), 3.41 - 3.40 (m, 4 H), 2.67 - 2.62 (m, 2 H), 2.36 - 2.34 (m, 2 H), 2.29 - 2.27 (m, 2 H), 2.16 - 2.13 (m, 2 H), 1.97 (s, 3 H), 1.29 (s, 6 H).

Example 201: Synthesis of compound 439

(4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzoyl)piperazin-1-yl)methyl)benzoate

[0568] Methyl 4-(((3R,5S)-4-(3-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-

yl)methyl)benzoate (formula 6-2, 0.200 g, 0.482 mmol), morpholine (0.069 g, 0.530 mmol) and Cs_2CO_3 (0.188 g, 0.578 mmol) were dissolved in acetonitrile (2 mL) at room temperature, and the solution was stirred overnight at the same temperature. Water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 10 %) and concentrated to afford the desired compound (0.163 g, 66.6 %) as a pale yellow liquid.

Step 2: Synthesis of compound 439

[0569] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzoyl)piperazin-1-yl)methyl)benzoate (formula 6-3, 0.163 g, 0.321 mmol), hydroxylamine (0.392 mL, 6.416 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.180 g, 3.208 mmol) were dissolved in methanol (1.5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 439** (0.105 g, 64.3 %) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.71 (d, 2 H, $J = 8.2$ Hz), 7.39 - 7.33 (m, 4 H), 7.22 (s, 1 H), 7.22 - 7.20 (m, 1 H), 4.41 (brs, 1 H) 3.57 - 3.55 (m, 4 H), 3.48 (s, 4 H), 2.65 - 2.61 (m, 2 H), 2.34 (s, 4 H), 2.15 - 2.11 (m, 2 H), 1.29 - 1.23 (m, 6 H).

Example 202: Synthesis of compound 440

4-(((3R,5S)-4-(3-(((1-(diethylamino)propan-2-yl)amino)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-(((1-(diethylamino)propan-2-yl)amino)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0570] Methyl 4-(((3R,5S)-4-(3-(chlorophenyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 6-2, 0.200 g, 0.482 mmol), N_1,N_1 -diethylpropane-1,2-diamine (0.069 g, 0.530 mmol) and Cs_2CO_3 (0.188 g, 0.578 mmol) were dissolved in acetonitrile (2 mL)

at room temperature, and the solution was stirred overnight at the same temperature. Water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/ hexane = from 0 % to 10 %) and concentrated to afford the desired compound (0.163 g, 66.6 %) as a pale yellow liquid.

Step 2: Synthesis of compound 440

[0571] Methyl 4-(((3R,5S)-4-(3-(((1-(diethylamino)propan-2-yl)amino)methyl)benzoyl)-3,5-dimethyl piperazin-1-yl)methyl)benzoate (formula 6-3, 0.163 g, 0.321 mmol), hydroxylamine (0.392 mL, 6.416 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.180 g, 3.208 mmol) were dissolved in methanol (1.5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 440** (0.105 g, 64.3 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.71 (d, 2 H, *J* = 8.2 Hz), 7.38 - 7.32 (m, 4 H), 7.25 (s, 1 H), 7.18 - 7.16 (m, 1 H), 4.37 (brs, 2 H), 3.83 - 3.80 (m, 1 H), 3.67 - 3.64 (m, 1 H), 3.52 (s, 2 H), 2.67 - 2.57 (m, 3 H), 2.45 - 2.37 (m, 2 H), 2.35 - 2.26 (m, 2 H), 2.25 - 2.11 (m, 5 H), 1.29 (s, 6 H), 0.93 - 0.86 (m, 9 H).

Example 203: Synthesis of compound 441

4-(((3R,5S)-4-(3-(((1-(benzyl(methyl)amino)propan-2-yl)amino)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-(((1-(benzyl(methyl)amino)propan-2-yl)amino)methyl)benzoyl)-3,5-d

imethylpiperazin-1-yl)methyl)benzoate

[0572] Methyl 4-(((3R,5S)-4-(3-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-

yl)methyl)benzoate (formula 6-2, 0.200 g, 0.482 mmol), N₁-benzyl-N₁-methylpropane-1,2-diamine (0.095 g, 0.530 mmol) and Cs₂CO₃ (0.188 g, 0.578 mmol) were dissolved in acetonitrile (2 mL) at room temperature, and the solution was stirred overnight at the same temperature. Water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 5 %) and concentrated to afford the desired compound (0.167 g, 62.2 %) as a pale yellow liquid.

Step 2: Synthesis of compound 441

[0573] Methyl 4-(((3R,5S)-4-(3-(((1-(benzyl(methyl)amino)propan-2-yl)amino)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 6-3, 0.167 g, 0.300 mmol), hydroxylamine (0.367 mL, 5.999 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.168 g, 3.000 mmol) were dissolved in methanol (1.5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 441** (0.134 g, 80.3 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.71 (d, 2 H, *J* = 8.2 Hz), 7.37 - 7.30 (m, 4 H), 7.28 - 7.19 (m, 6 H), 7.18 - 7.16 (m, 1 H), 4.42 (brs, 2 H), 3.83 - 3.79 (m, 1 H), 3.67 - 3.64 (m, 1 H), 3.50 (s, 2 H), 3.46 - 3.43 (m, 1 H), 3.31 (s, 1 H), 2.74 - 2.69 (m, 1 H), 2.60 (m, 1 H), 2.33 - 2.28 (m, 2 H), 2.13 - 2.08 (m, 3 H), 1.27 (s, 6 H), 0.93 - 0.91 (m, 3 H); LRMS (ES) *m/z* 558.4 (M⁺+1).

Example 204: Synthesis of compound 442

(N-hydroxy-4-(((3R,5S)-4-(3-((4-isopentylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(3-((4-isopentylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0574] Methyl 4-(((3R,5S)-4-(3-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-

yl)methyl)benzoate (formula 6-2, 0.200 g, 0.482 mmol), 1-isobutylpiperazine trifluoroacetate (0.136 g, 0.530 mmol) and Cs_2CO_3 (0.188 g, 0.578 mmol) were dissolved in acetonitrile (2 mL) at room temperature, and the solution was stirred overnight at the same temperature. Water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/ methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.162 g, 64.6 %) as a pale yellow liquid.

Step 2: Synthesis of compound 442

[0575] Methyl 4-(((3R,5S)-4-(3-((4-isopentylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 6-3, 0.162 g, 0.311 mmol), hydroxylamine (0.381 mL, 6.226 mmol, 50.00 % aqueous solution) and potassium hydroxide were dissolved in methanol (1.5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure to afford **compound 442** (0.121 g, 74.6 %) as a yellow solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.2 (brs, 1 H), 9.03 (brs, 1 H), 7.72 (d, 2 H, $J = 8.2$ Hz), 7.43 (d, 2 H, $J = 8.1$ Hz), 7.38 - 7.30 (m, 2 H), 7.23 - 7.19 (m, 2 H), 4.50 (brs, 2 H), 3.54 - 3.47 (m, 4 H), 2.62 (m, 2 H), 2.34 (m, 6 H), 2.26 - 2.22 (m, 3 H), 2.16 - 2.12 (m, 3 H), 1.56 - 1.53 (m, 1 H), 1.31 - 1.25 (m, 8 H), 0.86 - 0.84 (m, 6 H).

Example 205: Synthesis of compound 443

4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)benzoate

[0576] Methyl 4-(((3R,5S)-4-(3-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 6-2, 0.200 g, 0.482 mmol), 1-(2,2,2-trifluoroethyl)piperazine

trifluoroacetate (0.141 g, 0.530 mmol) and Cs_2CO_3 (0.188 g, 0.578 mmol) were dissolved in acetonitrile (2 mL) at room temperature, and the solution was stirred overnight at the same temperature. Water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.164 g, 62.3 %) as a pale yellow liquid.

Step 2: Synthesis of compound 443

[0577] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl)benzoyl) piperazin-1-yl)methyl)benzoate (0.148 g, 0.270 mmol), hydroxylamine (0.331 mL, 5.408 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.152 g, 2.704 mmol) were dissolved in methanol (1.5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure to afford **compound 443** (0.119 g, 80.5 %) as a pale yellow solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.2 (brs, 1 H), 9.08 (brs, 1 H), 7.72 (d, 2 H, $J = 8.2$ Hz), 7.39 - 7.19 (m, 6 H), 4.47 (brs, 2 H), 3.52 - 3.44 (m, 4 H), 3.17 - 3.10 (m, 2 H), 2.61 (s, 6 H), 2.36 (s, 4 H), 2.14 - 2.12 (m, 2 H), 1.29 (m, 6 H).

Example 206: Synthesis of compound 444

4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(methylsulfonyl)piperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(methylsulfonyl)piperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)benzoate

[0578] Methyl 4-(((3R,5S)-4-(3-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 6-2, 0.200 g, 0.482 mmol), 1-(methylsulfonyl)piperazine (0.087 g, 0.530 mmol) and Cs_2CO_3 (0.188 g, 0.578 mmol) were dissolved in acetonitrile (2 mL) at room

temperature, and the solution was stirred overnight at the same temperature. Water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/ methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.164 g, 62.8 %) as a white solid.

Step 2: Synthesis of compound 444

[0579] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(methylsulfonyl)piperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)benzoate (formula 6-3, 0.059 g, 0.109 mmol), hydroxylamine (0.133 mL, 2.178 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.061 g, 1.089 mmol) were dissolved in methanol (1.5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure to afford **compound 444** (0.042 g, 71.6 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.2 (brs, 1 H), 9.01 (brs, 1 H), 7.72 (d, 2 H, *J* = 8.2 Hz), 7.42 - 7.33 (m, 4 H), 7.25 - 7.21 (m, 2 H), 4.47 (brs, 2 H), 3.55 - 3.53 (m, 4 H), 3.10 (m, 4 H), 2.87 (m, 3 H), 2.69 - 2.56 (m, 2 H), 2.45 (s, 4 H), 2.16 - 2.12 (m, 2 H), 1.29 (m, 6 H).

Example 207: Synthesis of compound 446

4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholine-4-carbonyl)benzyl)piperazin-1-yl)methyl) -N-hydroxybenzamide)

Step 1: Synthesis of 3-(chloromethyl)benzoyl chloride

[0580] A mixture of 3-(bromomethyl)benzoic acid (1.000 g, 4.650 mmol) and SOCl₂ (10.120 mL, 139.509 mmol) was stirred at room temperature, and stirred at 70 °C for 16 hours, followed by cooling to room temperature to terminate the reaction. The reaction mixture was concentrated under reduced pressure, and the product was used without additional purification (0.879 g, 100.0 %, brown oil).

Step 2: Synthesis of (3-(chloromethyl)phenyl)(morpholino)methanone

[0581] 3-(Chloromethyl)benzoyl chloride (formula 6-1, 0.879 g, 4.650 mmol), morpholine (0.409 mL, 4.650 mmol) and TEA (1.289 mL, 9.300 mmol) were dissolved in methylene chloride (10 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; ethyl acetate/hexane = from 15 % to 40 %) and concentrated to afford the desired compound (0.415 g, 37.2 %) as a colorless oil.

Step 3: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholine-4-carbonyl)benzyl)piperazin-1-yl)methyl)benzoate

[0582] (3-(chloromethyl)phenyl)(morpholino)methanone (formula 6-4, 0.415 g, 1.730 mmol), methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.454 g, 1.730 mmol) and Cs₂CO₃ (1.127 g, 3.459 mmol) were dissolved in acetonitrile (2 mL), and the solution was stirred at room temperature for 16 hours, and then stirred at 100 °C for 6 hours, followed by cooling to room temperature to terminate the reaction. Water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.381 g, 47.3 %) as a yellow oil.

Step 4: Synthesis of compound 446

[0583] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholine-4-carbonyl)benzyl)piperazin-1-yl)methyl)benzoate (0.095 g, 0.204 mmol), hydroxylamine (0.250 mL, 4.085 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.115 g, 2.043 mmol) were dissolved in methanol (2 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure. A saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. **Compound 446** was used without additional purification (0.064 g, 67.4 %, white solid).

¹H-NMR (400 MHz, CDCl₃) δ 11.2 (brs, 1 H), 9.01 (brs, 1 H), 7.69 (d, 2 H, *J* = 8.0 Hz), 7.48 - 7.34 (m, 5 H), 7.21 (d, 1 H, *J* = 7.1 Hz), 3.75 (s, 2 H), 3.61 (brs, 7 H), 3.44 (s, 3 H), 2.66 - 2.63 (m, 4 H), 1.84 - 1.78 (m, 2 H), 0.87 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 467.2 (M⁺+1).

Example 208: Synthesis of compound 452**4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(methylsulfonyl)piperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)****Step 1: Synthesis of 1-benzyl-4-(methylsulfonyl)piperazine**

[0584] 1-benzylpiperazine (2.000 g, 11.347 mmol), MsCl (0.922 mL, 11.914 mmol) and TEA (2.372 mL, 17.020 mmol) were dissolved in methylene chloride (100 mL), and the solution was stirred at the same temperature for 3 hours. Water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was crystallized from diethyl ether (20 mL) and hexane (5 mL) at room temperature and filtered, and the resulting solid was washed with hexane and dried to yield the desired compound (0.857 g, 29.7 %) as a white solid.

Step 2: Synthesis of 1-(methylsulfonyl)piperazine

[0585] 1-benzyl-4-(methylsulfonyl)piperazine (0.700 g, 2.752 mmol) was dissolved in methanol (30 mL) at room temperature, and Pd/C (0.075 g) was slowly added to the solution, and then a hydrogen balloon was placed over the solution, followed by stirring at the same temperature for 3 hours. The reaction mixture was filtered through a celite pad to remove solids, and the filtrate was concentrated under reduced pressure to remove the solvent. The product was used without additional purification (0.335 g, 74.1 %, white solid).

Step 3: Methyl**4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(methylsulfonyl)piperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)benzoate**

[0586] Methyl 4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.200 g, 0.526 mmol) and 1-(methylsulfonyl)piperazine (0.129 g, 0.788 mmol) were dissolved in methylene chloride (5 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.223 g, 1.051 mmol) was added to the reaction solution, which was then further stirred at the same temperature for 17 hours. Then, a saturated aqueous solution

of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.254 g, 91.4 %) as a pale yellow oil.

Step 4: Synthesis of compound 452

[0587] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(methylsulfonyl)piperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)benzoate (formula 5-2, 0.254 g, 0.480 mmol), hydroxylamine (0.588 mL, 9.608 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.270 g, 4.804 mmol) were dissolved in methanol (7 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to remove solids, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter equipped with an anhydrous sodium sulfate cartridge to remove solid residue and an aqueous layer, and was then concentrated under reduced pressure to afford **compound 452** (0.115 g, 45.2 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.69 (d, 2 H, *J* = 7.7 Hz), 7.31 (d, 2 H, *J* = 7.8 Hz), 7.26 - 7.24 (m, 3 H), 7.12 (s, 1 H), 3.72 (s, 2 H), 3.51 (s, 2 H), 3.42 (s, 2 H), 3.10 (s, 4 H), 2.87 (s, 3 H), 2.64 (d, 2 H, *J* = 10.7 Hz), 2.57 - 2.55 (m, 2 H), 2.44 (s, 4 H), 1.81 (t, 2 H, *J* = 10.3 Hz), 0.90 (d, 6 H, *J* = 5.8 Hz).

Example 209: Synthesis of compound 453

4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of tert-butyl 4-(2,2,2-trifluoroethyl)piperazine-1-carboxylate

[0588] Tert-butyl piperazine-1-carboxylate (2.000 g, 10.738 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (1.625 mL, 11.275 mmol) and Cs₂CO₃ (4.198 g, 12.886 mmol) were dissolved in acetonitrile (100 mL) at room temperature, and the solution was stirred at the same temperature for 17 hours. The reaction mixture was filtered through a glass filter to remove solids, and the filtrate was concentrated under reduced pressure to remove the solvent. The concentrate was purified by column chromatography (silicon dioxide, 12 g

cartridge; ethyl acetate/hexane = from 0 % to 20 %) and concentrated to afford the desired compound (2.150 g, 74.7 %) as a colorless oil.

Step 2: Synthesis of 1-(2,2,2-trifluoroethyl)piperazine

[0589] Tert-butyl 4-(2,2,2-trifluoroethyl)piperazine-1-carboxylate (2.000 g, 7.455 mmol) was dissolved in methylene chloride (10 mL) / trifluoroacetic acid (5 mL) at room temperature, and the solution was stirred at the same temperature for 17 hours. The reaction mixture was concentrated under reduced pressure to remove the solvent, and the concentrate was crystallized from ethyl acetate (20 mL) at room temperature and filtered, and the resulting solid was washed with ethyl acetate and dried to afford the desired compound (0.457 g, 23.1 %) as a white solid.

Step 3: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)benzoate

[0590] Methyl 4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.200 g, 0.526 mmol) and 1-(2,2,2-trifluoroethyl)piperazine (0.209 g, 0.788 mmol) were dissolved in methylene chloride (5 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.223 g, 1.051 mmol) was added to the reaction solution, which was then further stirred at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.115 g, 41.1 %) as a pale yellow oil.

Step 4: Synthesis of compound 453

[0591] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)benzoate (formula 5-2, 0.115 g, 0.216 mmol), hydroxylamine (0.264 mL, 4.318 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.121 g, 2.159 mmol) were dissolved in methanol (5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction

with methylene chloride. The extract was filtered through a plastic filter equipped with an anhydrous sodium sulfate cartridge to remove solid residue and an aqueous layer, and was then concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈; 0.1 % trifluoroacetic acid aqueous solution/acetonitrile = from 0 % to 30 %), after which it was passed through a SPE cartridge (PL-HCO₃MP SPE) and concentrated to afford **compound 453** (0.012 g, 10.4 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 11.17 (brs, 1 H), 9.01 (brs, 1 H), 7.70 (d, 2 H, *J* = 8.3 Hz), 7.35 (d, 2 H, *J* = 8.2 Hz), 7.27 (s, 1 H), 7.23 - 7.22 (m, 2 H), 7.10 - 7.09 (m, 1 H), 3.72 (s, 2 H), 3.44 (s, 4 H), 3.14 (q, 2 H, *J* = 10.4 Hz), 2.68 - 2.65 (m, 2 H), 2.61 - 2.53 (m, 6 H), 2.37 - 2.33 (m, 4 H), 1.81 (t, 2 H, *J* = 10.3 Hz), 0.90 (d, 6 H, *J* = 6.0 Hz).

Example 210: Synthesis of compound 454

(N-hydroxy-4-(((3R,5S)-4-(3-((4-isopentylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamide)

Step 1: Synthesis of tert-butyl 4-isopentylpiperazine-1-carboxylate

[0592] Tert-butyl piperazine-1-carboxylate (2.000 g, 10.738 mmol), 1-bromo-3-methylbutane (1.352 mL, 11.275 mmol) and Cs₂CO₃ (4.198 g, 12.886 mmol) were dissolved in acetonitrile (150 mL) at room temperature, and the solution was stirred at the same temperature for 17 hours. The reaction mixture was filtered through a glass filter to remove solids, and the filtrate was concentrated under reduced pressure to remove the solvent. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; ethyl acetate/hexane = from 0 % to 10 %) and concentrated to afford the desired compound (1.220 g, 44.3 %) as a colorless oil.

Step 2: Synthesis of 1-isopentylpiperazine trifluoroacetate

[0593] Tert-butyl 4-isopentylpiperazine-1-carboxylate (1.000 g, 3.900 mmol) was dissolved in methylene chloride (10 mL) / trifluoroacetic acid (5 mL) at room temperature, and the solution was stirred at the same temperature for 17 hours. The reaction mixture was concentrated under reduced pressure to remove the solvent, and the concentrate was crystallized from ethyl acetate (20 mL) at room temperature and filtered, and the resulting solid was washed with ethyl acetate and dried to afford the desired compound (0.929 g, 94.0 %) as a white solid.

Step 3: Synthesis of methyl

4-(((3R,5S)-4-(3-((4-isopentylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0594] Methyl 4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.220 g, 0.578 mmol) and 1-isopentylpiperazine trifluoroacetate (0.220 g, 0.867 mmol) were dissolved in methylene chloride (5 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.245 g, 1.156 mmol) was added to the reaction solution, which was then further stirred at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.232 g, 77.0 %) as a pale yellow oil.

Step 4: Synthesis of compound 454

[0595] Methyl 4-(((3R,5S)-4-(3-((4-isopentylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-2, 0.232 g, 0.446 mmol), hydroxylamine (0.545 mL, 8.910 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.250 g, 4.455 mmol) were dissolved in methanol (5 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and was then concentrated under reduced pressure to afford **compound 454** (0.067g, 29.6 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.69 (d, 2 H, *J* = 8.2 Hz), 7.30 (d, 2 H, *J* = 8.1 Hz), 7.27 (s, 1 H), 7.23 - 7.21 (m, 2 H), 7.09 - 7.08 (m, 1 H), 3.72 (s, 2 H), 3.42 (s, 2 H), 3.41 (s, 2 H), 2.63 (d, 2 H, *J* = 10.2 Hz), 2.58 - 2.53 (m, 2 H), 2.34 - 2.27 (m, 8 H), 2.24 (t, 2 H, *J* = 7.6 Hz), 1.80 (t, 2 H, *J* = 10.5 Hz), 1.57 - 1.53 (m, 1 H), 1.31 - 1.25 (m, 2 H), 0.89 (d, 6 H, *J* = 6.1 Hz), 0.85 (d, 6 H, *J* = 6.6 Hz).

Example 211: Synthesis of compound 455

(4-(((3R,5S)-4-(3-(((1-(diethylamino)propan-2-yl)amino)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl**4-(((3R,5S)-4-(3-(((1-(diethylamino)propan-2-yl)amino)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate**

[0596] Methyl 4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.200 g, 0.526 mmol) and N₁,N₁-diethylpropane-1,2-diamine (0.103 g, 0.788 mmol) were dissolved in methylene chloride (5 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.223 g, 1.051 mmol) was added to the reaction solution, which was then further stirred at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.149 g, 57.3 %) as a pale yellow oil.

Step 2: Synthesis of compound 455

[0597] Methyl 4-(((3R,5S)-4-(3-(((1-(diethylamino)propan-2-yl)amino)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-2, 0.149 g, 0.301 mmol), hydroxylamine (0.368 mL, 6.024 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.169 g, 3.012 mmol) were dissolved in methanol (5 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and was then concentrated under reduced pressure to afford **compound 455** (0.064 g, 42.9 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.70 (d, 2 H, *J* = 8.2 Hz), 7.34 (d, 2 H, *J* = 8.0 Hz), 7.26 (s, 1 H), 7.24 - 7.18 (m, 2 H), 3.79 - 3.55 (m, 4 H), 3.43 (s, 2 H), 2.63 (d, 2 H, *J* = 10.1 Hz), 2.59 - 2.54 (m, 2 H), 2.46 - 2.37 (m, 2 H), 2.34 - 2.25 (m, 2 H), 2.23 - 2.15 (m, 2 H), 1.81 (t, 2 H, *J* = 10.4 Hz), 0.92 - 0.86 (m, 15 H).

Example 212: Synthesis of compound 456**4-(((3R,5S)-4-(3-(((1-(benzyl(methyl)amino)propan-2-yl)amino)methyl)benzyl)-3,5-d**

imethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)**Step 1: Synthesis of methyl****4-(((3R,5S)-4-(3-(((1-(benzyl(methyl)amino)propan-2-yl)amino)methyl)benzyl)-3,5-di methylpiperazin-1-yl)methyl)benzoate**

[0598] Methyl 4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.200 g, 0.526 mmol) and N₁-benzyl-N₁-methylpropane-1,2-diamine (0.141 g, 0.788 mmol) were dissolved in methylene chloride (5 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.223 g, 1.051 mmol) was added to the reaction solution, which was then further stirred at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.252 g, 88.3 %) as a pale yellow oil.

Step 2: Synthesis of compound 456

[0599] Methyl 4-(((3R,5S)-4-(3-(((1-(benzyl(methyl)amino)propan-2-yl)amino)methyl)benzyl)-3,5-di methylpiperazin-1-yl)methyl)benzoate (formula 5-2, 0.252 g, 0.464 mmol), hydroxylamine (0.568 mL, 9.286 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.261 g, 4.643 mmol) were dissolved in methanol (5 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and was then concentrated under reduced pressure to afford **compound 456** (0.196 g, 77.6 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.69 (d, 2 H, *J* = 8.2 Hz), 7.33 (d, 2 H, *J* = 8.2 Hz), 7.31 - 7.20 (m, 8 H), 7.12 (d, 1 H, *J* = 6.5 Hz), 3.80 - 3.57 (m, 4 H), 3.39 (s, 2 H), 2.70 - 2.69 (m, 1 H), 2.61 (d, 2 H, *J* = 10.8 Hz), 2.55 - 2.53 (m, 2 H), 2.34 - 2.29 (m, 1 H), 2.12 - 2.09 (m, 1 H), 1.79 (t, 2 H, *J* = 10.4 Hz), 0.92 (d, 3 H, *J* = 6.1 Hz), 0.88 (d, 6 H, *J* = 6.0 Hz).

