Description

Title of Invention: NOVEL HETEROCYCLIC DERIVATIVES AND THEIR USES

Technical Field

[1] The present invention relates to novel heterocyclic compounds useful in preparing drugs for treatment of diseases associated with various functions of the histamine 4 receptor. Especially, the said drugs are useful for treatment of inflammatory diseases, allergy, pain, nasal polyps, rhinitis, chronic sinusitis, nasal congestion, nasal itch, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis, eczema, pruritus, itchy skin, urticaria, idiopathic chronic urticaria, scleroderma, conjunctivitis, keratoconjunctivitis, ocular inflammation, dry eye, cardiac dysfunction, arrhythmia, atherosclerosis, multiple sclerosis, inflammatory bowel disease (including colitis, Crohn's disease