Example 213: Synthesis of compound 457

4-(((3R,5S)-3,5-dimethyl-4-(2-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of 2-(bromomethyl)benzaldehyde

[0600] 2-(bromomethyl)benzonitrile (2.500 g, 12.752 mmol) was dissolved in methylene chloride (30 mL) at 0 °C, and DIBAL-H (1.00 M solution, 13.390 mL, 13.390 mmol) was added to the solution, followed by stirring at the same temperature for 2 hours. Then, an aqueous solution of hydrochloric acid was added to the reaction mixture at 0 °C, followed by stirring for 30 minutes. After completion of the reaction, water was added to the reaction mixture, which was then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 40 g cartridge; ethyl acetate/hexane = from 0 % to 30 %) and concentrated to afford the desired compound (0.400 g, 15.8 %) as a brown oil.

Step 2: Synthesis of methyl

4-(((3R,5S)-4-(2-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0601] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 0.500 g, 1.906 mmol), 2-(bromomethyl)benzaldehyde (0.379 g, 1.906 mmol) and Cs₂CO₃ (0.931 g, 2.859 mmol) were dissolved in acetonitrile (10 mL), and the solution was stirred at the same temperature for 17 hours. Water was added to the reaction mixture, which was then extracted with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; ethyl acetate/hexane = from 0 % to 40 %) and concentrated to afford the desired compound (0.116 g, 16.0 %) as a pale brown oil.

Step 3: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(2-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)benzoate

[0602] Methyl 4-(((3R,5S)-4-(2-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

(formula 5-1, 0.116 g, 0.305 mmol) and morpholine (0.040 mL, 0.457 mmol) were dissolved in methylene chloride (10 mL), and the solution was stirred at room temperature for 30 minutes. Na(OAc)₃BH (0.129 g, 0.610 mmol) was added to the reaction solution, which was then further stirred at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 30 %) and concentrated to afford the desired compound (0.076 g, 55.2 %) as a pale yellow oil.

Step 4: Synthesis of compound 457

[0603] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(2-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)benzoate (formula 5-2, 0.076 g, 0.168 mmol), hydroxylamine (0.018 mL, 3.366 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.094 g, 1.683 mmol) were dissolved in methanol (5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter equipped with an anhydrous sodium sulfate cartridge to remove solid residue and an aqueous layer, and was then concentrated under reduced pressure to afford **compound 457** (0.060 g, 78.8 %) as a pale yellow solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.77 (d, 1 H, *J* = 7.8 Hz), 7.71 (d, 2 H, *J* = 8.1 Hz), 7.33 (d, 2 H, *J* = 8.1 Hz), 7.22 - 7.21 (m, 1 H), 7.11 - 7.08 (m, 2 H), 3.86 (s, 2 H), 3.52 (s, 4 H), 3.46 (s, 2 H), 3.43 (s, 2 H), 2.68 (d, 2 H, *J* = 10.8 Hz), 2.65 - 2.61 (m, 2 H), 2.33 (s, 4 H), 1.87 (t, 2 H, *J* = 10.3 Hz), 0.80 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 453.2 (*M*⁺+1).

Example 214: Synthesis of compound 458

(4-(((3R,5S)-3,5-dimethyl-4-(4-(morpholinomethyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of 4-(chloromethyl)benzoyl chloride

[0604] A mixture of 4-(bromomethyl)benzoic acid (5.000 g, 23.251 mmol) and SOCl₂ (8.444 mL, 116.257 mmol) was stirred at room temperature, and stirred at 50 °C for 17 hours, followed by cooling to room temperature to terminate the reaction. The reaction mixture was concentrated under reduced pressure to remove the solvent, and the product was used

without additional purification (4.400 g, 100.1 %, palet purple solid).

Step 2: Synthesis of methyl

4-(((3R,5S)-4-(4-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0605] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 4.400 g, 23.275 mmol), 4-(chloromethyl)benzoyl chloride (formula 6-1, 3.053 g, 11.638 mmol) and TEA (6.488 mL, 46.551 mmol) were dissolved in methylene chloride (150 mL) at 0 °C, and the solution was stirred at room temperature for 3 hours. Water was added to the reaction mixture, which was then extracted with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 40 g cartridge; ethyl acetate/hexane = from 5 % to 70 %) and concentrated, and then the resulting material was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 5 % to 20 %) and concentrated to afford the desired compound (1.720 g, 17.8 %) as an orange solid.

Step 3: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(4-(morpholinomethyl)benzoyl)piperazin-1-yl)methyl)benzoate

[0606] Methyl 4-(((3R,5S)-4-(4-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 6-2, 0.100 g, 0.241 mmol), morpholine (0.031 mL, 0.362 mmol) and Cs₂CO₃ (0.157 g, 0.482 mmol) were dissolved in acetonitrile (4 mL) at room temperature, and the solution was stirred at the same temperature for 17 hours. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and water was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.107 g, 95.4 %) as a colorless oil.

Step 4: Synthesis of compound 458

[0607] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(4-(morpholinomethyl)benzoyl)piperazin-1-

yl)methyl)benzoate (formula 6-3, 0.107 g, 0.230 mmol), hydroxylamine (0.281 mL, 4.596 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.129 g, 2.298 mmol) were dissolved in methanol (5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter equipped with an anhydrous sodium sulfate cartridge to remove solid residue and an aqueous layer, and was then concentrated under reduced pressure to afford **compound 458** (0.034 g, 31.6 %) as a pale orange solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.70 (d, 2 H, *J* = 8.0 Hz), 7.36 - 7.34 (m, 4 H), 7.28 (d, 2 H, *J* = 8.0 Hz), 4.12 (brs, 2 H), 3.57 (t, 4 H, *J* = 4.4 Hz), 3.52 (s, 2 H), 3.48 (s, 2 H), 2.62 - 2.61 (m, 2 H), 2.35 (s, 4 H), 2.13 (dd, 2 H, *J* = 11.2, 4.2 Hz), 1.28 - 1.25 (m, 6 H); LRMS (ES) *m/z* 467.2 (*M*⁺+1).

Example 215: Synthesis of compound 459

4-(((3R,5S)-3,5-dimethyl-4-(4-(piperidin-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(4-piperidine-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)benzoate

[0608] Methyl 4-(((3R,5S)-4-(4-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 6-2, 0.100 g, 0.241 mmol), piperidine (0.031 mL, 0.362 mmol) and Cs₂CO₃ (0.157 g, 0.482 mmol) were dissolved in acetonitrile (4 mL) at room temperature, and the solution was stirred at the same temperature for 17 hours. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and water was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.101 g, 90.4 %) as a colorless oil.

Step 2: Synthesis of compound 459

[0609] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(4-piperidine-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)benzoate (formula 6-3, 0.101 g, 0.218 mmol), hydroxylamine (0.267 mL, 4.357 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.122 g, 2.179 mmol) were dissolved in methanol (5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; ethyl acetate/hexane = from 0 % to 30 %) and concentrated to afford **compound 459** (0.073 g, 72.1 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.72 (d, 2 H, *J* = 8.2 Hz), 7.42 (d, 2 H, *J* = 8.2 Hz), 7.33 (d, 2 H, *J* = 8.1 Hz), 7.27 (d, 2 H, *J* = 8.1 Hz), 4.12 (brs, 1 H), 3.54 (s, 2 H), 3.43 (s, 2 H), 2.64 - 2.62 (m, 2 H), 2.31 (s, 4 H), 2.15 (dd, 2 H, *J* = 11.4, 4.2 Hz), 1.52 - 1.46 (m, 4 H), 1.39 - 1.38 (m, 2 H), 1.29 (d, 6 H, *J* = 6.1 Hz); LRMS (ES) *m/z* 465.2 (*M*⁺ + 1).

Example 216: Synthesis of compound 460

4-(((3R,5S)-4-(4-(((R)-3-fluoropyrrolidin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(4-(((R)-3-fluoropyrrolidin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0610] Methyl 4-(((3R,5S)-4-(4-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 6-2, 0.100 g, 0.241 mmol), (R)-3-fluoropyrrolidine (0.045 g, 0.362 mmol) and Cs₂CO₃ (0.157 g, 0.482 mmol) were dissolved in acetonitrile (4 mL) at room temperature, and the solution was stirred at the same temperature for 17 hours. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and water was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/ methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.103 g, 91.4 %) as a pale yellow oil.

Step 2: Synthesis of compound 460

[0611] Methyl 4-(((3R,5S)-4-(4-(((R)-3-fluoropyrrolidin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 6-3, 0.103 g, 0.220 mmol), hydroxylamine (0.269 mL, 4.406 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.124 g, 2.203 mmol) were dissolved in methanol (5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; ethyl acetate/hexane = from 0 % to 30 %) and concentrated to afford **compound 460** (0.082 g, 79.4 %) as a white solid.

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 11.19 (brs, 1 H), 9.04 (brs, 1 H), 7.72 (d, 2 H, $J = 8.2$ Hz), 7.43 (d, 2 H, $J = 8.1$ Hz), 7.36 (d, 2 H, $J = 8.1$ Hz), 7.29 (d, 2 H, $J = 8.1$ Hz), 5.20 (dt, 1 H, $J = 55.5, 5.8$ Hz), 4.15 (brs, 2 H), 3.62 (s, 2 H), 3.55 (s, 2 H), 2.82 - 2.73 (m, 2 H), 2.68 - 2.61 (m, 3 H), 2.33 - 2.28 (m, 1 H), 2.17 - 2.13 (m, 3 H), 1.94 - 1.89 (m, 1 H), 1.29 (d, 6 H, $J = 5.3$ Hz).

Example 217: Synthesis of compound 461

(4-(((3R,5S)-3,5-dimethyl-4-(4-(pyrrolidin-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(4-(pyrrolidin-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)benzoate

[0612] Methyl 4-(((3R,5S)-4-(4-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 6-2, 0.100 g, 0.241 mmol), pyrrolidine (0.030 mL, 0.362 mmol) and Cs_2CO_3 (0.157 g, 0.482 mmol) were dissolved in acetonitrile (4 mL) at room temperature, and the solution was stirred at the same temperature for 17 hours. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and water was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.102 g, 94.1 %) as a pale yellow oil.

Step 2: Synthesis of compound 461

[0613] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(4-(pyrrolidin-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)benzoate (formula 6-3, 0.102 g, 0.227 mmol), hydroxylamine (0.278 mL, 4.537 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.127 g, 2.269 mmol) were dissolved in methanol (5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; ethyl acetate/hexane = from 0 % to 30 %) and concentrated to afford **compound 461** (0.071 g, 69.5 %) as a pale yellow solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 11.18 (brs, 1 H), 9.04 (brs, 1 H), 7.72 (d, 2 H, *J* = 8.2 Hz), 7.43 (d, 2 H, *J* = 8.1 Hz), 7.35 (d, 2 H, *J* = 8.0 Hz), 7.27 (d, 2 H, *J* = 8.0 Hz), 4.19 (brs, 2 H), 3.58 (s, 2 H), 3.55 (s, 2 H), 2.63 (d, 2 H, *J* = 10.0 Hz), 2.41 (s, 4 H), 2.15 (dd, 2 H, *J* = 11.4, 4.2 Hz), 1.70 - 1.68 (m, 4 H), 1.29 (d, 6 H, *J* = 6.1 Hz).

Example 218: Synthesis of compound 462

4-(((3R,5S)-3,5-dimethyl-4-(4-((4-methylpiperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(4-((4-methylpiperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)benzoate

[0614] Methyl 4-(((3R,5S)-4-(4-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 6-2, 0.100 g, 0.241 mmol), 1-methylpiperazine (0.040 mL, 0.362 mmol) and Cs₂CO₃ (0.157 g, 0.482 mmol) were dissolved in acetonitrile (4 mL) at room temperature, and the solution was stirred at the same temperature for 17 hours. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and water was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column

chromatography (silicon dioxide, 4 g cartridge; methanol/ methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.102 g, 88.4 %) as a colorless oil.

Step 2: Synthesis of compound 462

[0615] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(4-((4-methylpiperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)benzoate (formula 6-3, 0.102 g, 0.213 mmol), hydroxylamine (0.261 mL, 4.262 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.120 g, 2.131 mmol) were dissolved in methanol (5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered, washed with water, and dried to yield **compound 462** (0.057 g, 55.8 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 11.20 (brs, 1 H), 9.04 (brs, 1 H), 7.72 (d, 2 H, *J* = 8.2 Hz), 7.43 (d, 2 H, *J* = 8.1 Hz), 7.33 (d, 2 H, *J* = 8.1 Hz), 7.27 (d, 2 H, *J* = 7.8 Hz), 4.21 (brs, 2 H), 3.54 (s, 2 H), 3.47 (s, 2 H), 2.63 (d, 2 H, *J* = 11.4 Hz), 2.33 - 2.32 (m, 8 H), 2.17 - 2.14 (m, 5 H), 1.30 (s, 6 H); LRMS (ES) *m/z* 480.2 (*M*⁺+1).

Example 219: Synthesis of compound 463

4-(((3R,5S)-3,5-dimethyl-4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)benzoate

[0616] Methyl 4-(((3R,5S)-4-(4-(chloromethyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 6-2, 0.100 g, 0.241 mmol), 1-(methylsulfonyl)piperazine (0.059 g, 0.362 mmol) and Cs₂CO₃ (0.157 g, 0.482 mmol) were dissolved in acetonitrile (4 mL) at room temperature, and the solution was stirred at the same temperature for 17 hours. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and water was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column

chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.126 g, 96.3 %) as a colorless oil.

Step 2: Synthesis of compound 463

[0617] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)benzoate (formula 6-3, 0.126 g, 0.297 mmol), hydroxylamine (0.364 mL, 5.950 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.167 g, 2.975 mmol) were dissolved in methanol (5 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; ethyl acetate/hexane = from 0 % to 30 %) and concentrated to afford **compound 463** (0.065 g, 53.2 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.72 (d, 2 H, *J* = 8.3 Hz), 7.42 (d, 2 H, *J* = 8.1 Hz), 7.36 (d, 2 H, *J* = 8.1 Hz), 7.30 (d, 2 H, *J* = 8.2 Hz), 4.25 (brs, 2 H), 3.55 (s, 4 H), 3.11 (t, 4 H, *J* = 4.5 Hz), 2.87 (s, 3 H), 2.63 (d, 2 H, *J* = 10.3 Hz), 2.47 (s, 4 H), 2.15 (dd, 2 H, *J* = 11.4, 4.1 Hz), 1.29 - 1.28 (m, 6 H).

Example 220: Synthesis of compound 466

4-(((3R,5S)-3,5-dimethyl-4-(4-(pyrrolidin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(4-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0618] Methyl 4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 1-2, 1.000 g, 3.812 mmol), 4-(bromomethyl)benzaldehyde (0.759 g, 3.812 mmol) and Cs₂CO₃ (2.484 g, 7.623 mmol) were dissolved in acetonitrile (25 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. The reaction mixture was filtered through a paper filter to remove solids, and the filtrate was concentrated under reduced pressure to remove the solvent. The concentrate was purified by column chromatography (silicon dioxide,

40 g cartridge; ethyl acetate/hexane = from 0 % to 25 %) and concentrated to afford the desired compound (0.934 g, 64.4 %) as a white solid.

Step 2: Synthesis of methyl 4-(((3R,5S)-3,5-dimethyl-4-(4-(pyrrolidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)benzoate

[0619] Methyl 4-(((3R,5S)-4-(4-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.180 g, 0.473 mmol) and pyrrolidine (0.044 mL, 0.520 mmol) were dissolved in methylene chloride (2 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.150 g, 0.710 mmol) was added to the reaction solution, which was then further stirred at the same temperature for 16 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 30 % to 100 %) and concentrated to afford the desired compound (0.098 g, 47.5 %) as a yellow solid.

Step 3: Synthesis of compound 466

[0620] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(4-(pyrrolidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)benzoate (formula 5-2, 0.098 g, 0.225 mmol) and hydroxylamine (0.275 mL, 4.490 mmol, 50.00 % aqueous solution) were dissolved in methanol (3 mL) at room temperature, and potassium hydroxide (0.126 g, 2.245 mmol) was added to the solution, which was then stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure to afford **compound 466** (0.055 g, 56.0 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 10.9 (brs, 1 H), 9.07 (brs, 1 H), 7.69 (d, 2 H, *J* = 7.9 Hz), 7.34 (d, 2 H, *J* = 7.8 Hz), 7.26 (d, 2 H, *J* = 7.8 Hz), 7.20 (d, 2 H, *J* = 7.8 Hz), 3.70 (s, 2 H), 3.51 (s, 2 H), 3.42 (s, 2 H), 2.66 - 2.64 (m, 2 H), 2.60 - 2.55 (m, 2 H), 2.39 (s, 4 H), 1.79 (t, 2 H, *J* = 10.4 Hz), 1.66 (s, 4 H), 0.90 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 437.3 (*M*⁺+1).

Example 221: Synthesis of compound 467

(4-(((3R,5S)-3,5-dimethyl-4-(4-(piperidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl**4-(((3R,5S)-3,5-dimethyl-4-(4-(piperidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)benzoate**

[0621] Methyl 4-(((3R,5S)-4-(4-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.180 g, 0.473 mmol) and piperidine (0.052 mL, 0.520 mmol) were dissolved in methylene chloride (2 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.150 g, 0.710 mmol) was added to the reaction solution, which was then further stirred at the same temperature for 16 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 30 % to 100 %) and concentrated to afford the desired compound (0.149 g, 70.1 %) as a white solid.

Step 2: Synthesis of compound 467

[0622] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(4-(piperidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)benzoate (formula 5-2, 0.149 g, 0.332 mmol) and hydroxylamine (0.406 mL, 6.637 mmol, 50.00 % aqueous solution) were dissolved in methanol (3 mL) at room temperature, and potassium hydroxide (0.186 g, 3.318 mmol) was added to the solution, which was then stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure to afford **compound 467** (0.118 g, 78.8 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 11.2 (brs, 1 H), 9.04 (brs, 1 H), 7.69 (d, 2 H, *J* = 7.7 Hz), 7.33 (d, 2 H, *J* = 7.7 Hz), 7.26 (d, 2 H, *J* = 7.7 Hz), 7.18 (d, 2 H, *J* = 7.8 Hz), 3.70 (s, 2 H), 3.42 (s, 2 H), 2.62 (d, 2 H, *J* = 10.4 Hz), 2.55 (m, 2 H), 2.27 (s, 4 H), 1.79 (t, 2 H, *J* = 10.4 Hz), 1.48 - 1.45 (m, 4 H), 1.37 - 1.36 (m, 2 H), 0.90 (d, 6 H, *J* = 5.9 Hz); LRMS (ES) *m/z* 451.2 (M⁺+1).

Example 222: Synthesis of compound 468**4-(((3R,5S)-3,5-dimethyl-4-(4-(4-methylpiperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)**

Step 1: Synthesis of methyl**4-(((3R,5S)-3,5-dimethyl-4-(4-((4-methylpiperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)benzoate**

[0623] Methyl 4-(((3R,5S)-4-(4-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.180 g, 0.473 mmol) and 1-methylpiperazine (0.058 mL, 0.520 mmol) were dissolved in methylene chloride (2 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.150 g, 0.710 mmol) was added to the reaction solution, which was then further stirred at the same temperature for 16 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 30 % to 100 %) and concentrated to afford the desired compound (0.193 g, 87.7 %) as a white solid.

Step 2: Synthesis of compound 468

[0624] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(4-((4-methylpiperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)benzoate (formula 5-2, 0.192 g, 0.413 mmol) and hydroxylamine (0.506 mL, 8.264 mmol, 50.00 % aqueous solution) were dissolved in methanol (3 mL) at room temperature, and potassium hydroxide (0.232 g, 4.132 mmol) was added to the solution, which was then stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure to afford **compound 468** (0.041 g, 21.5 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 11.1 (brs, 1 H), 9.06 (brs, 1 H), 7.68 (d, 2 H, *J* = 8.1 Hz), 7.31 (d, 2 H, *J* = 7.9 Hz), 7.27 (d, 2 H, *J* = 8.0 Hz), 7.18 (d, 2 H, *J* = 7.9 Hz), 3.70 (s, 2 H), 3.42 (s, 2 H), 3.39 (s, 2 H), 2.67 - 2.61 (m, 2 H), 2.59 - 2.54 (m, 2 H), 2.43 - 2.17 (m, 8 H), 2.13 (s, 3 H), 1.79 (t, 2 H, *J* = 11.1 Hz), 0.89 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 466.3 (*M*⁺+1).

Example 223: Synthesis of compound 472

((E)-3-(4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide)**Step 1: Synthesis of (E)-methyl****3-(4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)phenyl)acrylate**

[0625] (E)-methyl 3-(4-(((3R,5S)-3,5-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 9-1, 0.300 g, 1.040 mmol), 3-(bromomethyl)benzaldehyde (0.207 g, 1.040 mmol) and Cs₂CO₃ (0.678 g, 2.081 mmol) were dissolved in acetonitrile (3 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. Water was added to the reaction mixture, followed by extraction with methylene chloride, and the extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; methanol/ methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.250 g, 59.2 %) as a yellow oil.

Step 2: Synthesis of (E)-methyl**3-(4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)phenyl)acrylate**

[0626] (E)-methyl 3-(4-(((3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 10-1, 0.250 g, 0.616 mmol) and morpholine (0.060 mL, 0.677 mmol) were dissolved in methylene chloride (3 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.196 g, 0.924 mmol) was added to the reaction solution, which was then further stirred at the same temperature for 16 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 30 % to 100 %) and concentrated to afford the desired compound (0.186 g, 63.1 %) as a yellow oil.

Step 3: Synthesis of compound 472

[0627] (E)-methyl 3-(4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)phenyl)acrylate (formula 10-2, 0.186 g, 0.389 mmol) and hydroxylamine (0.476 mL, 7.788 mmol, 50.00 % aqueous solution) were dissolved in methanol (4 mL) at room temperature, and potassium hydroxide (0.219 g, 3.894 mmol) was added to the solution, which was then stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈; acetonitrile/0.1 % trifluoroacetic acid = from 5 % to 70 %), after which it was passed through a SPE cartridge (PL-HCO₃ MP SPE) and concentrated to afford the desired **compound 472** (0.142 g, 63.4 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 10.8 (brs, 1 H), 9.06 (brs, 1 H), 7.51 - 7.49 (m, 2 H), 7.45 - 7.41 (m, 1 H), 7.38 - 7.19 (m, 4 H), 7.17 - 7.11 (m, 2 H), 6.44 - 6.41 (m, 1 H), 3.71 (s, 2 H), 3.56 (s, 4 H), 3.43 - 3.41 (m, 4 H), 2.65 - 2.62 (m, 4 H), 2.33 (brs, 4 H), 1.82 - 1.72 (m, 2 H), 0.89 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 479.3 (M⁺+1).

Example 224: Synthesis of compound 475

((E)-3-(4-(((2S,6R)-2,6-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide)

Step 1: Synthesis of (3R,5S)-tert-butyl 3,5-dimethylpiperazine-1-carboxylate

[0628] (2S,6R)-2,6-dimethylpiperazine (10.000 g, 87.573 mmol) and TEA (24.278 mL, 175.147 mmol) were dissolved in methylene chloride (150 mL) at room temperature, and Boc₂O (20.119 mL, 87.573 mmol) was added to the solution, which was then stirred at the same temperature for 16 hours. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 80 g cartridge; methanol/ methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (15.393 g, 82.0 %) as a yellow solid.

Step 2: Synthesis of (3R,5S)-tert-butyl

4-(4-((E)-3-methoxy-3-oxoprop-1-en-1-yl)benzyl)-3,5-dimethylpiperazine-1-carboxylate

[0629] (3R,5S)-tert-butyl 3,5-dimethylpiperazine-1-carboxylate (formula 8-1, 5.000 g, 23.332 mmol), methyl 3-(4-bromomethyl)cinamate (formula 8-4, 5.952 g, 23.332 mmol) and Cs_2CO_3 (15.204 g, 46.664 mmol) were mixed in acetonitrile (150 mL) at room temperature, and the mixture was heated under reflux, and then cooled to room temperature. The reaction mixture was filtered through a paper filter to remove solids, and the filtrate was concentrated under reduced pressure to remove the solvent. The concentrate was purified by column chromatography (silicon dioxide, 80 g cartridge; ethyl acetate/hexane = from 0 % to 20 %) and concentrated to afford the desired compound (6.800 g, 75.0 %) as a yellow oil.

Step 3: Synthesis of (E)-methyl

3-(4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acrylate

[0630] (3R,5S)-tert-butyl 4-(4-((E)-3-methoxy-3-oxoprop-1-en-1-yl)benzyl)-3,5-dimethylpiperazine-1-carboxylate (6.800 g, 17.503 mmol) and HCl (4.00 M dioxane solution, 21.879 mL, 87.516 mmol) were dissolved in 1,4-dioxane (100 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The precipitated solid was filtered, washed with hexane and dried to afford the desired compound (2.970 g, 58.8 %) as a brown solid.

Step 4: Synthesis of (E)-methyl

3-(4-(((2S,6R)-4-(3-formylbenzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acrylate

[0631] (E)-methyl 3-(4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 17-1, 0.300 g, 1.040 mmol), 3-(bromomethyl)benzaldehyde (0.207 g, 1.040 mmol) and Cs_2CO_3 (0.678 g, 2.081 mmol) were dissolved in acetonitrile (3 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. The reaction mixture was filtered through a paper filter to remove solids, and the filtrate was concentrated under reduced pressure to remove the solvent. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.293 g, 69.3 %) as a white solid.

Step 5: Synthesis of (E)-methyl**3-(4-(((2S,6R)-2,6-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)phenyl)acrylate**

[0632] (E)-methyl 3-(4-(((2S,6R)-4-(3-formylbenzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 17-2, 0.130 g, 0.320 mmol) and pyrrolidine (0.029 mL, 0.352 mmol) were dissolved in methylene chloride (3 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.102 g, 0.480 mmol) was added to the reaction solution, which was then further stirred at the same temperature for 16 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.062 g, 42.0 %) as a yellow oil.

Step 6: Synthesis of compound 475

[0633] (E)-methyl 3-(4-(((2S,6R)-2,6-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)phenyl)acrylate (formula 17-3, 0.062 g, 0.133 mmol) and hydroxylamine (0.163 mL, 2.664 mmol, 50.00 % aqueous solution) were dissolved in methanol (2 mL) at room temperature, and potassium hydroxide (0.075 g, 1.332 mmol) was added to the solution, which was then stirred at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (10 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered, washed with hexane, and dried to yield **compound 475** (0.039 g, 63.8 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 9.58 (brs, 1 H), 7.45 - 7.40 (m, 2 H), 7.33 - 7.31 (m, 2 H), 7.27 - 7.21 (m, 3 H), 7.18 - 7.12 (m, 2 H), 6.39 - 6.35 (m, 1 H), 3.71 (s, 2 H), 3.53 (s, 2 H), 2.65 - 2.63 (m, 3 H), 2.55 - 2.50 (m, 3 H), 2.39 - 2.33 (m, 4 H), 1.78 (t, 2 H, *J* = 10.4 Hz), 1.67 (s, 4 H), 0.89 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 463.2 (*M*⁺ +1).

Example 225: Synthesis of compound 476**((E)-3-(4-(((2S,6R)-4-(3-((diethylamino)methyl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide)**

Step 1: Synthesis of (E)-methyl**3-(4-(((2S,6R)-4-(3-((diethylamino)methyl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acrylate**

[0634] (E)-methyl 3-(4-(((2S,6R)-4-(3-formylbenzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 17-2, 0.130 g, 0.320 mmol) and diethylamine (0.039 g, 0.352 mmol) were dissolved in methylene chloride (3 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.102 g, 0.480 mmol) was added to the reaction solution, which was then further stirred at the same temperature for 16 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.061 g, 41.1 %) as a yellow oil.

Step 2: Synthesis of compound 476

[0635] (E)-methyl 3-(4-(((2S,6R)-4-(3-((diethylamino)methyl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 17-3, 0.061 g, 0.134 mmol) and hydroxylamine (0.164 mL, 2.683 mmol, 50.00 % aqueous solution) were dissolved in methanol (2 mL) at room temperature, and potassium hydroxide (0.075 g, 1.342 mmol) was added to the solution, which was then stirred at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure to afford **compound 476** (0.026 g, 41.2 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 10.7 (brs, 1 H), 9.04 (brs, 1 H), 7.47 - 7.45 (m, 3 H), 7.37 - 7.36 (m, 2 H), 7.25 - 7.21 (m, 2 H), 7.16 - 7.11 (m, 2 H), 6.42 - 6.38 (m, 1 H), 3.72 (s, 2 H), 3.50 (s, 2 H), 3.37 (s, 2 H), 2.65 - 2.63 (m, 2 H), 2.62 - 2.50 (m, 2 H), 2.42 (q, 4 H, *J* = 7.1 Hz), 1.78 (t, 2 H, *J* = 10.4 Hz), 0.95 (t, 6 H, *J* = 7.1 Hz), 0.87 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 465.3 (*M*⁺+1).

Example 226: Synthesis of compound 477

((E)-3-(4-(((2S,6R)-4-(4-(furan-2-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide)**Step 1: Synthesis of (E)-methyl****3-(4-(((2S,6R)-4-(4-bromobenzyl)-2,6-dimethylpiperazin-1-yl-methyl)phenyl)acrylate**

[0636] (E)-methyl 3-(4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 17-1, 0.200 g, 0.694 mmol), 1-(bromomethyl)-4-bromobenzene (0.173 g, 0.694 mmol) and Cs₂CO₃ (0.452 g, 1.387 mmol) were dissolved in acetonitrile (3 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. The reaction mixture was filtered through a paper filter to remove solids, and the filtrate was concentrated under reduced pressure to remove the solvent. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.209 g, 65.9 %) as a white solid.

Step 2: Synthesis of (E)-methyl**3-(4-(((2S,6R)-4-(4-(furan-2-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acrylate**

[0637] 1,2-Dimethoxyethane (0.9 mL) / water (0.1 mL) were added to a mixture of (E)-methyl 3-(4-(((2S,6R)-4-(4-bromobenzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 18-1, 0.100 g, 0.219 mmol), furan-2-boronic acid (0.027 g, 0.240 mmol), Pd(dbpf)Cl₂ (0.007 g, 0.011 mmol) and Na₂CO₃ (0.070 g, 0.656 mmol) at room temperature, and the solution was stirred at 50 °C for 16 hours, and followed by cooling to room temperature to terminate the reaction. Water was added to the reaction mixture, which was then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; 4 g cartridge; methanol/ methylene chloride = from 0 % to 3 %) and concentrated to afford the desired compound (0.080 g, 82.4 %) as a white solid.

Step 3: Synthesis of compound 477

[0638] (E)-methyl 3-(4-(((2S,6R)-4-(4-(furan-2-yl)benzyl)-2,6-dimethylpiperazin-1-

yl)methyl)phenyl)acrylate (formula 18-2, 0.077 g, 0.174 mmol), hydroxylamine (0.213 mL, 3.478 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.098 g, 1.739 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered, washed with hexane, and dried to yield **compound 477** (0.075 g, 96.8 %) as a brown solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 9.23 (brs, 1 H), 7.73 - 7.72 (m, 1 H), 7.65 - 7.63 (m, 1 H), 7.50 - 7.48 (m, 1 H), 7.38 - 7.36 (m, 2 H), 7.33 - 7.27 (m, 3 H), 7.25 - 7.23 (m, 1 H), 7.06 - 7.02 (m, 1 H), 6.90 (d, 1 H, *J* = 3.3 Hz), 6.59 - 6.57 (m, 1 H), 6.37 - 6.32 (m, 1 H), 3.70 (s, 2 H), 3.39 (s, 2 H), 2.66 - 2.53 (m, 4 H), 1.82 - 1.76 (m, 2 H), 0.90 (d, 6 H, *J* = 5.9 Hz); LRMS (ES) *m/z* 446.2 (*M*⁺+1).

Example 227: Synthesis of compound 478

4-(((2S,6R)-4-(3-((diethylamino)methyl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide (hydrochloride salt)

Step 1: Synthesis of methyl

4-(((2S,6R)-4-(3-((diethylamino)methyl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate

[0639] Methyl 4-(((2S,6R)-4-(3-formylbenzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 17-2, 0.150 g, 0.394 mmol) and diethylamine hydrochloride (0.065 g, 0.591 mmol) were dissolved in methylene chloride (4 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.167 g, 0.788 mmol) was added to the reaction solution, which was then further stirred at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 5 % to 10 %) and concentrated to afford the desired compound (0.054 g, 31.3 %) as an orange oil.

[0640] Step 2: Synthesis of compound 478

[0641] methyl 4-(((2S,6R)-4-(3-((diethylamino)methyl)benzyl)-2,6-dimethylpiperazin-1-

yl)methyl)benzoate (formula 17-3, 0.054 g, 0.123 mmol), hydroxylamine (0.151 mL, 2.468 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.069 g, 1.234 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The product was used without additional purification (0.045 g, 83.1 %, pale brown oil).

Step 3: Synthesis of hydrochloride salt of compound 478

[0642] 4-(((2S,6R)-4-(3-((diethylamino)methyl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide (0.048 g, 0.110 mmol) and HCl (4.00 M dioxane solution, 0.137 mL, 0.548 mmol) were dissolved in 1,4-dioxane (3 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to remove the solvent, and ethyl acetate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered, washed with ethyl acetate, and dried to yield **compound 478** (0.039 g, 75.0 %) as a white solid.

¹H-NMR (400 MHz, D₂O) δ 7.65 (d, 2 H, *J* = 7.6 Hz), 7.51 (d, 2 H, *J* = 8.4 Hz), 7.46 - 7.42 (m, 4 H), 4.52 (s, 2 H), 2.22 (s, 2 H), 2.20 (s, 2 H), 3.47 - 3.44 (m, 4 H), 3.08 - 3.05 (m, 6 H), 1.42 (d, 6 H, *J* = 5.7 Hz), 1.17 (t, 6 H, *J* = 7.0 Hz).

Example 228: Synthesis of compound 479

4-(((2S,6R)-2,6-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((2S,6R)-2,6-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)benzoate

[0643] Methyl 4-(((2S,6R)-4-(3-formylbenzyl)-2,6-dimethylpiperazin-1-yl)methyl)benzoate (formula 17-2, 0.150 g, 0.394 mmol) and pyrrolidine (0.049 mL, 0.591 mmol) were dissolved in methylene chloride (4 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.167 g, 0.788 mmol) was added to the reaction solution, which was then further

stirred at the same temperature for 17 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 5 % to 10 %) and concentrated to afford the desired compound (0.122 g, 71.0 %) as an orange oil.

Step 2: Synthesis of compound 479

[0644] Methyl 4-(((2S,6R)-2,6-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)benzoate (formula 17-3, 0.122 g, 0.280 mmol), hydroxylamine (0.343 mL, 5.601 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.157 g, 2.801 mmol) were dissolved in methanol (5 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 479** (0.069 g, 56.4 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 11.11 (brs, 1 H), 9.05 (brs, 1 H), 7.66 (d, 2 H, *J* = 8.1 Hz), 7.41 (d, 2 H, *J* = 8.1 Hz), 7.26 - 7.22 (m, 2 H), 7.15 (dd, 2 H, *J* = 7.3, 7.3 Hz), 3.74 (s, 2 H), 3.54 (s, 2 H), 3.39 (s, 2 H), 2.65 (d, 2 H, *J* = 10.8 Hz), 2.56 - 2.55 (m, 2 H), 2.40 (s, 4 H), 1.79 (t, 2 H, *J* = 10.6 Hz), 1.67 (s, 4 H), 0.87 (d, 6 H, *J* = 6.1 Hz).

Example 229: Synthesis of compound 480

((E)-3-(4-(((2S,6R)-2,6-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide)

Step 1: Synthesis of (E)-methyl

3-(4-(((2S,6R)-4-(3-formylbenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acrylate

[0645] (E)-methyl 3-(4-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 17-1, 0.300 g, 1.040 mmol), 3-formylbenzoic acid (0.172 g, 1.144 mmol), EDCI (0.399 g, 2.081 mmol), HOBt (0.319 g, 2.081 mmol) and DIPEA (0.921 mL, 5.201 mmol) were dissolved in

methylene chloride (3 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. The reaction mixture was concentrated under reduced pressure to remove the solvent, and the concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/ hexane = from 30 % to 40 %) and concentrated to afford the desired compound (0.386 g, 88.2 %) as a white solid.

Step 2: Synthesis of (E)-methyl 3-(4-(((2S,6R)-2,6-dimethyl-4-(3-(pyrrolidin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)phenyl)acrylate

[0646] (E)-methyl 3-(4-(((2S,6R)-4-(3-formylbenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 17-2, 0.190 g, 0.452 mmol) and pyrrolidine (0.035 g, 0.497 mmol) were dissolved in methylene chloride (3 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.144 g, 0.678 mmol) was added to the reaction solution, which was then further stirred at the same temperature for 12 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/ methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.105 g, 49.0 %) as a white solid.

Step 3: Synthesis of compound 480

[0647] (E)-methyl 3-(4-(((2S,6R)-2,6-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)phenyl)acrylate (formula 17-3, 0.100 g, 0.210 mmol) and hydroxylamine (0.257 mL, 4.205 mmol, 50.00 % aqueous solution) were dissolved in methanol (3 mL) at room temperature, and potassium hydroxide (0.118 g, 2.103 mmol) was added to the solution, which was then stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure to afford **compound 480** (0.049 g, 48.8 %) as a white solid.

¹H-NMR (400 MHz, CD₃OD) δ 7.45 - 7.30 (m, 9 H), 6.51 - 6.46 (m, 1 H), 4.41 - 4.38 (m, 1 H), 3.85 (s, 2 H), 3.67 (s, 2 H), 3.54 - 3.48 (m, 1 H), 3.04 - 3.00 (m, 1 H), 2.79 - 2.76 (m, 1 H), 2.70 - 3.67 (m, 1 H), 2.54 (s, 6 H), 1.80 (s, 4 H), 1.14 - 1.08 (m, 3 H), 0.93 - 0.92 (m, 3 H); LRMS (ES) m/z 477.2 (M⁺+1).

Example 230: Synthesis of compound 481

4-(((3R,5S)-3,5-dimethyl-4-(2-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of tert-butyl

4-(2-(((2S,6R)-4-(4-(methoxycarbonyl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate

[0648] 1,2-dimethoxyethane (15 mL) / water (5 mL) were added to a mixture of methyl 4-(((3R,5S)-4-(2-iodobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 2-1, 1.600 g, 3.345 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaboran-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (2.068 g, 6.689 mmol), Pd(dbpf)₂Cl₂ (0.109 g, 0.167 mmol) and Na₂CO₃ (0.709 g, 6.689 mmol) at room temperature, and the solution was stirred at 50 °C for 17 hours, and followed by cooling to room temperature to terminate the reaction. A saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; ethyl acetate/hexane = from 5 % to 50 %) and concentrated to afford the desired compound (1.090 g, 61.1 %) as a brown oil.

Step 2: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(2-(1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)benzoate

[0649] Tert-butyl 4-(2-(((2S,6R)-4-(4-(methoxycarbonyl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate (formula 3-1, 1.080 g, 2.024 mmol) was dissolved in 1,4-dioxane (15 mL) at room temperature, and HCl (4.00 M 1,4-dioxane solution, 5.059 mL, 20.236 mmol) was added to the solution, which was then stirred at the same temperature for 17 hours. The reaction mixture was concentrated under reduced pressure to remove the solvent, and ethyl acetate (200 mL) and methanol (10 mL) were added to the concentrate, followed by stirring. The precipitated solid was filtered, washed with ethyl acetate, and dried to yield the desired compound (0.851 g, 89.5 %) as a pale yellow solid.

Step 3: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(2-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)benzoate

[0650] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(2-(1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)benzoate hydrochloride (formula 3-2, 0.060 g, 0.128 mmol) and TEA (0.053 mL, 0.383 mmol) were dissolved in methylene chloride (4 mL) at room temperature, and MsCl (0.015 mL, 0.191 mmol) was added to the solution, followed by stirring at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to remove the solvent, and the concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.055 g, 84.2 %) as a pale yellow oil.

Step 4: Synthesis of compound 481

[0651] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(2-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)benzoate (formula 3-3, 0.055 g, 0.107 mmol), hydroxylamine (0.131 mL, 2.150 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.060 g, 1.075 mmol) were dissolved in methanol (2 mL) / tetrahydrofuran (1 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 481** (0.048 g, 87.1 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.72 (d, 1 H, *J* = 8.2 Hz), 7.70 (d, 2 H, *J* = 8.2 Hz), 7.32 (d, 2 H, *J* = 8.1 Hz), 7.24 (dd, 1 H, *J* = 7.5, 7.5 Hz), 7.15 (dd, 1 H, *J* = 7.4, 7.4 Hz), 7.04 (d, 1 H, *J* = 7.4 Hz), 5.59 (s, 1 H), 3.83 (d, 2 H, *J* = 2.1 Hz), 3.62 (s, 2 H), 3.45 (s, 2 H), 3.40 - 3.38 (m, 2 H), 2.65 (d, 2 H, *J* = 10.7 Hz), 2.61 - 2.57 (m, 2 H), 2.40 (s, 2 H), 1.85 (t, 2 H, *J* = 10.3 Hz), 0.78 (d, 6 H, *J* = 6.0 Hz).

Example 231: Synthesis of compound 482

(4-(((3R,5S)-4-(2-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-*N*-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(2-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0652] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(2-(1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)benzoate hydrochloride (formula 3-2, 0.060 g, 0.128 mmol) and TEA (0.053 mL, 0.383 mmol) were dissolved in methylene chloride (4 mL) at room temperature, and acetic anhydride (0.020 g, 0.191 mmol) was added to the solution, followed by stirring at the same temperature for 1 hour. Water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 5 %) and concentrated to afford the desired compound (0.046 g, 75.8 %) as a pale yellow oil.

Step 2: Synthesis of compound 482

[0653] Methyl 4-(((3R,5S)-4-(2-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 3-3, 0.046 g, 0.097 mmol), hydroxylamine (0.118 mL, 1.934 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.054 g, 0.967 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 482** (0.036 g, 78.1 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 11.05 (brs, 1 H), 9.12 (brs, 1 H), 7.71 (d, 3 H, *J* = 7.9 Hz), 7.36 (d, 2 H, *J* = 7.9 Hz), 7.23 (dd, 1 H, *J* = 7.7, 7.7 Hz), 7.14 (dd, 1 H, *J* = 7.4, 7.4 Hz), 7.03 (d, 1 H, *J* = 7.5 Hz), 5.55 (s, 1 H), 4.08 (d, 2 H, *J* = 21.4 Hz), 3.68 - 3.62 (m, 4 H), 3.46 (s, 2 H), 2.68 - 2.57 (m, 4 H), 2.35 (s, 1 H), 2.25 (s, 1 H), 2.07 (d, 3 H, *J* = 8.5 Hz), 1.85 (t, 2 H, *J* = 10.0 Hz), 0.78 (d, 6 H, *J* = 5.9 Hz).

Example 232: Synthesis of compound 483

(4-(((3R,5S)-3,5-dimethyl-4-(2-(1-(2,2,2-trifluoroethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl**4-(((3R,5S)-3,5-dimethyl-4-(2-(1-(2,2,2-trifluoroethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)benzoate**

[0654] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(2-(1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)benzoate (0.050 g, 0.115 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (formula 3-2, 0.025 mL, 0.173 mmol) and K₂CO₃ (0.032 g, 0.231 mmol) were dissolved in acetonitrile (4 mL) at room temperature, and the solution was stirred at the same temperature for 4 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; ethyl acetate/hexane = from 0 % to 30 %) and concentrated to afford the desired compound (0.032 g, 53.9 %) as a yellow oil.

Step 2: Synthesis of compound 483

[0655] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(2-(1-(2,2,2-trifluoroethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)benzoate (formula 3-3, 0.032 g, 0.062 mmol), hydroxylamine (0.076 mL, 1.241 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.035 g, 0.621 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters, C₁₈; acetonitrile/0.1 % trifluoroacetic acid aqueous solution = from 5 % to 70 %), after which it was passed through a SPE cartridge (PL-HCO₃ MPS PE) and concentrated to afford **compound 483** (0.007 g, 21.8 %) as a white solid.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 9.03 (s, 1 H), 7.71 - 7.69 (m, 3 H), 7.39 - 7.38 (m, 2 H), 7.22 (dd, 1 H, *J* = 7.3, 7.3 Hz), 7.13 (dd, 1 H, *J* = 7.2, 7.2 Hz), 7.03 (d, 1 H, *J* = 7.4 Hz), 5.49 (s, 1 H), 3.62 (s, 2 H), 3.47 (s, 2 H), 3.31 - 3.28 (m, 4 H), 2.88 (t, 2 H, *J* = 5.0 Hz), 2.68 - 2.61 (m, 4 H), 2.33 - 2.30 (m, 2 H), 1.85 - 1.84 (m, 2 H), 0.79 (d, 6 H, *J* = 5.7 Hz).

Example 233: Synthesis of compound 484**(N-hydroxy-4-(((3R,5S)-4-(2-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-**

dimethylpiperazin-1-yl)methyl)benzamide)Step 1: Synthesis of methyl4-(((3R,5S)-4-(2-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0656] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(2-(1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)benzoate hydrochloride (formula 3-2, 0.150 g, 0.319 mmol) and TEA (0.222 mL, 1.596 mmol) were dissolved in methylene chloride (10 mL) at room temperature, and 2-iodopropane (0.075 g, 0.479 mmol) was added to the solution, which was then heated under reflux for 5 hours, followed by cooling to room temperature to terminate the reaction. Water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 20 %) and concentrated, and then the resulting material was purified by chromatography (Waters, C₁₈; acetonitrile/0.1 % trifluoroacetic acid aqueous solution = from 5 % to 70 %), after which it was passed through a SPE cartridge (PL-HCO₃ MP SPE) and concentrated to afford the desired compound (0.032 g, 21.1 %) as a pale yellow oil.

Step 2: Synthesis of compound 484

[0657] Methyl 4-(((3R,5S)-4-(2-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 3-3, 0.032 g, 0.067 mmol), hydroxylamine (0.082 mL, 1.345 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.038 g, 0.673 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered, washed with water, and dried to yield **compound 484** (0.006 g, 18.7 %) as a white solid.

¹H-NMR (400 MHz, CD₃OD) δ 7.78 (d, 1 H, *J* = 6.7 Hz), 7.74 (d, 2 H, *J* = 8.3 Hz), 7.47 (d, 2 H, *J* = 8.1 Hz), 7.20 (dd, 1 H, *J* = 6.5, 6.5 Hz), 7.13 (dd, 1 H, *J* = 7.2, 7.2 Hz), 7.03 (d, 1 H, *J* = 7.4 Hz), 5.55 (s, 1 H), 3.75 (s, 2 H), 3.57 (s, 2 H), 3.30 (s, 2 H), 2.87 - 2.81 (m, 3 H), 2.76 - 2.69 (m, 4 H), 2.42 (s, 2 H), 1.97 (t, 2 H, *J* = 10.4 Hz), 1.19 (d, 6 H, *J* = 6.5 Hz), 0.87 (d, 6 H, *J* = 6.0 Hz).

Example 234: Synthesis of compound 485

4-(((3R,5S)-4-(2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0658] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(2-(1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)benzoate hydrochloride (formula 3-2, 0.150 g, 0.319 mmol) and TEA (0.222 mL, 1.596 mmol) were dissolved in methylene chloride (4 mL) at room temperature, and 2-iodopropane (0.048 mL, 0.479 mmol) was added to the solution, which was then stirred at the same temperature for 3 hours. Water was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/methylene chloride = from 0 % to 20 %) and concentrated to afford the desired compound (0.048 g, 32.6 %) as a yellow liquid.

Step 2: Synthesis of compound 485

[0659] Methyl 4-(((3R,5S)-4-(2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 3-3, 0.048 g, 0.104 mmol), hydroxylamine (0.127 mL, 2.080 mmol, 50.00 % aqueous solution) and potassium hydroxide (0.058 g, 1.040 mmol) were dissolved in methanol (3 mL) at room temperature, and the solution was stirred at the same temperature for 30 minutes. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure to afford **compound 485** (0.033 g, 68.6 %) as a white solid.

[0660] ¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.70 (d, 3 H, *J* = 8.2 Hz), 7.35 (d, 2 H, *J* = 8.1 Hz), 7.20 (dd, 1 H, *J* = 7.5, 7.5 Hz), 7.12 (dd, 1 H, *J* = 7.5, 7.5 Hz), 7.00 (dd, 1 H, *J* = 7.5, 1.3 Hz), 5.49 (s, 1 H), 3.62 (s, 2 H), 3.46 (s, 2 H), 3.03 (s, 2 H), 2.66 - 2.56 (m, 6 H), 2.45 (q, 2 H, *J* =

7.2 Hz), 2.28 (brs, 2 H), 1.84 (t, 2 H, $J = 10.4$ Hz), 1.07 (t, 3 H, $J = 7.2$ Hz), 0.78 (d, 6 H, $J = 6.1$ Hz).

Example 235: Synthesis of compound 486

4-(((3R,5S)-4-(4-((4-acetylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamide (hydrochloride salt)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-(4-((4-acetylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate

[0661] Methyl 4-(((3R,5S)-4-(4-formylbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-1, 0.180 g, 0.473 mmol) and 1-(piperazin-1-yl)ethanone (0.067 g, 0.520 mmol) were dissolved in methylene chloride (2 mL), and the solution was stirred at room temperature for 1 hour. $\text{Na}(\text{OAc})_3\text{BH}$ (0.150 g, 0.710 mmol) was added to the reaction solution, which was then further stirred at the same temperature for 16 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The extract was filtered through a plastic filter to remove solid residue and an aqueous layer, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide; 4 g cartridge; ethyl acetate/hexane = from 30 % to 100 %) and concentrated to afford the desired compound (0.112 g, 48.2 %) as a white solid.

Step 2: Synthesis of compound 486

[0662] Methyl 4-(((3R,5S)-4-(4-((4-acetylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzoate (formula 5-2, 0.112 g, 0.228 mmol) and hydroxylamine (0.279 mL, 4.563 mmol, 50.00 % aqueous solution) were dissolved in methanol (3 mL) at room temperature, and potassium hydroxide (0.128 g, 2.282 mmol) were added to the solution, which was then stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (Waters,

C₁₈; acetonitrile/0.1 % trifluoroacetic acid aqueous solution = from 5 % to 70 %), after which it was passed through a SPE cartridge (PL-HCO₃ MP SPE) and concentrated to afford **compound 486** (0.049 g, 43.5 %) as a white solid.

Step 3: Synthesis of hydrochloride salt of compound 486

[0663] Compound 486 (0.049 g, 0.099 mmol) and HCl (4.00 M dioxane solution, 0.124 mL, 0.496 mmol) were dissolved in 1,4-dioxane (1 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. The precipitated solid was filtered, washed with ethyl acetate, and dried to yield the desired compound (0.034 g, 63.9 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.72 (d, 2 H, *J* = 8.2 Hz), 7.61 - 7.55 (m, 4 H), 7.52 (d, 2 H, *J* = 8.0 Hz), 4.59 (s, 2 H), 4.39 (s, 2 H), 4.23 (s, 2 H), 3.71 - 3.69 (m, 8 H), 3.56 - 3.46 (m, 6 H), 3.06 (m, 3 H), 2.11 (s, 3 H), 1.51 - 1.50 (m, 6 H); LRMS (ES) *m/z* 494.2 (*M*⁺+1).

Example 236: Synthesis of compound 487

((E)-3-(4-(((2S,6R)-4-(3-((diethylamino)methyl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamide)

Step 1: Synthesis of (E)-methyl

3-(4-(((2S,6R)-4-(3-((diethylamino)methyl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acrylate

[0664] (E)-methyl 3-(4-(((2S,6R)-4-(3-formylbenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 17-2, 0.190 g, 0.452 mmol) and diethylamine (0.054 g, 0.497 mmol) were dissolved in methylene chloride (3 mL), and the solution was stirred at room temperature for 1 hour. Na(OAc)₃BH (0.144 g, 0.678 mmol) was added to the reaction solution, which was then further stirred at the same temperature for 12 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; methanol/ methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (0.060 g, 27.8 %) as a white solid.

Step 2: Synthesis of compound 487

[0665] (E)-methyl 3-(4-(((2S,6R)-4-(3-((diethylamino)methyl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)acrylate (formula 17-3, 0.060 g, 0.126 mmol) and hydroxylamine (0.154 mL, 2.512 mmol, 50.00 % aqueous solution) were dissolved in methanol (2 mL) at room temperature, and potassium hydroxide (0.070 g, 1.256 mmol) was added to the solution, which was then stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure to afford **compound 487** (0.006 g, 9.3 %) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.57 - 7.53 (m, 1 H), 7.51 - 7.46 (m, 3 H), 7.45 - 7.39 (m, 4 H), 7.36 - 7.34 (m, 1 H), 6.45 (d, 1 H, *J* = 15.9 Hz), 4.42 - 4.39 (m, 1 H), 3.87 - 3.82 (m, 2 H), 3.53 - 3.50 (m, 1 H), 3.07 - 3.01 (m, 1 H), 2.83 - 2.77 (m, 2 H), 2.73 - 2.68 (m, 4 H), 2.57 (s, 1 H), 1.29 (m, 2 H), 1.15 - 1.11 (m, 9 H), 0.93 - 0.88 (m, 3 H); LRMS (ES) *m/z* 479.2 (*M*⁺+1).

Example 237: Synthesis of compound 520

(3-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxy-1H-indole-6-carboxamide)

Step 1: Synthesis of methyl

3-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-1H-indole-6-carboxylate

[0666] Methyl 3-formyl-1H-indole-6-carboxylate (formula 8-4, 0.500 g, 2.461 mmol), (2S,6R)-1-benzyl-2,6-dimethylpiperazine (0.553 g, 2.707 mmol) and STAB (0.782 g, 3.691 mmol) were dissolved in methylene chloride (20 mL) at room temperature, and the solution was stirred at the same temperature for 5 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; ethyl acetate/hexane = from 0 % to 30 %) and concentrated to afford the desired compound (0.551 g, 57.2 %) as an ivory solid.

Step 2: Synthesis of compound 520

[0667] Methyl 3-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-1H-indole-6-carboxylate (formula 8-5, 0.150 g, 0.383 mmol), hydroxylamine (50.00 % aqueous solution, 0.234 mL, 3.831 mmol) and potassium hydroxide (0.215 g, 3.831 mmol) were dissolved in methylene chloride (10 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 520** (0.149 g, 99.4 %) as a white solid.

¹H-NMR (400 MHz, CD₃OD) δ 7.80 (s, 1 H), 7.56 (d, 2 H, *J* = 8.3 Hz), 7.42 (d, 1 H, *J* = 8.3 Hz), 7.34 - 7.25 (m, 5 H), 7.16 (t, 1 H, *J* = 7.2 Hz), 3.70 (s, 2 H), 3.55 (s, 2 H), 2.72 (d, 2 H, *J* = 10.0 Hz), 2.55 - 2.53 (m, 2 H), 1.78 (t, 2 H, *J* = 10.6 Hz), 0.89 (s, 3 H), 0.87 (s, 3 H); LRMS (ES) *m/z* 393.0 (*M*⁺+1).

Example 238: Synthesis of compound 569

(5-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxy-1H-indole-2-carboxamide)

Step 1: Synthesis of 1-(tert-butyl) 2-ethyl

5-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-1H-indole-1,2-dicarboxylate

[0668] 1-(tert-butyl)2-ethyl5-(bromomethyl)-1H-indole-1,2-dicarboxylate (formula 22-1, 2.000 g, 5.232 mmol), DIPEA (2.779 mL, 15.697 mmol) and (2S,6R)-1-benzyl-2,6-dimethylpiperazine (1.069 g, 5.232 mmol) were dissolved in methylene chloride (10 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. The precipitated solid was filtered, washed with acetonitrile, and dried to yield the desired compound (1.100 g, 41.6 %) as a white solid.

Step 2: Synthesis of ethyl

5-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-1H-indole-2-carboxylate

[0669] 1-(tert-butyl)2-ethyl 5-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-1H-indole-

1,2-dicarboxylate (formula 22-2, 1.100 g, 2.175 mmol) and hydrochloric acid (4.00 M 1,4-dioxane solution, 2.719 mL, 10.877 mmol) were mixed in 1,4-dioxane (2 mL) at room temperature, and the mixture was stirred at the same temperature for 16 hours. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and diethyl ether (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered, washed with diethyl ether, and dried to yield the desired compound (0.832 g, 94.3 %) as a pale pink solid.

Step 3: Synthesis of compound 569

[0670] Ethyl 5-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-1H-indole-2-carboxylate (formula 22-3, 0.100 g, 0.247 mmol), hydroxylamine (50.00 % aqueous solution, 0.151 mL, 2.466 mmol) and potassium hydroxide (0.138 g, 2.466 mmol) were dissolved in methanol (1 mL) / tetrahydrofuran (1 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 569** (0.079 g, 81.6 %) as a white solid.

¹H-NMR (400 MHz, CD₃OD) δ 7.46 (s, 1 H), 7.38 - 7.28 (m, 5 H), 7.24 - 7.20 (m, 1 H), 7.11 (dd, 1 H, *J* = 8.4, 1.3 Hz), 6.79 (s, 1 H), 3.91 (s, 2 H), 3.53 (s, 2 H), 2.79 (d, 2 H, *J* = 11.0 Hz), 2.72 - 2.68 (m, 2 H), 1.93 (t, 2 H, *J* = 11.1 Hz), 1.11 (s, 3 H), 1.10 (s, 3 H) ; LRMS (ES) *m/z* 393.0 (*M*⁺+1).

Example 239: Synthesis of compound 571

(5-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzofuran-2-carboxamide)

Step 1: Synthesis of methyl

5-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)benzofuran-2-carboxylate

[0671] Methyl 5-(bromomethyl)benzofuran-2-carboxylate (formula 8-4, 0.500 g, 1.858 mmol), DIPEA (0.720 g, 5.574 mmol) and (2S,6R)-1-benzyl-2,6-dimethylpiperazine (0.380 g, 1.858 mmol) were dissolved in acetonitrile (10 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to remove the solvent, and the precipitated solid was filtered, washed with

acetonitrile, and dried to yield the desired compound (0.200 g, 27.4 %) as a white solid.

[0672] Step 2: Synthesis of compound 571

[0673] Methyl 5-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)benzofuran-2-carboxylate (formula 8-5, 0.050 g, 0.127 mmol), hydroxylamine (50.00 % aqueous solution, 0.078 mL, 1.274 mmol) and potassium hydroxide (0.071 g, 1.274 mmol) were dissolved in methanol (1 mL) / tetrahydrofuran (1 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 571** (0.010 g, 19.4 %) as a pale pink solid.

¹H-NMR (400 MHz, CD₃OD) δ 7.60 (s, 1 H), 7.49 (d, 1 H, *J* = 8.4 Hz), 7.38 - 7.34 (m, 3 H), 7.31 (t, 1 H, *J* = 7.5 Hz), 7.25 - 7.21 (m, 2 H), 3.92 (s, 2 H), 3.56 (s, 2 H), 2.77 (d, 2 H, *J* = 10.8 Hz), 2.73 - 2.66 (m, 2 H), 1.94 (t, 2 H, *J* = 10.9 Hz), 1.12 (s, 3 H), 1.10 (s, 3 H); LRMS (ES) *m/z* 392.2 (*M*⁺-1).

Example 240: Synthesis of compound 573

(6-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxy-1H-indole-2-carboxamide)

Step 1: Synthesis of 1-(tert-butyl) 2-methyl

6-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-1H-indole-1,2-dicarboxylate

[0674] 1-(tert-butyl) 2-methyl 6-(bromomethyl)-1H-indole-1,2-dicarboxylate (formula 22-1, 0.410 g, 1.113 mmol), DIPEA (0.432 g, 3.340 mmol) and (2S,6R)-1-benzyl-2,6-dimethylpiperazine (0.227 g, 1.113 mmol) were dissolved in acetonitrile (10 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 40 g cartridge; ethyl acetate/hexane = from 0 % to 20 %) and concentrated to afford the desired compound (0.224 g, 40.9 %) as a yellow liquid.

Step 2: Synthesis of methyl

6-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-1H-indole-2-carboxylate (hydrochloride salt)

[0675] 1-(tert-butyl)2-methyl 6-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-1H-indole-1,2-dicarboxylate (formula 22-2, 0.224 g, 0.456 mmol) and hydrochloric acid (4.00 M 1,4-dioxane solution, 0.570 mL, 2.278 mmol) were dissolved in 1,4-dioxane (2 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and diethyl ether (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered, washed with diethyl ether, and dried to yield the desired compound (0.167 g, 85.6 %) as a white solid.

Step 3: Synthesis of compound 573

[0676] Methyl 6-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-1H-indole-2-carboxylate (formula 22-3, 0.050 g, 0.117 mmol), hydroxylamine (50.00 % aqueous solution, 0.071 mL, 1.168 mmol) and potassium hydroxide (0.066 g, 1.168 mmol) were dissolved in methanol (1 mL) / tetrahydrofuran (1 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 573** (0.025 g, 53.4 %) as a yellow solid.

¹H-NMR (400 MHz, CD₃OD) δ 7.49 (d, 1 H, *J* = 8.3 Hz), 7.37 (d, 2 H, *J* = 7.4 Hz), 7.31 (t, 3 H, *J* = 7.5 Hz), 7.23 (t, 1 H, *J* = 7.4 Hz), 7.00 (d, 1 H, *J* = 8.2 Hz), 6.81 (s, 1 H), 3.91 (s, 2 H), 3.55 (s, 2 H), 2.79 (d, 2 H, *J* = 10.9 Hz), 2.71 - 2.68 (m, 2 H), 1.93 (t, 2 H, *J* = 10.7 Hz), 1.11 (s, 3 H), 1.10 (s, 3 H); LRMS (ES) *m/z* 391.2 (*M*⁺-1)

Example 241: Synthesis of compound 574

(2-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzofuran-5-carboxamide)

Step 1: Synthesis of methyl

2-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)benzofuran-5-carboxylate

[0677] Methyl 2-(bromomethyl)benzofuran-5-carboxylate (formula 8-4, 0.691 g, 2.568 mmol), DIPEA (1.364 mL, 7.704 mmol) and (2S,6R)-1-benzyl-2,6-dimethylpiperazine (0.525 g, 2.568 mmol) were dissolved in acetonitrile (10 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. Water was added to the reaction mixture, which was then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 40 g cartridge; ethyl acetate/hexane = from 0 % to 20 %) and concentrated to afford the desired compound (0.460 g, 45.6 %) as an ivory solid.

Step 2: Synthesis of compound 574

[0678] Methyl 2-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)benzofuran-5-carboxylate (formula 8-5, 0.100 g, 0.254 mmol), hydroxylamine (50.00 % aqueous solution, 0.155 mL, 2.541 mmol) and potassium hydroxide (0.143 g, 2.541 mmol) were dissolved in methanol (1 mL) / tetrahydrofuran (1 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 574** (0.013 g, 13.0 %) as a pale pink solid.

¹H-NMR (400 MHz, CD₃OD) δ 8.00 (d, 1 H, *J* = 1.4 Hz), 7.72 (dd, 1 H, *J* = 8.6, 1.8 Hz), 7.50 (d, 1 H, *J* = 8.7 Hz), 7.38 - 7.20 (m, 5 H), 6.80 (s, 1 H), 3.90 (s, 2 H), 3.70 (s, 2 H), 2.85 (d, 1 H, *J* = 10.7 Hz), 2.76 - 2.71 (m, 2 H), 2.07 (t, 2 H, *J* = 11.0 Hz), 1.12 (s, 3 H), 1.10 (s, 3 H); LRMS (ES) *m/z* 394.0 (*M*⁺+1).

Example 242: Synthesis of compound 609

(5-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxypicolinamide)

Step 1: Synthesis of tert-butyl

(3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazine-1-carboxylate

[0679] (3R,5S)-tert-butyl 3,5-dimethylpiperazine-1-carboxylate (formula 8-1, 2.730 g, 12.739 mmol), 3-(bromomethyl)benzaldehyde (2.789 g, 14.013 mmol) and Cs_2CO_3 (8.301 g, 25.478 mmol) were mixed in acetonitrile (50 mL) at room temperature, and the mixture was stirred at the same temperature for 18 hours. The reaction mixture was filtered through a paper filter to remove solids, and the filtrate was purified by column chromatography (silicon dioxide, 120 g cartridge; ethyl acetate/hexane = from 5 % to 30 %) and concentrated to afford the desired compound (2.730 g, 64.5 %) as a yellow oil.

Step 2: Synthesis of tert-butyl

(3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazine-1-carboxylate

[0680] Tert-butyl (3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazine-1-carboxylate (formula 23-1, 1.246 g, 3.749 mmol), morpholine (0.656 mL, 7.497 mmol) and acetic acid (0.429 mL, 7.497 mmol) were mixed in methylene chloride (15 mL), and the mixture was stirred at room temperature for 1 hour. $\text{Na}(\text{CN})\text{BH}_3$ (0.942 g, 14.995 mmol) was added to the reaction mixture, which was then further stirred at the same temperature for 4 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 24 g cartridge; methanol/methylene chloride = from 0 % to 10 %) and concentrated to afford the desired compound (1.272 g, 84.0 %) as a yellow oil.

Step 3: Synthesis of

4-(3-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzyl)morpholine (hydrochloride salt)

[0681] Tert-butyl (3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazine-1-carboxylate (formula 23-2, 1.270 g, 3.147 mmol) and HCl (4.00 M 1,4-dioxane solution, 3.934 mL, 15.735 mmol) were dissolved in methylene chloride (15 mL) at room temperature, and the solution was stirred at the same temperature for 18 hours. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate was added to the resulting concentrate, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The product was used without additional purification (0.855 g, 89.5 %, yellow oil).

Step 4: Synthesis of methyl**5-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)picolinate**

[0682] Methyl 5-formylpicolinate (0.200 g, 1.211 mmol), 4-(3-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzyl)morpholine (0.735 g, 2.422 mmol) and acetic acid (0.139 mL, 2.422 mmol) were mixed in methylene chloride (8 mL), and the mixture was stirred at room temperature for 1 hour. Na(CN)BH₃ (0.304 g, 4.844 mmol) was added to the reaction mixture, which was then further stirred at the same temperature for 15 hours. Then, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; ethyl acetate/hexane = from 60 % to 100 %) and concentrated to afford the desired compound (0.317 g, 57.8 %) as a yellow oil.

Step 5: Synthesis of compound 609

[0683] Methyl 5-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)picolinate (formula 23-4, 0.059 g, 0.130 mmol) and hydroxylamine (0.333 mL, 2.594 mmol, 50.00 % aqueous solution) were mixed in methanol (1 mL), and potassium hydroxide (0.130 mL, 1.297 mmol, 10.00 M aqueous solution) was added thereto at 0 °C. Then, the mixture was stirred at the same temperature for 5 minutes, and then stirred at room temperature for 15 hours. The reaction mixture was concentrated under reduced pressure, and the concentrate was purified by column chromatography (Waters, C₁₈; 0.1%-formic acid (methanoic acid) aqueous solution/acetonitrile = from 5 % to 30 %), after which it was passed through a SPE cartridge (PL-HCO₃MP SPE) and concentrated to afford **compound 609** (0.006 g, 10.2 %) as a brown oil.

¹H NMR (400 MHz, CD₃OD) δ 8.52 (s, 1 H), 7.99 - 7.87 (m, 2 H), 7.36 (s, 1 H), 7.28 - 7.27 (m, 2 H), 7.21 - 7.20 (m, 1 H), 3.90 (s, 2 H), 3.69 - 3.67 (m, 4 H), 3.54 - 3.52 (m, 4 H), 2.73 - 2.65 (m, 4 H), 2.45 (s, 4 H), 1.96 (t, 2 H, *J* = 10.6 Hz), 1.09 (d, 6 H, *J* = 6.0 Hz); LRMS (ES) *m/z* 454.5 (M⁺+1).

Example 243: Synthesis of compound 652**(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N,2-dihydroxybenzamide)**

Step 1: Synthesis of methyl**4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-2-hydroxybenzoate**

[0684] Methyl 4-(bromomethyl)-2-hydroxybenzoate (formula 8-4, 1.144 g, 4.668 mmol), TEA (0.776 mL, 5.602 mmol) and (2S,6R)-1-benzyl-2,6-dimethylpiperazine (0.954 g, 4.668 mmol) were dissolved in acetonitrile (10 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 40 g cartridge; ethyl acetate/hexane = from 0 % to 20 %) and concentrated to afford the desired compound (0.583 g, 33.9 %) as a yellow liquid.

Step 2: Synthesis of compound 652

[0685] Methyl 4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-2-hydroxybenzoate (formula 8-5, 0.050 g, 0.136 mmol), hydroxylamine (50.00 % aqueous solution, 0.083 mL, 1.357 mmol) and potassium hydroxide (0.076 g, 1.357 mmol) were dissolved in methanol (1 mL) / tetrahydrofuran (1 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 652** (0.035 g, 70.0 %) as a pink solid.

¹H-NMR (400 MHz, CD₃OD) δ 7.61 (d, 1 H, *J* = 8.1 Hz), 7.39 (d, 2 H, *J* = 7.1 Hz), 7.33 (t, 2 H, *J* = 7.5 Hz), 7.25 (t, 1 H, *J* = 7.2 Hz), 6.90 (s, 1 H), 6.86 (d, 1 H, *J* = 8.1 Hz), 3.96 (s, 2 H), 3.45 (s, 2 H), 2.78 - 2.72 (m, 4 H), 1.99 - 1.94 (m, 4 H), 1.15 (s, 3 H), 1.32 (s, 3 H); LRMS (ES) *m/z* 370.2 (*M*⁺+1).

Example 244: Synthesis of compound 653**(4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-N,2 - dihydroxybenzamide)****Step 1: Synthesis of tert-butyl**

(3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazine-1-carboxylate

[0686] Tert-butyl (3R,5S)-4-(3-formylbenzyl)-3,5-dimethylpiperazine-1-carboxylate (formula 23-1, 10.439 g, 31.401 mmol) was dissolved in methylene chloride (150 mL) at room temperature, and morpholine (2.747 mL, 31.401 mmol) was added to the solution, followed by stirring at the same temperature for 1 hour. STAB (13.310 g, 62.802 mmol) was added to the reaction mixture, which was then further stirred at the same temperature for 16 hours. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 80 g cartridge; ethyl acetate/hexane = from 0 % to 80 %) and concentrated to afford the desired compound (11.080 g, 87.4 %) as a colorless liquid.

Step 2: Synthesis of**4-(3-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzyl)morpholine(hydrochloride salt)**

[0687] Tert-butyl (3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazine-1-carboxylate (formula 23-2, 11.080 g, 27.456 mmol) and hydrochloric acid (4.00 M 1,4-dioxane solution, 34.320 mL, 137.278 mmol) were dissolved in 1,4-dioxane (2 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and diethyl ether (150 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield the desired compound (7.800 g, 83.6 %) as a white solid.

Step 3: Synthesis of methyl**4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-2-hydroxybenzoate**

[0688] 4-(3-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzyl)morpholine hydrochloride (formula 23-3, 0.832 g, 2.448 mmol) and methyl 4-(bromomethyl)-2-hydroxybenzoate (0.600 g, 2.448 mmol), TEA (0.407 mL, 2.938 mmol) were dissolved in acetonitrile (10 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. Water was

added to the reaction solution, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 40 g cartridge; ethyl acetate/hexane = from 0 % to 50 %) and concentrated to afford the desired compound (0.441 g, 38.5 %) as a yellow liquid.

Step 4: Synthesis of compound 653

[0689] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-2-hydroxybenzoate (formula 23-4, 0.050 g, 0.107 mmol), hydroxylamine (50.00 % aqueous solution, 0.065 mL, 1.069 mmol) and potassium hydroxide (0.060 g, 1.069 mmol) were dissolved in methanol (1 mL) / tetrahydrofuran (1 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 653** (0.033 g, 83.7 %) as a reddish brown solid.

¹H-NMR (400 MHz, CD₃OD) δ 7.65 (d, 1 H, *J* = 8.0 Hz), 7.38 (s, 1 H), 7.30 (d, 2 H, *J* = 5.2 Hz), 7.23 - 7.22 (m, 1 H), 6.81 (s, 1 H), 6.74 (d, 2 H, *J* = 7.8 Hz), 3.92 (s, 2 H), 3.71 - 3.69 (m, 4 H), 3.54 (s, 2 H), 3.41 (s, 2 H), 2.77 - 2.67 (m, 4 H), 2.47 (m, 4 H), 1.93 - 1.90 (m, 2 H), 1.11 (s, 3 H), 1.10 (s, 3 H); LRMS (ES) *m/z* 469.3 (*M*⁺+1).

Example 245: Synthesis of compound 696

4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-3-fluoro-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-3-fluorobenzoate

[0690] 4-(3-(((2S,6R)-2,6-dimethylpiperazin-1-yl)methyl)benzyl)morpholine (formula 23-3, 1.376 g, 4.048 mmol), TEA (0.673 mL, 4.857 mmol) and methyl 4-(bromomethyl)-3-fluorobenzoate (1.000 g, 4.048 mmol) were dissolved in acetonitrile (150 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. Water was

added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 80 g cartridge; ethyl acetate/hexane = from 0 % to 20 %) and concentrated to afford the desired compound (0.438 g, 35.5 %) as a yellow liquid.

Step 2: Synthesis of compound 696

[0691] Methyl 4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-3-fluorobenzoate (formula 23-4, 0.100 g, 0.213 mmol), hydroxylamine (0.070 g, 2.130 mmol) and potassium hydroxide (0.119 g, 2.130 mmol) were dissolved in methanol (2 mL) at room temperature, and the solution was stirred at the same temperature for 3 hours. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 696** (0.025 g, 25.0 %) as a yellow solid.

¹H-NMR (400 MHz, CD₃OD) δ 7.58 - 7.20 (m, 7 H), 3.90 (s, 2 H), 3.71 - 3.68 (m, 4 H), 3.57 (s, 2 H), 3.53 (s, 2 H), 2.77 (d, 2 H, J = 10.2 Hz), 2.71 - 2.67 (m, 2 H), 2.46 - 2.45 (m, 4 H), 1.99 (t, 2 H, J = 10.8 Hz), 1.10 (s, 3 H), 1.09 (s, 3 H); LRMS (ES) m/z 471.2 ($M^{+}+1$).

Example 246: Synthesis of compound 812

(5-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxypicolinamide)

Step 1: Synthesis of methyl

5-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)picolinate

[0692] Methyl 5-formylpicolinate (formula 8-4, 0.200 g, 0.831 mmol), (2S,6R)-1-benzyl-2,6-dimethylpiperazine (0.151 g, 0.914 mmol) and STAB (0.264 g, 1.246 mmol) were dissolved in methylene chloride (5 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; ethyl acetate/hexane = from 0 % to 20 %) and concentrated to afford the

desired compound (0.116 g, 39.5 %) as a yellow liquid.

Step 2: Synthesis of compound 812

[0693] Methyl 5-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)picolinate (formula 8-5, 0.116 g, 0.328 mmol), hydroxylamine (50.00 % aqueous solution, 0.100 mL, 1.641 mmol) and potassium hydroxide (0.092 g, 1.641 mmol) were dissolved in methanol (1 mL) / tetrahydrofuran (1 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 812** (0.088 g, 75.7 %) as a white solid.

¹H-NMR (400 MHz, CDCl₃) δ 8.47 (s, 1 H), 8.07 (d, 1 H, *J* = 7.9 Hz), 7.83 (d, 1 H, *J* = 7.9 Hz), 7.38 - 7.24 (m, 5 H), 3.91 (s, 2 H), 3.53 (s, 2 H), 2.75 - 2.68 (m, 4 H), 2.09 - 2.03 (m, 2 H), 1.11 (s, 3 H), 1.10 (s, 3 H); LRMS (ES) *m/z* 353.1 (*M*⁺+1).

Example 247: Synthesis of compound 813

4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-3-fluoro-N-hydroxybenzamide

Step 1: Synthesis of methyl

4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-3-fluorobenzoate

[0694] Methyl 4-(bromomethyl)-3-fluorobenzoate (formula 8-4, 0.200 g, 0.831 mmol), (2S,6R)-1-benzyl-2,6-dimethylpiperazine (0.226 g, 0.914 mmol) and sodium carbonate (0.230 g, 1.661 mmol) were dissolved in acetonitrile (5 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; ethyl acetate/hexane = from 0 % to 20 %) and concentrated to afford the desired compound (0.135 g, 43.9 %) as an ivory solid.

Step 2: Synthesis of compound 813

[0695] Methyl 4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-3-fluorobenzoate (formula 8-5, 0.135 g, 0.364 mmol), hydroxylamine (50.00 % aqueous solution, 0.111 mL, 1.822 mmol) and potassium hydroxide (0.102 g, 1.822 mmol) were dissolved in methanol (1 mL) / tetrahydrofuran (1 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 813** (0.087 g, 64.3 %) as an ivory solid.

¹H-NMR (400 MHz, CDCl₃) δ 8.47 (s, 1 H), 8.07 (d, 1 H, *J* = 7.9 Hz), 7.83 (d, 2 H, *J* = 8.2 Hz), 7.38 - 7.24 (m, 5 H), 3.91 (s, 2 H), 3.53 (s, 2 H), 2.75 - 2.68 (m, 4 H), 2.10 - 2.04 (m, 2 H), 1.11 (s, 3 H), 1.10 (s, 3 H); LRMS (ES) *m/z* 372.1 (*M*⁺+1).

Example 248: Synthesis of compound 814

4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazine-1-carbonyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazine-1-carbonyl)benzoate

[0696] Methyl 4-(chlorocarbonyl)benzoate (formula 8-4, 0.200 g, 0.831 mmol), (2S,6R)-1-benzyl-2,6-dimethylpiperazine (0.181 g, 0.914 mmol) and TEA (0.232 mL, 1.661 mmol) were dissolved in methylene chloride (5 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 12 g cartridge; ethyl acetate/hexane = from 0 % to 20 %) and concentrated to afford the desired compound (0.152 g, 49.9 %) as a white solid.

Step 2: Synthesis of compound 814

[0697] Methyl 4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazine-1-carbonyl)benzoate (formula 8-4, 0.152 g, 0.415 mmol), hydroxylamine (50.00 % aqueous solution, 0.127 mL, 2.074 mmol) and potassium hydroxide (0.116 g, 2.074 mmol) were dissolved in methanol (1 mL) / tetrahydrofuran (1 mL) at room temperature, and the solution was stirred at the same

temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 814** (0.118 g, 77.4 %) as a white solid.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.66 (d, 2 H, $J = 6.7$ Hz), 7.20 - 6.99 (m, 7 H), 3.61 (s, 2 H), 2.74 - 2.68 (m, 2 H), 2.49 (m, 2 H), 2.37 - 2.33 (m, 2 H), 0.92 (s, 3 H), 0.71 (s, 3 H); LRMS (ES) m/z 368.1 ($\text{M}^+ + 1$)

Example 249: Synthesis of compound 818

(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)sulfonyl)-N-hydroxybenzamide)

Step 1: Synthesis of methyl

4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)sulfonyl)benzoate

[0698] Methyl 4-(chlorosulfonyl)benzoate (formula 8-4, 0.200 g, 0.852 mmol), (2S,6R)-1-benzyl-2,6-dimethylpiperazine (0.186 g, 0.938 mmol) and TEA (0.236 mL, 1.705 mmol) were dissolved in methylene chloride (10 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 50 %) and concentrated to afford the desired compound (0.181 g, 52.8 %) as a white solid.

Step 2: Synthesis of compound 818

[0699] Methyl 4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)sulfonyl)benzoate (formula 8-5, 0.100 g, 0.248 mmol), hydroxylamine (50.00 % aqueous solution, 0.076 mL, 1.242 mmol) and potassium hydroxide (0.070 g, 1.242 mmol) were dissolved in methanol (1 mL) / tetrahydrofuran (1 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 818** (0.042 g, 41.9 %) as an ivory solid.

¹H-NMR (400 MHz, CD₃OD) δ 8.00 (d, 2 H, *J* = 8.3 Hz), 7.81 (d, 2 H, *J* = 8.4 Hz), 7.32 - 7.25 (m, 4 H), 7.19 (t, 1 H, *J* = 7.0 Hz), 3.82 (s, 2 H), 3.52 (d, 2 H, *J* = 11.2 Hz), 2.73 - 2.68 (m, 2 H), 2.19 (t, 2 H, *J* = 10.6 Hz), 1.07 (s, 3 H), 1.05 (s, 3 H); LRMS (ES) *m/z* 404.1 (*M*⁺+1).

Example 250: Synthesis of compound 820

2-(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)sulfonyl)phenyl)-N-hydroxyacetamide)

Step 1: Synthesis of methyl

2-(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)sulfonyl)phenyl)acetate

[0700] Methyl 2-(4-(chlorosulfonyl)phenyl)acetate (formula 8-4, 0.200 g, 0.804 mmol), (2S,6R)-1-benzyl-2,6-dimethylpiperazine (0.176 g, 0.885 mmol) and TEA (0.223 mL, 1.608 mmol) were dissolved in methylene chloride (10 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 20 %) and concentrated to afford the desired compound (0.198 g, 59.2 %) as a colorless liquid.

Step 2: Synthesis of compound 820

[0701] Methyl 2-(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)sulfonyl)phenyl)acetate (formula 8-5, 0.198 g, 0.475 mmol), hydroxylamine (50.00 % aqueous solution, 0.145 mL, 2.377 mmol) and potassium hydroxide (0.133 g, 2.377 mmol) were dissolved in methanol (1 mL) / tetrahydrofuran (1 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 820** (0.124 g, 62.5 %) as a white solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.67 (d, 2 H, *J* = 7.6 Hz), 7.37 - 7.15 (m, 7 H), 3.74 (s, 2 H), 3.49 (d, 2 H, *J* = 7.8 Hz), 3.21 (s, 2 H), 2.74 (m, 2 H), 2.23 - 2.18 (m, 2 H), 0.99 (s, 3 H), 0.98 (s, 3 H); LRMS (ES) *m/z* 418.1 (*M*⁺+1).

Example 251: Synthesis of compound 822**(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxycyclohexane-1-carboxamide)****Step 1: Synthesis of methyl****4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)cyclohexane-1-carboxylate**

[0702] Methyl 4-formylcyclohexane-1-carboxylate (formula 8-4, 0.150 g, 0.881 mmol), (2S,6R)-1-benzyl-2,6-dimethylpiperazine (0.212 g, 0.881 mmol) and STAB (0.280 g, 1.322 mmol) were dissolved in methylene chloride (10 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/hexane = from 0 % to 50 %) and concentrated to afford the desired compound (0.175 g, 55.4 %) as a colorless liquid.

Step 2: Synthesis of compound 822

[0703] Methyl 4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)cyclohexane-1-carboxylate (formula 8-5, 0.175 g, 0.488 mmol), hydroxylamine (50.00 % aqueous solution, 0.149 mL, 2.441 mmol) and potassium hydroxide (0.137 g, 2.441 mmol) were dissolved in methanol (1 mL) / tetrahydrofuran (1 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 822** (0.050 g, 28.5 %) as a white solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.38 (d, 2 H, *J* = 7.4 Hz), 7.32 - 7.28 (m, 2 H), 7.21 (t, 1 H, *J* = 7.3 Hz), 3.82 (s, 2 H), 2.72 - 2.67 (m, 4 H), 2.19 - 1.96 (m, 3 H), 1.83 - 1.67 (m, 6 H), 1.48 - 1.45 (m, 5 H), 1.03 (s, 6 H); LRMS (ES) *m/z* 360.2 (*M*⁺+1).

Example 252: Synthesis of compound 823

(2-(4-((3R,5S)-4-benzyl-3,5-dimethylpiperazine-1-carbonyl)phenyl)-N-hydroxyacetamide)**Step 1: Synthesis of methyl****2-(4-((3R,5S)-4-benzyl-3,5-dimethylpiperazine-1-carbonyl)phenyl)acetate**

[0704] 4-(2-methoxy-2-oxoethyl)benzoic acid (formula 8-4, 0.150 g, 0.772 mmol), (2S,6R)-1-benzyl-2,6-dimethylpiperazine (0.186 g, 0.772 mmol), EDC (0.296 g, 1.545 mmol), HOBt (0.237 g, 1.545 mmol) and DIPEA (0.684 mL, 3.862 mmol) were dissolved in methylene chloride (10 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/ hexane = from 0 % to 50 %) and concentrated to afford the desired compound (0.133 g, 45.3 %) as a colorless liquid.

Step 2: Synthesis of compound 823

[0705] Methyl 2-(4-((3R,5S)-4-benzyl-3,5-dimethylpiperazine-1-carbonyl)phenyl)acetate (formula 8-5, 0.133 g, 0.350 mmol), hydroxylamine (50.00 % aqueous solution, 0.107 mL, 1.748 mmol) and potassium hydroxide (0.098 g, 1.748 mmol) were dissolved in methanol (1 mL) / tetrahydrofuran (1 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 823** (0.015 g, 11.2 %) as a white solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.36 (d, 2 H, *J* = 7.5 Hz), 7.30 (t, 3 H, *J* = 7.5 Hz), 7.25 - 7.21 (m, 5 H), 4.44 (d, 1 H, *J* = 9.6 Hz), 3.84 - 3.75 (m, 2 H), 3.51 (d, 1 H, *J* = 11.2 Hz), 3.23 (m, 2 H), 2.95 - 2.88 (m, 1 H), 2.69 (m, 1 H), 2.53 (m, 1 H), 1.11 (s, 3 H), 0.88 (s, 3 H); LRMS (ES) *m/z* 382.2 (*M*⁺+1).

Example 253: Synthesis of compound 824**(3-(4-((3R,5S)-4-benzyl-3,5-dimethylpiperazine-1-carbonyl)phenyl)-N-hydroxypropanamide)**

Step 1: Synthesis of methyl**3-(4-((3R,5S)-4-benzyl-3,5-dimethylpiperazine-1-carbonyl)phenyl)propanoate**

[0706] 4-(3-methoxy-3-oxopropyl)benzoic acid (formula 8-4, 0.150 g, 0.724 mmol), (2S,6R)-1-benzyl-2,6-dimethylpiperazine (0.174 g, 0.724 mmol), EDC (0.278 g, 1.448 mmol), HOBt (0.222 g, 1.448 mmol) and DIPEA (0.641 mL, 3.620 mmol) were dissolved in methylene chloride (10 mL) at room temperature, and the solution was stirred at the same temperature for 16 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (silicon dioxide, 4 g cartridge; ethyl acetate/ hexane = from 0 % to 50 %) and concentrated to afford the desired compound (0.089 g, 31.2 %) as a clear liquid.

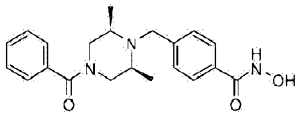
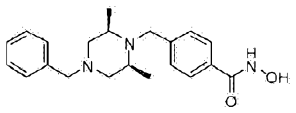
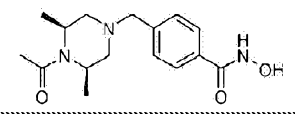
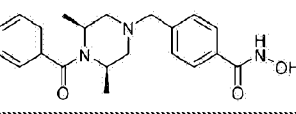
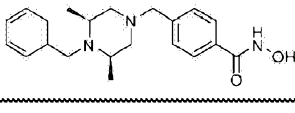
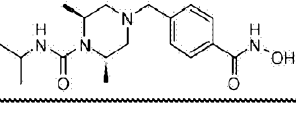
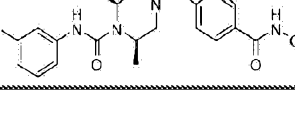
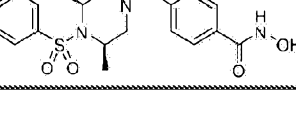
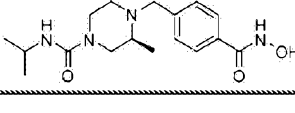
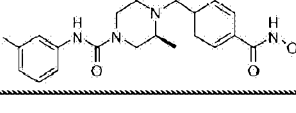
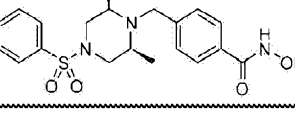
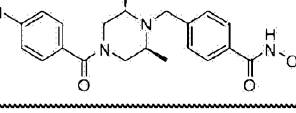
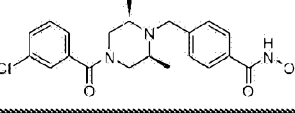
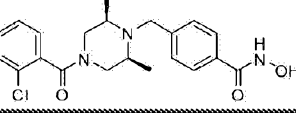
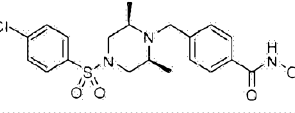
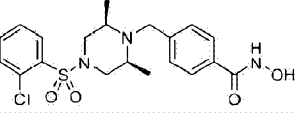
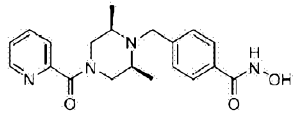
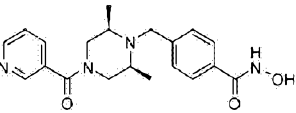
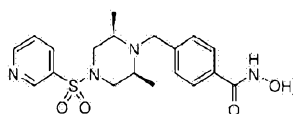
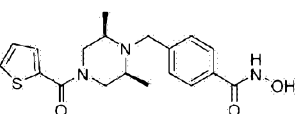
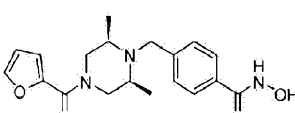
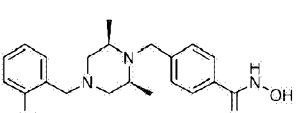
Step 2: Synthesis of compound 824

[0707] Methyl 3-(4-((3R,5S)-4-benzyl-3,5-dimethylpiperazine-1-carbonyl)phenyl)propanoate (formula 8-5, 0.089 g, 0.226 mmol), hydroxylamine (50.00 % aqueous solution, 0.069 mL, 1.128 mmol) and potassium hydroxide (0.063 g, 1.128 mmol) were dissolved in methanol (1 mL) / tetrahydrofuran (1 mL) at room temperature, and the solution was stirred at the same temperature for 1 hour. Then, the reaction mixture was concentrated under reduced pressure to remove the solvent, and a saturated aqueous solution of sodium hydrogen carbonate (20 mL) was added to the concentrate, followed by stirring. The precipitated solid was filtered and dried to yield **compound 824** (0.052 g, 58.3 %) as a white solid.

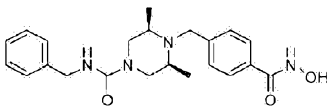
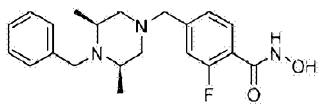
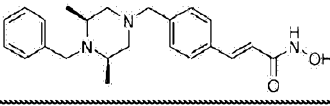
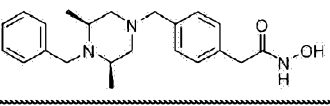
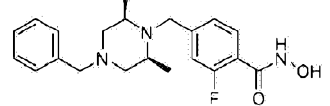
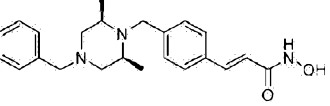
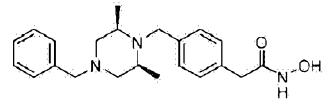
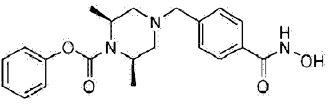
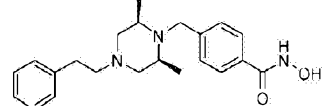
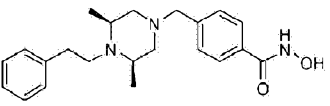
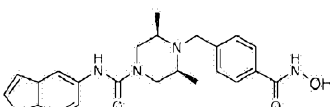
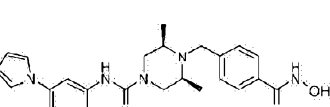
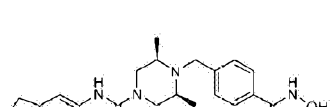
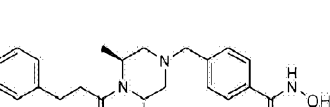
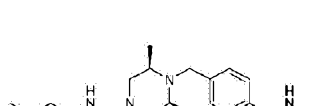
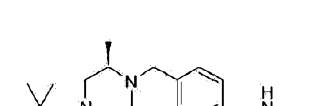
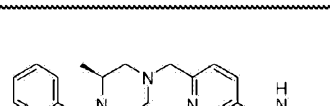
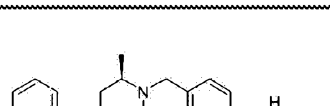
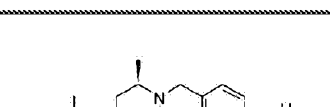
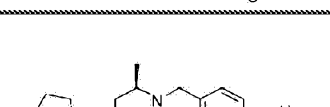
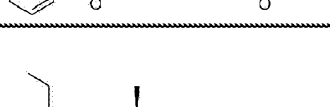
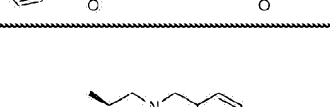
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[0708] The structural formulas of compounds 080 to 824 prepared as described above are shown in Table 16 below.

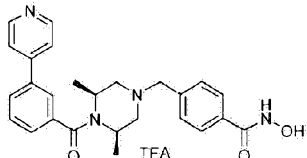
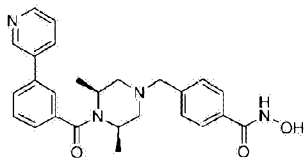
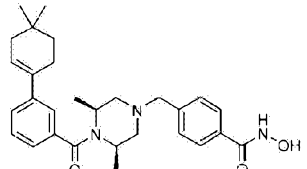
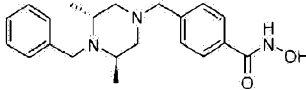
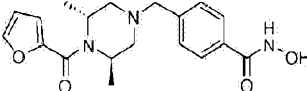
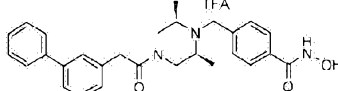
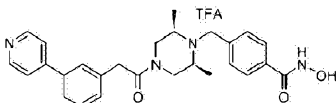
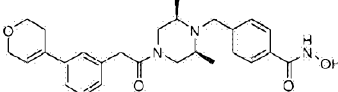
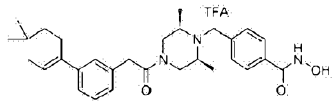
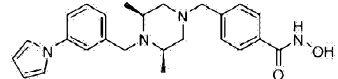
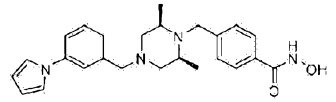
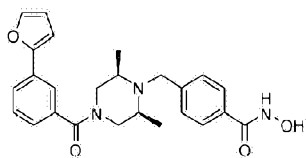
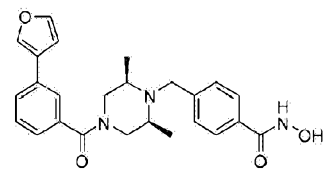
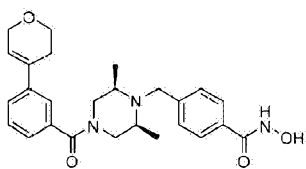
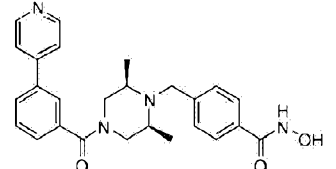
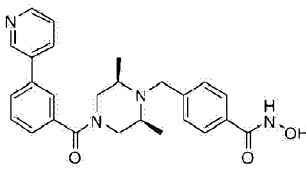
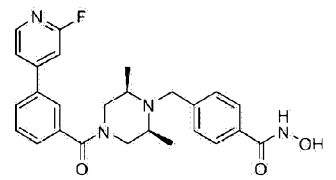
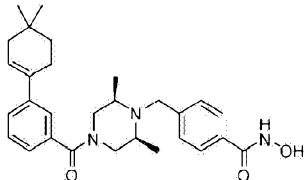
[Table 16] Structural formulas of dimethylpiperazine derivative compounds

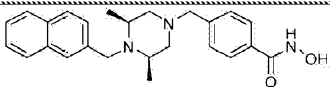
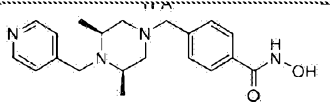
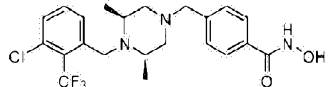
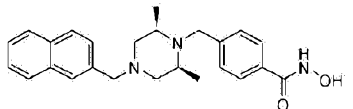
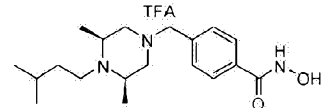
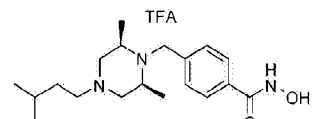
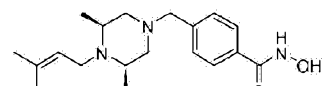
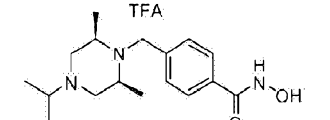
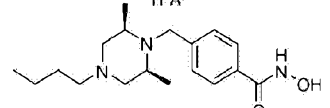
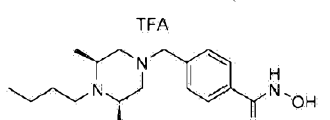
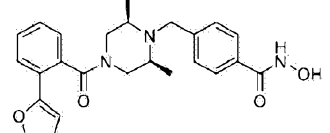
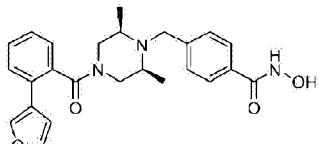
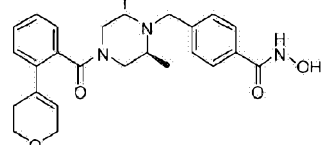
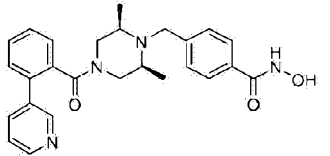
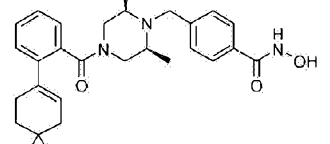
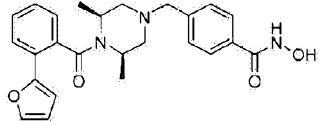
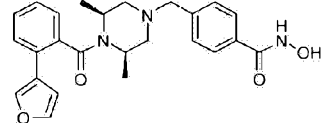
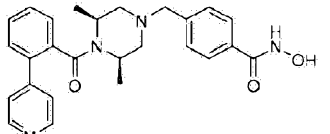
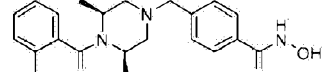
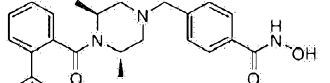
Compound	Formula	Compound	Formula
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082		083	
084		098	
099		100	
103		104	
105		106	
107		108	
109		110	
111		112	
113		114	
115		118	

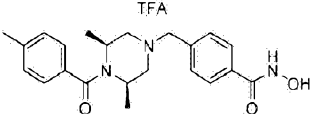
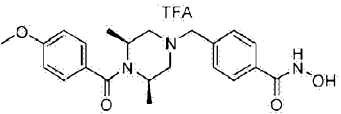
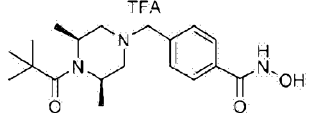
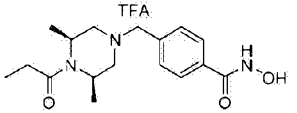
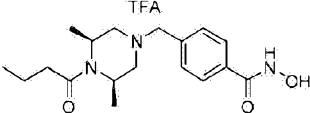
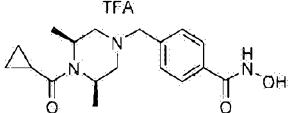
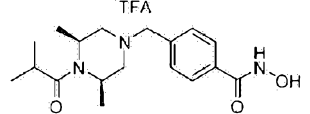
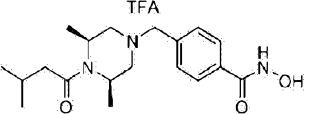
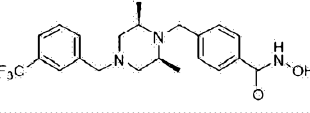
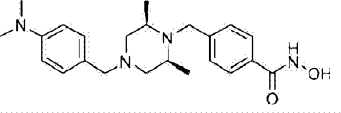
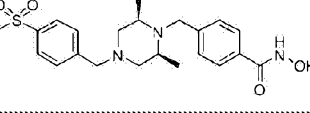
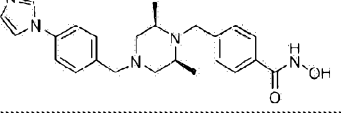
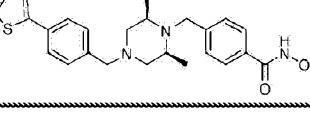
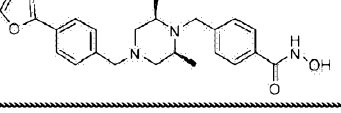
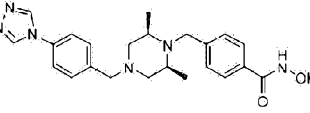
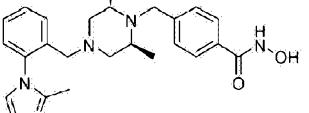
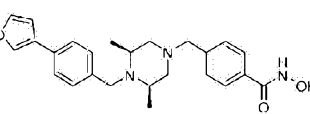
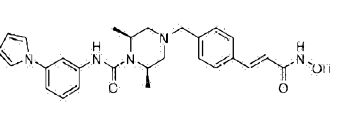
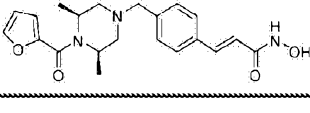
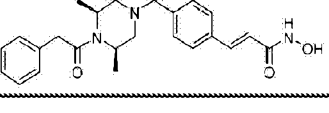
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123		125	
126		127	
128		145	
146		147	
148		149	
154		159	
160		161	
162		163	
164		165	
166		167	

Compound	Formula	Compound	Formula
168		171	
172		173	
174		17.5	
176		177	
183		184	
185		186	
187		188	
189		193	
194		195	
196		197	
198		204	

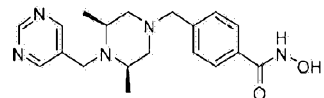
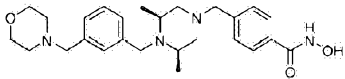
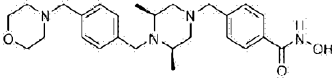
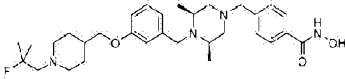
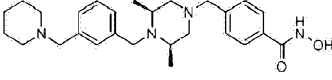
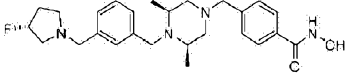
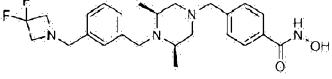
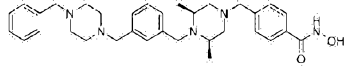
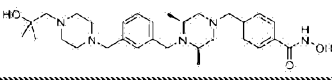
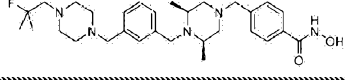
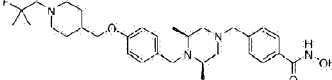
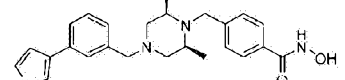
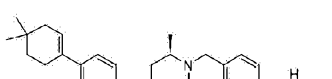
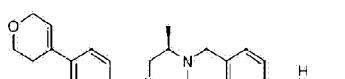
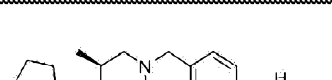
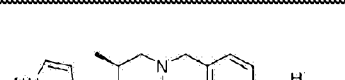
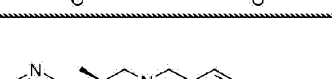
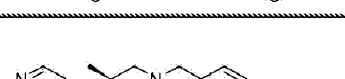
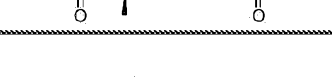
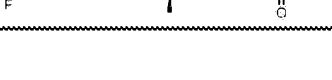
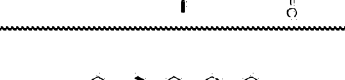
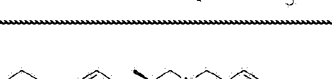
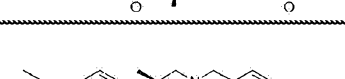
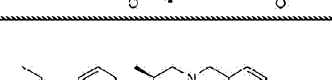
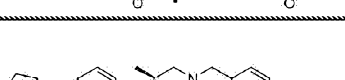
Compound	Formula	Compound	Formula
211		212	
213		214	
215		218	
219		220	
222		223	
224		225	
230		231	
232		233	
234		242	
243		244	

Compound	Formula	Compound	Formula
245		246	
217		248	
249		250	
251		252	
253		255	
256		257	
258		259	
260		261	
262		263	

Compound	Formula	Compound	Formula
265		266	
267		268	
270		271	
272		273	
274		275	
276		277	
278		279	
280		283	
284		285	
286		288	

Compound	Formula	Compound	Formula
			
290		291	
292		293	
294		295	
296		297	
298		299	
300		301	
302		303	
304		305	
309		321	
322		323	
			

Compound	Formula	Compound	Formula
326		327	
328		329	
330		331	
332		340	
342		343	
344		345	
346		347	
348		349	
350		351	
352		354	

Compound	Formula	Compound	Formula
355		356	
376		380	
382		383	
384		385	
386		387	
388		396	
400		401	
402		403	
404		405	
411		412	
413		423	
424		425	
126		427	

Compound	Formula	Compound	Formula
428		429	
430		431	
432		433	
434		435	
439		440	
441		442	
443		444	
446		452	
453		454	
455		456	
457		458	
459		460	
461		462	

Compound	Formula	Compound	Formula
463		466	
467		468	
472		475	
476		477	
478		479	
480		481	
482		483	
484		485	
486		487	
520		569	

Compound	Formula	Compound	Formula
571		573	
574		609	
652		653	
696		812	
813		814	
818		820	
822		823	
824			

Experimental Example 1: HDAC enzyme activity inhibition assays (*in vitro*)

[0709] In order to examine the HDAC6 selectivity of the compounds of formula I of the present invention by HDAC1 and HDAC6 enzymatic activity inhibition assays, an experiment was performed using a conventional substance as a control.

[0710] HDAC enzyme activity was measured using a HDAC Fluorimetric Drug Discovery Kit (BML-AK511, 516, Enzo Life Science). For the HDAC1 enzyme activity test, human recombinant HDAC1 (BML-SE456) was used as an enzyme source, and *Fluor de Lys®*-SIRT1 (BNL-KI177) was used as a substrate. A 5-fold dilution of the compound was seeded into a 96-

well plate, and then 0.3 μg of the enzyme and 10 μM of the substrate were added to each well of the plate and allowed to react at 30 °C for 60 minutes. Then, *Fluor de Lys*® Developer II (BML-KI176) was added thereto and allowed to react for 30 minutes, after which the fluorescence value (Ex 360, Em 460) was measured using a multi-plate reader (Flexstation 3, Molecular Device). The HDAC6 enzyme was tested using human recombinant HDAC6 (382180) (Calbiochem) according to the same protocol as the HDAC1 enzyme activity test method. Based on the resulting values, each IC_{50} value was calculated using GraphPad Prism4.0 program.

[Table 17] Results of HDAC enzyme activity inhibition assays

Compound	HDAC1 (μM)	HDAC6 (μM)	HDAC6 selectivity (fold)
080	6.6	0.179	37
081	11.2	0.144	78
082	12.5	0.034	369
083	2.0	0.010	201
084	11.9	0.023	517
098	>10	0.075	>133
099	12.4	0.242	51
100	>10	0.095	>105
103	2.6	0.173	15
104	0.7	0.082	9
105	1.6	0.060	27
106	7.3	0.119	61
107	8.3	0.166	79
108	13.1	0.166	79
109	5.1	0.075	67
110	5.0	0.085	59
111	>10	0.461	>22
112	>10	0.154	>65
113	2.8	0.104	27
114	2.4	0.185	13
115	3.2	0.181	18
118	5.5	0.113	48
119	8.2	0.309	26
120	5.5	0.018	304
121	11.8	0.029	407
122	3.6	0.005	717
123	15.5	0.006	2584

Compound	HDAC1 (μM)	HDAC6 (μM)	HDAC6 selectivity (fold)
125	>10	0.003	>3333
126	6.1	0.001	1525
127	>10	0.011	>909
128	11.1	0.002	5540
145	17.1	0.033	519
146	6.0	0.019	314
147	>10	0.111	>90
148	15.4	0.117	132
149	>10	0.080	>125
154	8.4	0.193	44
159	3.6	0.033	109
160	8.8	0.050	177
161	2.9	0.016	182
162	0.4	0.079	5
163	1.1	0.497	2
164	0.5	0.135	4
165	1.4	0.560	2
166	4.3	0.452	10
167	0.8	0.077	10
168	2.2	0.316	7
171	ND	0.039	>256
172	1.3	0.038	35
173	7.2	0.085	85
174	>10	0.097	>103
175	6.1	0.068	90
176	ND	0.429	>23
177	5.8	0.031	186
183	>10	0.500	>20
184	ND	0.249	>40
185	0.8	0.249	3
186	0.3	0.005	65
187	1.1	0.239	5
188	13.6	0.191	71
189	3.0	0.303	10
193	16.3	0.271	60

Compound	HDAC1 (μ M)	HDAC6 (μ M)	HDAC6 selectivity (fold)
194	24.8	0.082	303
195	22.4	0.410	55
196	14.4	0.148	97
197	2.1	0.177	12
198	12.2	0.241	51
204	>10	0.807	>12
211	>10	0.065	>154
212	>10	0.358	>28
213	>10	0.349	>29
214	>10	0.165	>61
215	>10	0.523	2
218	11.1	0.749	15
219	>10	0.170	>59
220	15.9	1.231	13
222	1.6	0.100	16
223	0.9	0.118	8
224	1.7	0.120	14
225	1.9	0.052	36
230	2.4	0.687	3
231	1.5	0.763	2
232	7.9	0.286	28
233	16.9	1.476	11
234	8.9	0.512	17
242	2.4	0.098	24
243	3.0	0.074	40
244	3.4	0.097	35
245	3.6	0.116	31
246	3.4	0.129	26
247	13.3	0.441	30
248	8.5	0.089	96
249	15.6	0.120	130
250	9.5	0.168	57
251	13.7	0.242	57
252	17.5	0.221	79

Compound	HDAC1 (μ M)	HDAC6 (μ M)	HDAC6 selectivity (fold)
253	22.6	1.535	15
255	8.5	0.024	354
256	4.6	0.303	15
257	1.6	0.255	6
258	1.7	0.258	7
259	2.5	0.400	6
260	1.7	0.529	3
261	2.0	0.577	3
2G2	2.4	0.727	3
263	6.8	>1.000	<7
265	6.2	0.074	84
266	19.1	0.282	68
267	14.2	0.188	75
268	2.8	1.267	2
270	>10	2.217	>5
271	12.5	>1.000	<13
272	12.2	0.182	67
273	13.7	0.441	31
274	13.5	0.378	36
275	>10	0.475	>21
276	12.3	0.337	36
277	10.4	0.455	23
278	14.4	0.911	16
279	>10	0.769	>13
280	17.7	0.388	46
283	3.5	0.023	154
284	5.7	0.068	84
285	7.0	0.093	75
286	13.1	0.161	81
288	10.7	0.326	33
290	3.8	0.079	48
291	1.3	0.055	24
292	5.6	0.074	76
293	5.8	0.131	44
294	8.2	0.220	37

Compound	HDAC1 (μ M)	HDAC6 (μ M)	HDAC6 selectivity (fold)
295	5.7	0.079	72
296	6.9	0.204	34
297	5.6	0.090	62
298	5.5	0.369	15
299	1.2	0.243	5
300	3.7	0.530	7
301	2.8	0.253	11
302	3.6	1.126	3
303	2.9	1.106	3
304	2.3	0.280	8
305	5.6	0.032	174
309	1.6	0.073	21
321	1.1	0.125	8
322	1.1	0.175	6
323	>10	0.921	>11
326	>10	0.058	>172
327	>10	0.235	>43
328	18.7	0.102	183
329	14.6	0.052	280
330	18.0	0.024	749
331	ND	0.731	13
332	21.9	0.106	207
340	1.6	0.606	3
342	8.7	0.019	456
343	8.8	0.027	328
344	5.8	0.012	481
345	5.5	0.016	341
346	8.3	0.025	332
347	>10	0.408	>25
348	4.7	0.843	6
349	5.0	0.005	1000
350	3.3	0.194	17
351	5.1	0.351	15
352	13.8	1.059	>1.3

Compound	HDAC1 (μ M)	HDAC6 (μ M)	HDAC6 selectivity (fold)
354	>10	0.005	>2000
355	21.0	1.060	20
356	12.3	0.022	558
376	>10	0.084	>119
380	>10	0.162	>62
382	>10	0.083	>120
383	>10	0.098	>102
384	>10	0.106	>94
385	>10	0.189	>53
386	>10	0.130	>77
387	>10	0.085	>118
388	9.0	0.083	109
396	1.7	0.406	4
400	11.3	2.822	4
401	2.0	0.301	7
402	5.2	0.161	32
403	3.2	0.061	53
404	5.5	0.182	30
405	4.3	0.248	17
411	4.3	0.008	538
412	1.1	0.032	36
413	>10	0.013	>769
423	1.0	0.046	22
424	1.2	0.043	27
425	1.5	0.086	17
426	5.0	0.142	35
427	6.0	0.152	40
428	4.7	0.117	41
429	4.4	0.100	44
430	4.5	0.082	55
431	13.4	0.022	611
432	3.4	0.042	81
433	3.5	0.049	71
434	3.7	0.060	61
435	5.1	0.090	57

Compound	HDAC1 (μ M)	HDAC6 (μ M)	HDAC6 selectivity (fold)
439	10.9	0.104	105
440	5.6	0.078	71
441	5.4	0.035	154
442	7.8	0.120	65
443	9.6	0.141	68
444	8.5	0.058	146
446	3.8	0.114	33
452	9.1	0.065	140
453	11.9	0.077	154
454	ND	0.044	>237
455	9.6	0.103	93
456	11.1	0.144	77
457	0.3	0.146	2
458	6.1	0.266	21
459	3.8	0.149	25
460	4.4	0.219	20
461	4.2	0.238	18
462	3.2	0.264	12
463	4.7	0.256	18
466	0.7	0.019	35
467	>10	0.049	204
468	20	0.029	690
472	0.2	0.055	3
475	0.8	0.114	7
476	0.9	0.142	6
477	2.7	0.253	11
478	6.57	0.64	10
479	5.3	0.433	12
480	1.0	0.467	2
481	16.2	0.106	153
482	12.5	0.103	121
483	17.1	0.103	166
484	19.6	0.130	151
485	14.7	0.145	101

Compound	HDAC1 (μ M)	HDAC6 (μ M)	HDAC6 selectivity (fold)
486	>10	0.126	>79
487	1.1	0.296	4
520	>10	0.86	>11
569	>10	0.84	82
571	10.0	0.21	48
573	>10	1.44	36
574	3.9	0.81	4
609	>10	0.754	>13.3
652	>10	0.88	>11
653	>10	0.42	>23
696	>10	0.01	>1000
812	>10	1.54	>6
813	17.2	0.01	1720
814	20.6	0.99	20
818	>10	0.87	>11
820	2.25	0.25	9
822	>10	0.28	>35
823	2.7	0.04	66
824	4.1	0.18	22

[0711] As can be seen in Table 16 above, the dimethylpiperazine hydroxamic acid derivative compounds of the present invention showed about 2 to about 5500 times higher selective HDAC6 inhibitory activities in the HDAC1 and HDAC6 activity inhibition assays.

Industrial Applicability

[0712] The compounds represented by formula I, stereoisomers thereof or pharmaceutically acceptable salts thereof can be used for prevention or treatment of histone deacetylase 6 activity-associated diseases.

REFERENCES CITED IN THE DESCRIPTION

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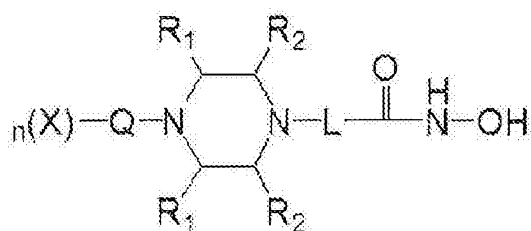
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Patentkrav

1. Forbindelse med følgende formel I, en stereoisomer deraf eller et farmaceutisk acceptabelt salt deraf:

Formel I



5

hvor

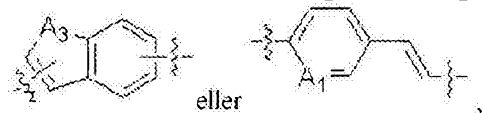
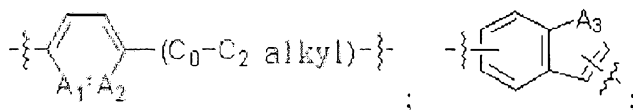
R₁ er hydrogen eller -CH₃,

R₂ er hydrogen eller -CH₃, forudsat at R₂ er -CH₃, når R₁ er hydrogen, og R₂ er hydrogen, når R₁ er -CH₃

10 L er -(C₄-C₅alkyl)-; -(C₁-C₃alkyl)-L₁-; -C(=O)-L₁- eller -S(=O)₂-L₁-,

hvor -(C₄-C₅alkyl)- og -(C₁-C₃alkyl)- kan være usubstitueret eller substitueret med -CH₃,

L₁ er -(C₃-C₆)cycloalkyl-;



15

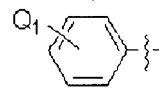
A₁ og A₂ hver for sig er -N- eller -CR₃-, forudsat at A₁ og A₂ ikke begge kan være -N-,

R₃ er hydrogen; -F, -Cl, -Br, -I eller -OH, og

A₃ er -NH- eller -O-,

20 Q er valgt fra gruppen, der består af -(C₁-C₆)alkyl-; -(C₂-

C₆)alkenyl-; -C(=O)-; -C(=S)-; -S(=O)₂- eller



hvor -(C₁-C₆)alkyl- og -(C₂-C₆)alkenyl- kan være usubstitueret eller substitueret hver for sig med 1 til 3 -CH₃-grupper eller halogenatomer,

25 Q₁ er hydrogen; -F, -Cl, -Br eller -I,

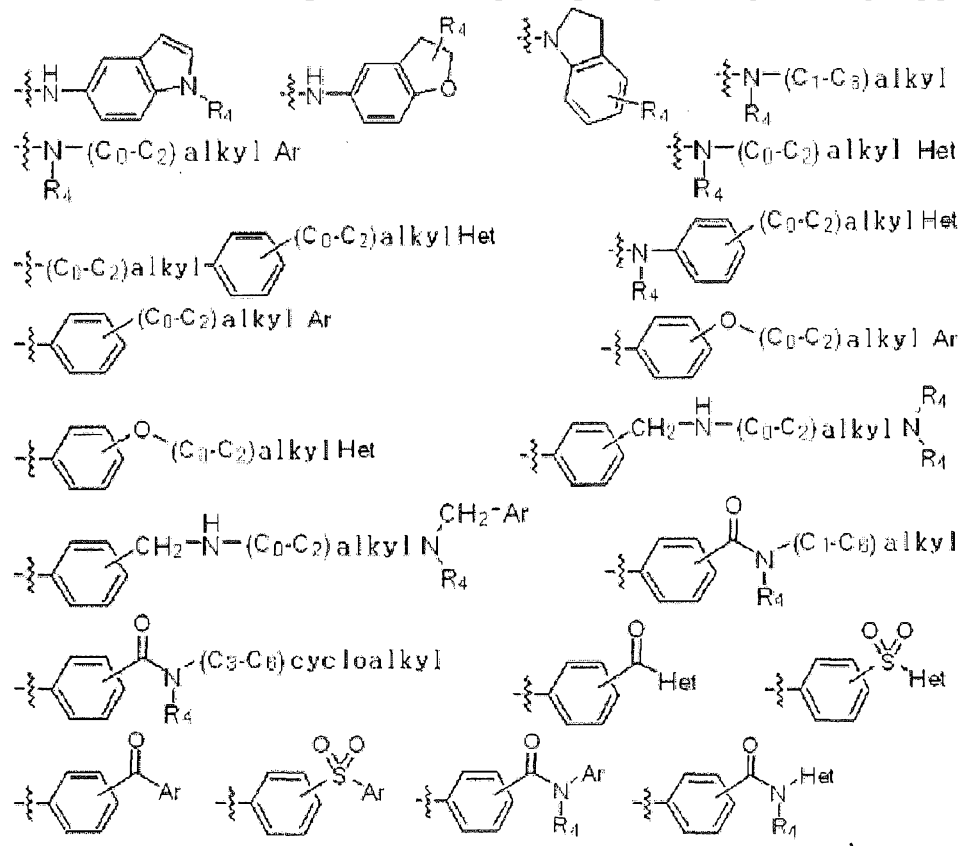
n er et helt tal på 0, 1 eller 2, forudsat at n er 0, når Q er



, n er 1, når Q er -C(=O)-; -C(=S)- eller -S(=O)₂-, og n er 1 eller 2, når Q er -(C₁-C₆)alkyl- eller -(C₂-C₆)alkenyl-,

og

X kan være valgt fra gruppen, der består af $-C_1-C_6$ alkyl; $-C_3-C_6$ cycloalkyl; $-C_2-C_6$ alkenyl; $-C_3-C_6$ cycloalkenyl; $-(C_0-C_2$ alkyl)Ar; $-O$ Ar; $-(C_0-C_2$ alkyl)Het; naphthyl og følgende grupper:



5

hvor R_4 er H eller $-C_1-C_4$ alkyl,

$-C_0-C_2$ alkyl, $-C_2-C_6$ alkenyl og $-C_1-C_6$ alkyl kan være usubstitueret eller substitueret med 1 til 2 $-CH_3$ -grupper; 1 til 3 $-F$ -grupper eller en kombination deraf,

- 10 Ar er en C_6 -monocyklisk aromatisk forbindelse, der kan være usubstitueret eller substitueret med et eller flere halogenatomer; $-OH$; $-NH_2$; $-C_1-C_6$ alkyl; $-O(C_1-C_6)$ alkyl; $-C_3-C_6$ cycloalkenyl; $-NH(C_1-C_6)$ alkyl; $-N(C_1-C_3)$ alkyl;₂; $-CH_2N(C_1-C_3)$ alkyl;₂; $-S(=O)_2(C_1-C_3)$ alkyl eller phenylgrupper, hvor $-C_1-C_3$ alkyl; $-C_1-C_6$ alkyl og $-C_3-C_6$ cycloalkenyl hver for sig kan være
- 15 substitueret med 1 til 5 $-F$ eller $-CH_3$ -grupper, og

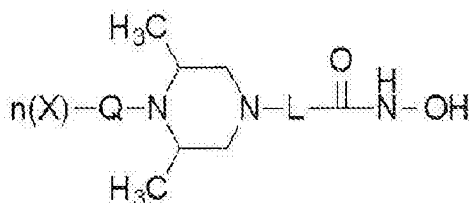
Het er en 4- til 6-leddet heteroaromatisk eller ikke-aromatisk ringforbindelse, der indeholder 1 til 3 elementer valgt fra gruppen, der består af N, O og S, idet den har 0 til

20 3 dobbeltbindinger og kan være usubstitueret eller substitueret med et eller flere halogenatomer; $-C_1-C_6$ alkyl; $-C(=O)(C_1-C_3)$ alkyl; $-S(=O)_2(C_1-C_3)$ alkyl eller benzylgrupper,

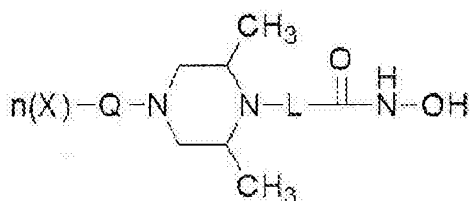
hvor $-C_1-C_3$ alkyl og $-C_1-C_6$ alkyl hver for sig kan være substitueret med $-OH$; 1 til 5 $-F$ eller $-CH_3$ -grupper.

2. Forbindelse med formel I, en stereoisomer deraf eller et
5 farmaceutisk acceptabelt salt deraf ifølge krav 1, hvor forbindelsen med formel I er en forbindelse med følgende formel II eller formel III:

Formel II



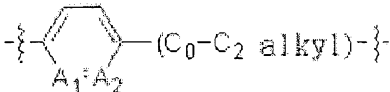
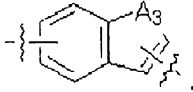
Formel III

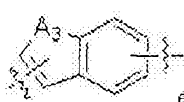
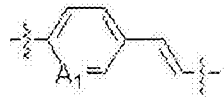


hvor

- 10 L er $-(C_5\text{alkyl})-$; $-(C_1-C_2\text{alkyl})-L_1-$; $-C(=O)-L_1-$ eller $-S(=O)_2-L_1-$,

hvor $-(C_5\text{alkyl})-$ og $-(C_1-C_2\text{alkyl})-$ er ligekædede og kan være usubstitueret eller substitueret med $-CH_3$,

L_1 er $-(C_3-C_6)\text{cycloalkyl}-$;  ;  ;

- 15  eller  ,

A_1 og A_2 hver for sig er $-N-$ eller $-CR_3-$, forudsat at A_1 og A_2 ikke begge kan være $-N-$,

R_3 er hydrogen; $-F$ eller $-OH$, og

A_3 er $-NH-$ eller $-O-$,

- 20 Q er valgt fra gruppen, der består af $-(C_1-C_3)\text{alkyl}-$; $-C(=O)-$; $-$

$C(=S)-$; $-S(=O)_2-$ eller  ,

hvor $-(C_1-C_3)\text{alkyl}-$ kan være usubstitueret eller substitueret med 1 til 3 $-CH_3$ -grupper eller halogenatomer,

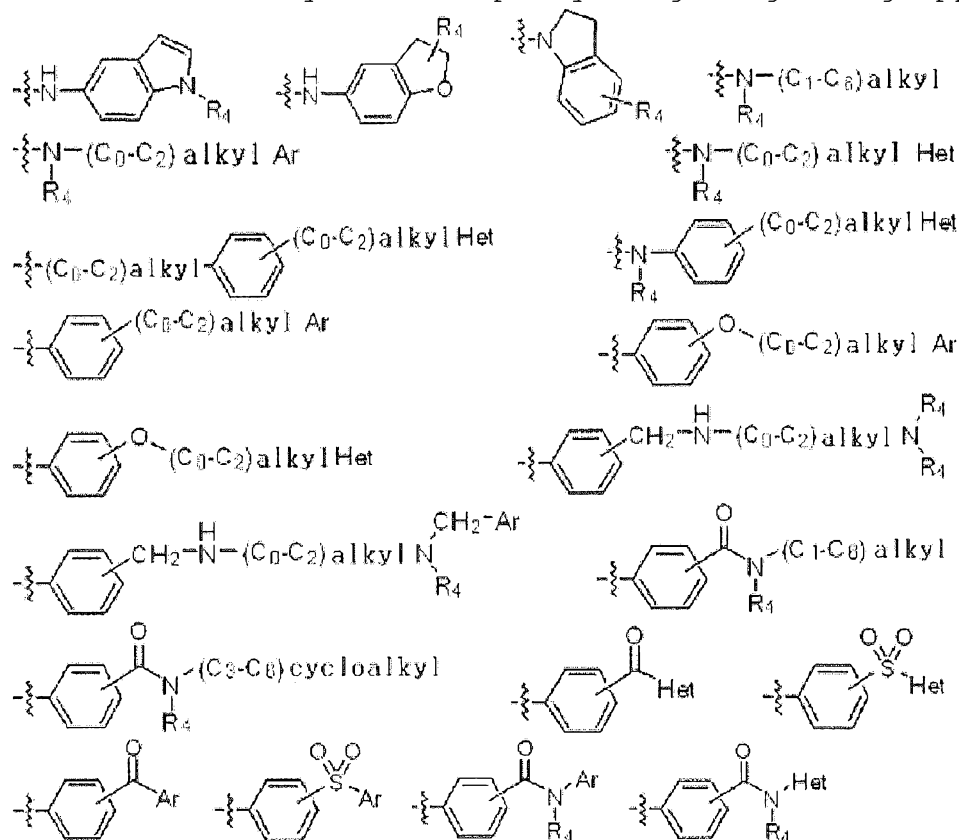
Q_1 er hydrogen; $-F$ eller $-Cl$,

- 25 n er et helt tal på 0 eller 1, forudsat at n er 0, når Q er



, og n er 1, når Q er $-C(=O)-$, $-C(=S)-$, $-S(=O)_2-$ eller $-(C_1-C_3)alkyl-$, og

X kan være valgt fra gruppen, der består af $-C_1-C_6alkyl$; $-C_3-C_6cycloalkyl$; $-C_2-C_6alkenyl$; $-C_3-C_6cycloalkenyl$; $-(C_0-C_2alkyl)Ar$; $-OAr$; $-(C_0-C_2alkyl)Het$; naphthyl; og følgende grupper:



hvor R_4 er H eller $-C_1-C_4alkyl$,

$-C_0-C_2alkyl$; $-C_2-C_6alkenyl$ og $-C_1-C_6alkyl$ kan være usubstitueret eller substitueret med 1 eller 2 $-CH_3$ -grupper eller 1 til 3 $-F$ -grupper,

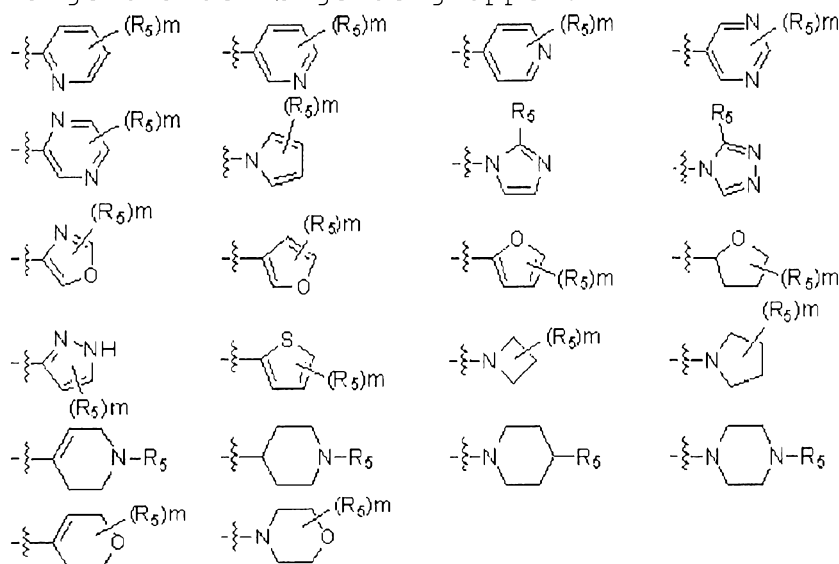
Ar er en C_6 -monocyklisk aromatisk forbindelse, der kan være usubstitueret eller substitueret med et eller flere halogenatomer; $-OH$; $-NH_2$; $-C_1-C_6alkyl$; $-O(C_1-C_6)alkyl$; $-C_3-C_6cycloalkenyl$; $-NH(C_1-C_6alkyl)$; $-N(C_1-C_3alkyl)_2$; $-CH_2N(C_1-C_3alkyl)_2$; $-S(=O)_2-(C_1-C_3alkyl)$ eller phenyl-grupper, hvor $-C_1-C_3alkyl$; $-C_1-C_6alkyl$ og $-C_3-C_6cycloalkenyl$ hver for sig kan være substitueret med 1 til 5 $-F$ eller $-CH_3$ -grupper, og

Het er en 4- til 6-leddet heteroaromatisk eller ikke-aromatisk ringforbindelse, der indeholder 1 til 3 elementer valgt fra gruppen, der består af N; O og S, idet den har 0 til 3 dobbeltbindinger og kan være usubstitueret eller substitueret

med et eller flere halogenatomer; $-C_1-C_6$ alkyl; $-C(=O)(C_1-C_3$ alkyl); $-S(=O)_2(C_1-C_3$ alkyl) eller benzyl-grupper, hvor $-C_1-C_3$ alkyl og $-C_1-C_6$ alkyl hver for sig kan være substitueret med $-OH$; eller 1 til 5 $-F$ eller $-CH_3$ -grupper.

5

3. Forbindelse med formel I, en stereoisomer deraf eller et farmaceutisk acceptabelt salt deraf ifølge krav 1, hvor Het er valgt blandt følgende grupper:



10 hvor R_5 hver for sig er hydrogen; $-F$; $-Cl$; $-C_1-C_6$ alkyl; $-C(=O)(C_1-C_3$ alkyl); $-S(=O)_2(C_1-C_3$ alkyl) eller benzyl, hvor $-C_1-C_3$ alkyl og $-C_1-C_6$ alkyl hver for sig kan være substitueret med $-OH$; 1 til 5 $-F$ eller $-CH_3$ -grupper,

m er et helt tal på 0, 1, 2 eller 3, og

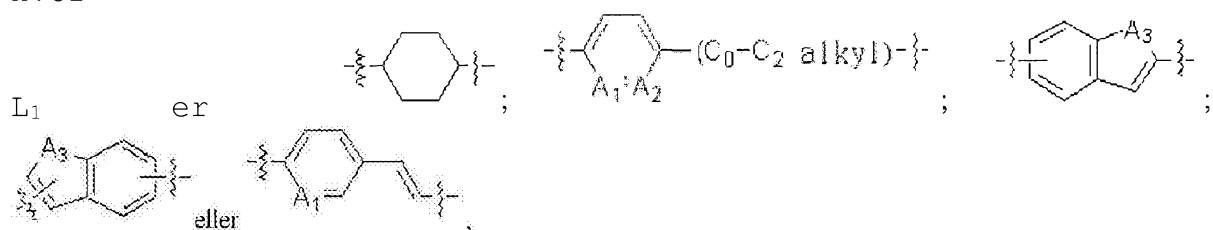
15 Het er usubstitueret, når m er 0, og Het kan være substitueret med uafhængig R_5 , når m er 1, 2 eller 3.

4. Forbindelse med formel I, en stereoisomer deraf eller et farmaceutisk acceptabelt salt deraf ifølge krav 1, hvor L, L_1 ,

20 A_1 , A_2 , A_3 , R_3 , R_4 , Q og X er defineret som ovenfor:

L er $-CH_2-L_1-$,

hvor



25 A_1 og A_2 hver for sig er $-N-$ eller $-CR_3-$, forudsat at A_1 og A_2

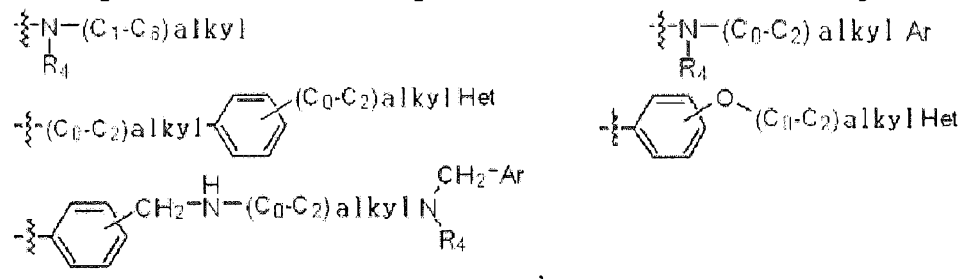
ikke begge kan være -N-,

R₃ er hydrogen; -F eller -OH, og

A₃ er -NH- eller -O-,

Q er -CH₂-, -C(=O)- eller -S(=O)₂-, og

- 5 X kan være valgt fra gruppen, der består af -C₁-C₆alkyl; -(C₀-C₂alkyl)Ar; -(C₀-C₂alkyl)Het; -OAr; eller følgende grupper:



hvor R₄ er H eller -C₁-C₄alkyl,

- 10 -C₀-C₂alkyl og -C₁-C₆alkyl kan være usubstitueret eller substitueret med 1 eller 2 -CH₃-grupper og/eller 1 til 3 -F-grupper, og

Ar og Het hver for sig er som defineret i formel I til formel III.

- 15 5. Forbindelse med formel I, en stereoisomer deraf eller et farmaceutisk acceptabelt salt deraf ifølge krav 1, hvor forbindelsen med formel I er en hvilken som helst af forbindelserne, der er angivet i følgende tabel:

Nr.	Navn på forbindelse
080	4-(((2S,6R)-4-benzoyl-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
081	4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
082	4-(((3R,5S)-4-acetyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
083	4-(((3R,5S)-4-benzoyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
084	4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
098	(2S,6R)-4-(4-(hydroxybenzamoyl)benzyl)-N-isopropyl-2,6-dimethylpiperazin-1-carboxamid

099	(2S, 6R) -N- (3-chlorophenyl) -4- (4- (hydroxycarbamoyl) benzyl) -2, 6-dimethylpiperazin-1-carboxamid
100	4- (((3R, 5S) -3, 5-dimethyl-4- (phenylsulfonyl) piperazin-1-yl) methyl) -N-hydroxybenzamid
103	(3R, 5S) -4- (4- (hydroxycarbamoyl) benzyl) -N-isopropyl-3, 5-dimethylpiperazin-1-carboxamid
104	(3R, 5S) -N- (3-chlorophenyl) -4- (4- (hydroxycarbamoyl) benzyl) -3, 5-dimethylpiperazin-1-carboxamid
105	4- (((2S, 6R) -2, 6-dimethyl-4- (phenylsulfonyl) piperazin-1-yl) methyl) -N-hydroxybenzamid
106	4- (((2S, 6R) -4- (4-chlorobenzoyl) -2, 6-dimethylpiperazin-1-yl) methyl) -N-hydroxybenzamid
107	4- (((2S, 6R) -4- (3-chlorobenzoyl) -2, 6-dimethylpiperazin-1-yl) methyl) -N-hydroxybenzamid
108	4- (((2S, 6R) -4- (2-chlorobenzoyl) -2, 6-dimethylpiperazin-1-yl) methyl) -N-hydroxybenzamid
109	4- (((2S, 6R) -4- ((4-chlorophenyl) sulfonyl) -2, 6-dimethylpiperazin-1-yl) methyl) -N-hydroxybenzamid
110	4- (((2S, 6R) -4- ((2-chlorophenyl) sulfonyl) -2, 6-dimethylpiperazin-1-yl) methyl) -N-hydroxybenzamid
111	4- (((2S, 6R) -2, 6-dimethyl-4-picolinoylpiperazin-1-yl) methyl) -N-hydroxybenzamid
112	4- (((2S, 6R) -2, 6-dimethyl-4-nicotinoylpiperazin-1-yl) methyl) -N-hydroxybenzamid
113	4- (((2S, 6R) -2, 6-dimethyl-4- (pyridin-3-ylsulfonyl) piperazin-1-yl) methyl) -N-hydroxybenzamid
114	4- (((2S, 6R) -2, 6-dimethyl-4- (thiophene-2-carbonyl) piperazin-1-yl) methyl) -N-hydroxybenzamid
115	4- (((2S, 6R) -4- (furan-2-carbonyl) -2, 6-dimethylpiperazin-1-yl) methyl) -N-hydroxybenzamid
118	4- (((2S, 6R) -4- (2-chlorobenzyl) -2, 6-dimethylpiperazin-1-yl) methyl) -N-hydroxybenzamid
119	4- (((2R, 6S) -4- (4-fluorophenyl) -2, 6-dimethylpiperazin-1-

	yl)methyl)-N-hydroxybenzamid
120	4-(((3R,5S)-4-(2-chlorbenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
121	4-(((3R,5S)-4-(3-chlorbenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
122	4-(((3R,5S)-4-(4-chlorbenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
123	4-((3R,5S)-3,5-dimethyl-4-picolinoylpiperazin-1-yl)methyl)-N-hydroxybenzamid
125	4-((3R,5S)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
126	4-(((3R,5S)-3,5-dimethyl-4-(thiophene-2-carbonyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
127	4-(((3R,5S)-4-(2-chlorbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
128	4-(((3R,5S)-4-(3-chlorbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
145	4-(((3R,5S)-4-(furan-2-ylmethyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
146	4-(((3R,5S)-3,5-dimethyl-4-(2-phenylacetyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
147	4-(((3R,5S)-4-ethyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
148	4-(((3R,5S)-3,5-dimethyl-4-propylpiperazin-1-yl)methyl)-N-hydroxybenzamid
149	4-(((3R,5S)-3,5-dimethyl-4-(2,2,2-trifluorethyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
154	6-((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)-N-hydroxyhexanamid
159	(2S,6R)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-phenylpiperazin-1-carboxamid
160	(2S,6R)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-(o-tolyl)piperazin-1-carboxamid

161	(2S, 6R) -N-benzyl-4- (4- (hydroxycarbamoyl)benzyl) -2, 6-dimethylpiperazin-1-carboxamid
162	(3R, 5S) -4- (4- (hydroxycarbamoyl)benzyl) -3, 5-dimethyl-N-phenylpiperazin-1-carboxamid
163	(3R, 5S) -4- (4- (hydroxycarbamoyl)benzyl) -N- (2-methoxyphenyl) -3, 5-dimethylpiperazin-1-carboxamid
164	(3R, 5S) -4- (4- (hydroxycarbamoyl)benzyl) -N- (3-methoxyphenyl) -3, 5-dimethylpiperazin-1-carboxamid
165	(3R, 5S) -4- (4- (hydroxycarbamoyl)benzyl) -N- (4-methoxyphenyl) -3, 5-dimethylpiperazin-1-carboxamid
166	(3R, 5S) -4- (4- (hydroxycarbamoyl)benzyl) -3, 5-dimethyl-N- (o-tolyl)piperazin-1-carboxamid
167	(3R, 5S) -4- (4- (hydroxycarbamoyl)benzyl) -3, 5-dimethyl-N- (m-tolyl)piperazin-1-carboxamid
168	(3R, 5S) -N-benzyl-4- (4- (hydroxycarbamoyl)benzyl) -3, 5-dimethylpiperazin-1-carboxamid
171	4- (((3R, 5S) -4-benzyl-3, 5-dimethylpiperazin-1-yl)methyl) -2-fluor-N-hydroxybenzamid
172	(E) -3- (4- (((3R, 5S) -4-benzyl-3, 5-dimethylpiperazin-1-yl)methyl)phenyl) -N-hydroxyacrylamid
173	2- (4- (((3R, 5S) -4-benzyl-3, 5-dimethylpiperazin-1-yl)methyl)phenyl) -N-hydroxyacetamid
174	4- (((2S, 6R) -4-benzyl-2, 6-dimethylpiperazin-1-yl)methyl) -2-fluor-N-hydroxybenzamid
175	(E) -3- (4- (((2S, 6R) -4-benzyl-2, 6-dimethylpiperazin-1-yl)methyl)phenyl) -N-hydroxyacrylamid
176	2- (4- (((2S, 6R) -4-benzyl-2, 6-dimethylpiperazin-1-yl)methyl)phenyl) -N-hydroxyacetamid
177	phenyl- (2S, 6R) -4- (4- (hydroxycarbamoyl)benzyl) -2, 6-dimethylpiperazin-1-carboxylat
183	4- (((2S, 6R) -2, 6-dimethyl-4-phenethylpiperazin-1-yl)methyl) -N-hydroxybenzamid
184	4- (((3R, 5S) -3, 5-dimethyl-4-phenethylpiperazin-1-

	yl)methyl)-N-hydroxybenzamid
185	(3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-N-(1-methyl-1H-indol-5-yl)piperazin-1-carboxamid
186	(3R,5S)-N-(3-(1H-pyrrol-1-yl)phenyl)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethylpiperazin-1-carboxamid
187	(3R,5S)-N-(2,3-dihydrobenzofuran-5-yl)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethylpiperazin-1-carboxamid
188	4-(((3R,5S)-3,5-dimethyl-4-(3-phenylpropanoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
189	4-(((2S,6R)-2,6-dimethyl-4-(m-tolylcarbamothioyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
193	4-(((2S,6R)-4-(2-fluor-2-methylpropyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
194	6-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxynicotinamid
195	6-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxynicotinamid
196	(3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-N,3,5-trimethyl-N-phenylpiperazin-1-carboxamid
197	N-hydroxy-4-(((2S,6R)-4-(indoline-1-carboxonyl)-2,6-dimethylpiperazin-1-yl)methyl)benzamid
198	(3R,5S)-N-butyl-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-N-phenylpiperazin-1-carboxamid
204	4-(((3R,5S)-3,5-dimethyl-4-(4,4,4-trifluorbutyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
211	4-(((3R,5S)-4-(2-fluorbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
212	4-(((3R,5S)-4-(2,5-difluorbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
213	4-(((3R,5S)-3,5-dimethyl-4-(2,4,5-

	trifluorbenzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
214	4-(((3R,5S)-4-(3,5-bis(trifluormethyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
215	4-(((2S,6R)-2,6-dimethyl-4-(2,4,5-trifluorbenzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
218	4-(2-((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)ethyl)-N-hydroxybenzamid
219	4-(1-((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)ethyl)-N-hydroxybenzamid
220	4-(((2S,6R)-2,6-dimethyl-4-(1-phenylethyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
222	4-(((3R,5S)-4-(2-(3-fluorphenyl)acetyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
223	4-(((3R,5S)-3,5-dimethyl-4-(2-(3-(trifluormethyl)phenyl)acetyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
224	4-(((3R,5S)-4-(2-(3-chlorphenyl)acetyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
225	4-(((3R,5S)-4-(3-fluorbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
230	(3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-N-(3-methoxybenzyl)-3,5-dimethylpiperazin-1-carboxamid (trifluoreddikesyresalt)
231	(3R,5S)-N-(3-fluorbenzyl)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethylpiperazin-1-carboxamid
232	(2S,6R)-N-(3-fluorbenzyl)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylpiperazin-1-carboxamid
233	4-(((2S,6R)-4-(2-(3-chlorphenyl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
234	4-(((3R,5S)-4-(2-([1,1'-biphenyl]-3-yl)acetyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
242	4-(((3R,5S)-4-(3-(furan-2-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid

243	4-(((3R,5S)-4-(3-(furan-3-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
244	4-(((3R,5S)-4-(3-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
245	4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-4-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)
246	4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
247	4-(((3R,5S)-4-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
248	4-(((3R,5R)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
249	4-(((3R,5R)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
250	4-(((2S,6R)-4-(2-([1,1'-biphenyl]-3-yl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)
251	4-(((2S,6R)-2,6-dimethyl-4-(2-(3-(pyridin-4-yl)phenyl)acetyl)piperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)
252	4-(((2S,6R)-4-(2-(3-(3,6-dihydro-2H-pyran-4-yl)phenyl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
253	4-(((2S,6R)-4-(2-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-yl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)
255	4-(((3R,5S)-4-(3-(1H-pyrrol-1-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
256	4-(((2S,6R)-4-(3-(1H-pyrrol-1-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
257	4-(((2S,6R)-4-(3-(furan-2-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid

258	4-(((2S,6R)-4-(3-(furan-3-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
259	4-(((2S,6R)-4-(3-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
260	4-(((2S,6R)-2,6-dimethyl-4-(3-(pyridin-4-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
261	4-(((2S,6R)-2,6-dimethyl-4-(3-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
262	4-(((2S,6R)-4-(3-(2-fluorpyridin-4-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
263	4-(((2S,6R)-4-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-carbonyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
265	4-(((3R,5S)-3,5-dimethyl-4-(naphthalen-2-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
266	4-(((3R,5S)-3,5-dimethyl-4-(pyridin-4-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)
267	4-(((3R,5S)-4-(3-chlor-2-(trifluormethyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
268	4-(((2S,6R)-2,6-dimethyl-4-(naphthalen-2-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
270	N-hydroxy-4-(((3R,5S)-4-isopentyl-3,5-dimethylpiperazin-1-yl)methyl)benzamid (trifluoreddikesyresalt)
271	N-hydroxy-4-(((2S,6R)-4-isopentyl-2,6-dimethylpiperazin-1-yl)methyl)benzamid (trifluoreddikesyresalt)
272	4-(((3R,5S)-3,5-dimethyl-4-(3-methylbut-2-en-1-yl)piperazin-1-yl)methyl)-N-hydroxybenzamid
273	N-hydroxy-4-(((2S,6R)-4-isopropyl-2,6-dimethylpiperazin-1-yl)methyl)benzamid (trifluoreddikesyresalt)
274	4-(((2S,6R)-4-butyl-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)
275	4-(((3R,5S)-4-butyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)

276	4-(((2S,6R)-4-(2-(furan-2-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
277	4-(((2S,6R)-4-(2-(furan-3-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
278	4-(((2S,6R)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
279	4-(((2S,6R)-2,6-dimethyl-4-(2-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
280	4-(((2S,6R)-4-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-carbonyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
283	4-(((3R,5S)-4-(2-(furan-2-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
284	4-(((3R,5S)-4-(2-(furan-3-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
285	4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-4-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
286	4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
288	4-(((3R,5S)-4-(4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
290	4-(((3R,5S)-3,5-dimethyl-4-(4-methylbenzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)
291	N-hydroxy-4-(((3R,5S)-4-(4-methoxybenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamid (trifluoreddikesyresalt)
292	4-(((3R,5S)-3,5-dimethyl-4-pivaloylpiperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)
293	4-(((3R,5S)-3,5-dimethyl-4-propionylpiperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)
294	4-(((3R,5S)-4-butyryl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)

295	4-(((3R,5S)-4-(cyclopropanecarbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)
296	N-hydroxy-4-(((3R,5S)-4-isobutyryl-3,5-dimethylpiperazin-1-yl)methyl)benzamid (trifluoreddikesyresalt)
297	4-(((3R,5S)-3,5-dimethyl-4-(3-methylbutanoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)
298	4-(((2S,6R)-2,6-dimethyl-4-(3-(trifluormethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
299	4-(((2S,6R)-4-(4-(dimethylamino)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
300	4-(((2S,6R)-2,6-dimethyl-4-(4-(methylsulfonyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
301	4-(((2S,6R)-4-(4-(1H-imidazol-1-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
302	4-(((2S,6R)-2,6-dimethyl-4-(4-(thiophen-2-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
303	4-(((2S,6R)-4-(4-(furan-2-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
304	4-(((2S,6R)-4-(4-(4H-1,2,4-triazol-4-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
305	4-(((2S,6R)-2,6-dimethyl-4-(2-(2-methyl-1H-imidazol-1-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
309	4-(((3R,5S)-4-(4-(furan-3-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
321	(2S,6R)-N-(3-(1H-pyrrol-1-yl)phenyl)-4-(4-((E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)benzyl)-2,6-dimethylpiperazin-1-carboxamid
322	(E)-3-(4-(((3R,5S)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamid
323	(E)-3-(4-(((3R,5S)-3,5-dimethyl-4-(2-

	phenylacetyl)piperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamid
326	4-(((3R,5S)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
327	4-(((3R,5S)-4-(2-(furan-2-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
328	4-(((3R,5S)-4-(2-(furan-3-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
329	4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
330	4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
331	4-(((3R,5S)-4-((4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
332	4-(((3R,5S)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
340	4-(((3R,5S)-4-(4-(furan-2-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
342	4-(((3R,5S)-4-(3-(furan-2-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
343	4-(((3R,5S)-4-(3-(furan-3-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
344	4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
345	4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
346	4-(((3R,5S)-4-(3-(3,6-dihydro-2H-pyran-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
347	4-(((3R,5S)-4-((4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-yl)methyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
348	4-(((2S,6R)-4-(2-(furan-3-yl)benzyl)-2,6-

	dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
349	4-(((2S,6R)-2,6-dimethyl-4-(2-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
350	4-(((2S,6R)-2,6-dimethyl-4-(2-(pyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
351	4-(((2S,6R)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
352	4-(((2S,6R)-4-((4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
354	4-(((3R,5S)-3,5-dimethyl-4-(oxazol-4-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
355	4-(((3R,5S)-3,5-dimethyl-4-(pyrimidin-5-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
356	4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
376	4-(((3R,5S)-3,5-dimethyl-4-(4-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
380	4-(((3R,5S)-4-(3-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
382	4-(((3R,5S)-3,5-dimethyl-4-(3-(piperidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
383	4-(((3R,5S)-4-(3-((R)-3-fluorpyrrolidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
384	4-(((3R,5S)-4-(3-((3,3-difluorazetidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
385	4-(((3R,5S)-4-(3-((4-benzylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid

386	N-hydroxy-4-(((3R,5S)-4-(3-((4-(2-hydroxy-2-methylpropyl)piperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamid
387	4-(((3R,5S)-4-(3-((4-(2-fluor-2-methylpropyl)piperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
388	4-(((3R,5S)-4-(4-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
396	4-(((2S,6R)-4-(3-(furan-3-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
400	4-(((2S,6R)-4-((4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-4-yl)methyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
401	4-(((2S,6R)-4-(4-(3,6-dihydro-2H-pyran-4-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
402	4-(((3R,5S)-3,5-dimethyl-4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
403	4-(((3R,5S)-3,5-dimethyl-4-(1H-pyrazole-3-carbonyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
404	4-(((3R,5S)-3,5-dimethyl-4-(pyrazine-2-carbonyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
405	N-hydroxy-4-(((3R,5S)-4-isonicotinoyl-3,5-dimethylpiperazin-1-yl)methyl)benzamid
411	4-(((3R,5S)-4-(4-((R)-3-fluorpyrrolidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
412	4-(((3R,5S)-4-(4-((3,3-difluorazetidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
413	4-(((3R,5S)-4-(4-((4-benzylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
423	4-(((3R,5S)-3,5-dimethyl-4-(3-(pyrrolidin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid

424	4-(((3R,5S)-3,5-dimethyl-4-(3-(piperidin-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
425	4-(((3R,5S)-4-(3-((diethylamino)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
426	4-(((3R,5S)-4-(3-((diethylamino)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
427	4-(((3R,5S)-3,5-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
428	4-(((3R,5S)-3,5-dimethyl-4-(3-((4-methylpiperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
429	4-(((3R,5S)-4-(3-((4-ethylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
430	N-hydroxy-4-(((3R,5S)-4-(3-((4-isopropylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamid
431	4-(((3R,5S)-4-(3-((4-acetyl piperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
432	4-(((3R,5S)-3,5-dimethyl-4-(3-((4-methylpiperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
433	4-(((3R,5S)-4-(3-((4-ethylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
434	N-hydroxy-4-(((3R,5S)-4-(3-((4-isopropylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamid
435	4-(((3R,5S)-4-(3-((4-acetyl piperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
439	4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
440	4-(((3R,5S)-4-(3-(((1-(diethylamino)propan-2-yl)amino)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid

441	4-(((3R,5S)-4-(3-((1-(benzyl(methyl)amino)propan-2-yl)amino)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
442	N-hydroxy-4-(((3R,5S)-4-(3-((4-isopentylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamid
443	4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(2,2,2-trifluorethyl)piperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
444	4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(methylsulfonyl)piperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
446	4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholine-4-carbonyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
452	4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(methylsulfonyl)piperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
453	4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(2,2,2-trifluorethyl)piperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
454	N-hydroxy-4-(((3R,5S)-4-(3-((4-isopentylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamid
455	4-(((3R,5S)-4-(3-((1-(diethylamino)propan-2-yl)amino)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
456	4-(((3R,5S)-4-(3-((1-(benzyl(methyl)amino)propan-2-yl)amino)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
457	4-(((3R,5S)-3,5-dimethyl-4-(2-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
458	4-(((3R,5S)-3,5-dimethyl-4-(4-(morpholinomethyl)benzoyl)piperazin-1-yl)methyl)-N-

	hydroxybenzamid
459	4-(((3R,5S)-3,5-dimethyl-4-(4-(piperidin-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
460	4-(((3R,5S)-4-(4-((R)-3-fluorpyrrolidin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
461	4-(((3R,5S)-3,5-dimethyl-4-(4-(pyrrolidin-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
462	4-(((3R,5S)-3,5-dimethyl-4-(4-(4-methylpiperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
463	4-(((3R,5S)-3,5-dimethyl-4-(4-(4-(methylsulfonyl)piperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
466	4-(((3R,5S)-3,5-dimethyl-4-(4-(pyrrolidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
467	4-(((3R,5S)-3,5-dimethyl-4-(4-(piperidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
468	4-(((3R,5S)-3,5-dimethyl-4-(4-(4-methylpiperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
472	(E)-3-(4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamid
475	(E)-3-(4-(((2S,6R)-2,6-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamid
476	(E)-3-(4-(((2S,6R)-4-(3-((diethylamino)methyl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamid
477	(E)-3-(4-(((2S,6R)-4-(4-(furan-2-yl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamid
478	4-(((2S,6R)-4-(3-((diethylamino)methyl)benzyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid (hydrochloridsalt)

479	4-(((2S,6R)-2,6-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
480	(E)-3-(4-(((2S,6R)-2,6-dimethyl-4-(3-(pyrrolidin-1-ylmethyl)benzoyl)piperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamid
481	4-(((3R,5S)-3,5-dimethyl-4-(2-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
482	4-(((3R,5S)-4-(2-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
483	4-(((3R,5S)-3,5-dimethyl-4-(2-(1-(2,2,2-trifluorethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
484	N-hydroxy-4-(((3R,5S)-4-(2-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamid
485	4-(((3R,5S)-4-(2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
486	4-(((3R,5S)-4-(4-((4-acetylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid (hydrochloridsalt)
487	(E)-3-(4-(((2S,6R)-4-(3-((diethylamino)methyl)benzoyl)-2,6-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamid
520	3-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxy-1H-indole-6-carboxamid
569	5-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxy-1H-indole-2-carboxamid
571	5-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzofuran-2-carboxamid
573	6-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxy-1H-indole-2-carboxamid

574	2-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzofuran-5-carboxamid
609	5-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxypicolinamid
652	4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N,2-dihydroxybenzamid
653	4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholmomethyl)benzyl)piperazin-1-yl)methyl)-N,2-dihydroxybenzamid
696	4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-3-fluor-N-hydroxybenzamid
812	5-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxypicolinamid
813	4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-3-fluor-N-hydroxybenzamid
814	4-((3R,SS)-4-benzyl-3,5-dimethylpiperazin-1-carbonyl)-N-hydroxybenzamid
818	4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)sulfonyl)-N-hydroxybenzamid
820	2-(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)sulfonyl)phenyl)-N-hydroxyacetamid
822	4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxycyclohexane-1-carboxamid
823	2-(4-((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-carbonyl)phenyl)-N-hydroxyacetamid
824	3-(4-((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-carbonyl)phenyl)-N-hydroxypropanamid

6. Forbindelse med formel I, en stereoisomer deraf eller et farmaceutisk acceptabelt salt deraf ifølge krav 5, hvor forbindelsen med formel I er en hvilken som helst af 5 forbindelserne, der er angivet i følgende tabel:

Nr.	Navn på forbindelse
081	4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
082	4-(((3R,5S)-4-acetyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
083	4-(((3R,5S)-4-benzoyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
084	4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
098	(2S,6R)-4-(4-(hydroxycarbamoyl)benzyl)-N-isopropyl-2,6-dimethylpiperazin-1-carboxamid
099	(2S,6R)-N-(3-chlorphenyl)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylpiperazin-1-carboxamid
100	4-(((3R,5S)-3,5-dimethyl-4-(phenylsulfonyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
106	4-(((2S,6R)-4-(4-chlorbenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
107	4-(((2S,6R)-4-(3-chlorbenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
108	4-(((2S,6R)-4-(2-chlorbenzoyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
109	4-(((2S,6R)-4-((4-chlorphenyl)sulfonyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
110	4-(((2S,6R)-4-((2-chlorphenyl)sulfonyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
112	4-(((2S,6R)-2,6-dimethyl-4-nicotinoylpiperazin-1-yl)methyl)-N-hydroxybenzamid
120	4-(((3R,5S)-4-(2-chlorbenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
121	4-(((3R,5S)-4-(3-chlorbenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
122	4-(((3R,5S)-4-(4-chlorbenzoyl)-3,5-dimethylpiperazin-1-

	yl)methyl)-N-hydroxybenzamid
123	4-(((3R,5S)-3,5-dimethyl-4-picolinoylpiperazin-1-yl)methyl)-N-hydroxybenzamid
125	4-(((3R,5S)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
126	4-(((3R,5S)-3,5-dimethyl-4-(thiophene-2-carbonyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
127	4-(((3R,5S)-4-(2-chlorbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
128	4-(((3R,5S)-4-(3-chlorbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
145	4-(((3R,5S)-4-(furan-2-ylmethyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
146	4-(((3R,5S)-3,5-dimethyl-4-(2-phenylacetyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
147	4-(((3R,5S)-4-ethyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
148	4-(((3R,5S)-3,5-dimethyl-4-propylpiperazin-1-yl)methyl)-N-hydroxybenzamid
149	4-(((3R,5S)-3,5-dimethyl-4-(2,2,2-trifluorethyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
159	(2S,6R)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-phenylpiperazin-1-carboxamid
160	(2S,6R)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-(o-tolyl)piperazin-1-carboxamid
161	(2S,6R)-N-benzyl-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylpiperazin-1-carboxamid
171	4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-2-fluor-N-hydroxybenzamid
173	2-(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacetamid
174	4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)-2-fluor-N-hydroxybenzamid

175	(E)-3-(4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)phenyl)-N-hydroxyacrylamid
177	Phenyl-(2S,6R)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylpiperazin-1-carboxylat
186	(3R,5S)-N-(3-(1H-pyrrol-1-yl)phenyl)-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethylpiperazin-1-carboxamid
188	4-(((3R,5S)-3,5-dimethyl-4-(3-phenylpropanoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
193	4-(((2S,6R)-4-(2-fluor-2-methylpropyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
194	6-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxynicotinamid
195	6-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxynicotinamid
196	(3R,5S)-4-(4-(hydroxycarbamoyl)benzyl)-N,3,5-trimethyl-N-phenylpiperazin-1-carboxamid
198	(3R,5S)-N-butyl-4-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-N-phenylpiperazin-1-carboxamid
211	4-(((3R,5S)-4-(2-fluorbenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
214	4-(((3R,5S)-4-(3,5-bis(trifluormethyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
219	4-(1-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)ethyl)-N-hydroxybenzamid
248	4-(((3R,5R)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
249	4-(((3R,5R)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
250	4-(((2S,6R)-4-(2-([1,1'-biphenyl]-3-yl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)
251	4-(((2S,6R)-2,6-dimethyl-4-(2-(3-(pyridin-4-

	yl)phenyl)acetyl)piperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)
252	4-(((2S,6R)-4-(2-(3-(3,6-dihydro-2H-pyran-4-yl)phenyl)acetyl)-2,6-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
255	4-(((3R,5S)-4-(3-(1H-pyrrol-1-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
265	4-(((3R,5S)-3,5-dimethyl-4-(naphthalen-2-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
266	4-(((3R,5S)-3,5-dimethyl-4-(pyridin-4-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)
267	4-(((3R,5S)-4-(3-chlor-2-(trifluormethyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
272	4-(((3R,5S)-3,5-dimethyl-4-(3-methylbut-2-en-1-yl)piperazin-1-yl)methyl)-N-hydroxybenzamid
283	4-(((3R,5S)-4-(2-(furan-2-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
284	4-(((3R,5S)-4-(2-(furan-3-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
285	4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-4-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
286	4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-3-yl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
292	4-(((3R,5S)-3,5-dimethyl-4-pivaloylpiperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)
295	4-(((3R,5S)-4-(cyclopropanecarbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)
297	4-(((3R,5S)-3,5-dimethyl-4-(3-methylbutanoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid (trifluoreddikesyresalt)
305	4-(((2S,6R)-2,6-dimethyl-4-(2-(2-methyl-1H-imidazol-1-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid

326	4-(((3R,5S)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
328	4-(((3R,5S)-4-(2-(furan-3-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
329	4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
330	4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
332	4-(((3R,5S)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
342	4-(((3R,5S)-4-(3-(furan-2-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
343	4-(((3R,5S)-4-(3-(furan-3-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
344	4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
345	4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
346	4-(((3R,5S)-4-(3-(3,6-dihydro-2H-pyran-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
349	4-(((2S,6R)-2,6-dimethyl-4-(2-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
354	4-(((3R,5S)-3,5-dimethyl-4-(oxazol-4-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
356	4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
376	4-(((3R,5S)-3,5-dimethyl-4-(4-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
380	4-(((3R,5S)-4-(3-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid

382	4-(((3R,5S)-3,5-dimethyl-4-(3-(piperidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
383	4-(((3R,5S)-4-(3-((R)-3-fluorpyrrolidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
384	4-(((3R,5S)-4-(3-((3,3-difluorazetidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
385	4-(((3R,5S)-4-(3-((4-benzylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
386	N-hydroxy-4-(((3R,5S)-4-(3-((4-(2-hydroxy-2-methylpropyl)piperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamid
387	4-(((3R,5S)-4-(3-((4-(2-fluor-2-methylpropyl)piperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
388	4-(((3R,5S)-4-(4-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
403	4-(((3R,5S)-3,5-dimethyl-4-(1H-pyrazole-3-carbonyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
411	4-(((3R,5S)-4-(4-((R)-3-fluorpyrrolidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
413	4-(((3R,5S)-4-(4-((4-benzylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
430	N-hydroxy-4-(((3R,5S)-4-(3-((4-isopropylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamid
431	4-(((3R,5S)-4-(3-((4-acetyl)piperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid

432	4-(((3R,5S)-3,5-dimethyl-4-(3-((4-methylpiperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
433	4-(((3R,5S)-4-(3-((4-ethylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
434	N-hydroxy-4-(((3R,5S)-4-(3-((4-isopropylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamid
435	4-(((3R,5S)-4-(3-((4-acetylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
439	4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
440	4-(((3R,5S)-4-(3-((1-(diethylamino)propan-2-yl)amino)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
441	4-(((3R,5S)-4-(3-((1-(benzyl(methyl)amino)propan-2-yl)amino)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
442	N-hydroxy-4-(((3R,5S)-4-(3-((4-isopentylpiperazin-1-yl)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamid
443	4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(2,2,2-trifluorethyl)piperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
444	4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(methylsulfonyl)piperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
452	4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(methylsulfonyl)piperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
453	4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(2,2,2-

	trifluorethyl)piperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
454	N-hydroxy-4-(((3R,5S)-4-(3-((4-isopentylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamid
455	4-(((3R,5S)-4-(3-((1-(diethylamino)propan-2-yl)amino)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
456	4-(((3R,5S)-4-(3-((1-(benzyl(methyl)amino)propan-2-yl)amino)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
467	4-(((3R,5S)-3,5-dimethyl-4-(4-(piperidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
468	4-(((3R,5S)-3,5-dimethyl-4-(4-((4-methylpiperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
481	4-(((3R,5S)-3,5-dimethyl-4-(2-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
482	4-(((3R,5S)-4-(2-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
483	4-(((3R,5S)-3,5-dimethyl-4-(2-(1-(2,2,2-trifluorethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
484	N-hydroxy-4-(((3R,5S)-4-(2-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamid
485	4-(((3R,5S)-4-(2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
486	4-(((3R,5S)-4-(4-((4-acetylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid (hydrochloridsalt)

569	5-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxy-1H-indole-2-carboxamid
696	4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-3-fluor-N-hydroxybenzamid
813	4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-3-fluor-N-hydroxybenzamid
823	2-(4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-carbonyl)phenyl)-N-hydroxyacetamid

7. Forbindelse med formel I, en stereoisomer deraf eller et farmaceutisk acceptabelt salt deraf ifølge krav 6, hvor forbindelsen med formel I er en hvilken som helst af

5 forbindelserne, der er angivet i følgende tabel:

Nr.	Navn på forbindelse
082	4-(((3R,5S)-4-acetyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
083	4-(((3R,5S)-4-benzoyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
084	4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
098	(2S,6R)-4-(4-(hydroxycarbamoyl)benzyl)-N-isopropyl-2,6-dimethylpiperazin-1-carboxamid
100	4-(((3R,5S)-3,5-dimethyl-4-(phenylsulfonyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
120	4-(((3R,5S)-4-(2-chlorbenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
121	4-(((3R,5S)-4-(3-chlorbenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
122	4-(((3R,5S)-4-(4-chlorbenzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
123	4-(((3R,5S)-3,5-dimethyl-4-picolinoylpiperazin-1-yl)methyl)-N-hydroxybenzamid

125	4-(((3R,5S)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
126	4-(((3R,5S)-3,5-dimethyl-4-(thiophene-2-carbonyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
127	4-(((3R,5S)-4-(2-chlorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
128	4-(((3R,5S)-4-(3-chlorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
145	4-(((3R,5S)-4-(furan-2-ylmethyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
146	4-(((3R,5S)-3,5-dimethyl-4-(2-phenylacetyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
148	4-(((3R,5S)-3,5-dimethyl-4-propylpiperazin-1-yl)methyl)-N-hydroxybenzamid
149	4-(((3R,5S)-3,5-dimethyl-4-(2,2,2-trifluorethyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
159	(2S,6R)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-phenylpiperazin-1-carboxamid
160	(2S,6R)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-(o-tolyl)piperazin-1-carboxamid
161	(2S,6R)-N-benzyl-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylpiperazin-1-carboxamid
171	4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-2-fluor-N-hydroxybenzamid
174	4-(((2S,6R)-4-benzyl-2,6-dimethylpiperazin-1-yl)methyl)-2-fluor-N-hydroxybenzamid
177	phenyl-(2S,6R)-4-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylpiperazin-1-carboxylat
194	6-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxynicotinamid
211	4-(((3R,5S)-4-(2-fluorobenzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
249	4-(((3R,5R)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-

	1-yl)methyl)-N-hydroxybenzamid
255	4-(((3R,5S)-4-(3-(1H-pyrrol-1-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
283	4-(((3R,5S)-4-(2-(furan-2-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
305	4-(((2S,6R)-2,6-dimethyl-4-(2-(2-methyl-1H-imidazol-1-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
326	4-(((3R,5S)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
328	4-(((3R,5S)-4-(2-(furan-3-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
329	4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
330	4-(((3R,5S)-3,5-dimethyl-4-(2-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
332	4-(((3R,5S)-4-(2-(3,6-dihydro-2H-pyran-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
342	4-(((3R,5S)-4-(3-(furan-2-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
343	4-(((3R,5S)-4-(3-(furan-3-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
344	4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-3-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
345	4-(((3R,5S)-3,5-dimethyl-4-(3-(pyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
346	4-(((3R,5S)-4-(3-(3,6-dihydro-2H-pyran-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
349	4-(((2S,6R)-2,6-dimethyl-4-(2-(pyridin-3-yl)methyl)-N-hydroxybenzamid
354	4-(((3R,5S)-3,5-dimethyl-4-(oxazol-4-ylmethyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
356	4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-N-

	hydroxybenzamid
376	4-(((3R,5S)-3,5-dimethyl-4-(4-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
382	4-(((3R,5S)-3,5-dimethyl-4-(3-(piperidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
383	4-(((3R,5S)-4-(3-((R)-3-fluorpyrrolidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
387	4-(((3R,5S)-4-(3-((4-(2-fluor-2-methylpropyl)piperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
388	4-(((3R,5S)-4-(4-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
411	4-(((3R,5S)-4-(4-((R)-3-fluorpyrrolidin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
413	4-(((3R,5S)-4-(4-((4-benzylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
431	4-(((3R,5S)-4-(3-((4-acetylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
439	4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
441	4-(((3R,5S)-4-(3-((1-(benzyl(methyl)amino)propan-2-yl)amino)methyl)benzoyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
444	4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(methysulfonyl)piperazin-1-yl)methyl)benzoyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
452	4-(((3R,5S)-3,5-dimethyl-4-(3-((4-

	(methylsulfonyl)piperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
453	4-(((3R,5S)-3,5-dimethyl-4-(3-((4-(2,2,2-trifluorethyl)piperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
454	N-hydroxy-4-(((3R,5S)-4-(3-((4-isopentylpiperazin-1-yl)methyl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamid
467	4-(((3R,5S)-3,5-dimethyl-4-(4-(piperidin-1-ylmethyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
468	4-(((3R,5S)-3,5-dimethyl-4-(4-((4-methylpiperazin-1-yl)methyl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
481	4-(((3R,5S)-3,5-dimethyl-4-(2-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
482	4-(((3R,5S)-4-(2-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
483	4-(((3R,5S)-3,5-dimethyl-4-(2-(1-(2,2,2-trifluorethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzyl)piperazin-1-yl)methyl)-N-hydroxybenzamid
484	N-hydroxy-4-(((3R,5S)-4-(2-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)benzamid
485	4-(((3R,5S)-4-(2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)benzyl)-3,5-dimethylpiperazin-1-yl)methyl)-N-hydroxybenzamid
696	4-(((3R,5S)-3,5-dimethyl-4-(3-(morpholinomethyl)benzyl)piperazin-1-yl)methyl)-3-fluor-N-hydroxybenzamid
813	4-(((3R,5S)-4-benzyl-3,5-dimethylpiperazin-1-yl)methyl)-3-fluor-N-hydroxybenzamid

8. Farmaceutisk sammensætning, der omfatter en forbindelse med formel I, en stereoisomer deraf eller et farmaceutisk acceptabelt salt deraf ifølge et hvilket som helst af kravene 1 til 7.

5

9. Farmaceutisk sammensætning ifølge krav 8 til anvendelse til forebyggelse eller behandling af cancer, inflammationssygdomme, autoimmunsygdomme, neurologiske sygdomme eller neurodegenerative sygdomme.

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10. Forbindelse med formel I, en stereoisomer deraf eller et farmaceutisk acceptabelt salt deraf ifølge et hvilket som helst af kravene 1 til 7 til anvendelse til forebyggelse eller behandling af cancer, inflammationssygdomme, autoimmunsygdomme, neurologiske sygdomme eller neurodegenerative forstyrrelser.

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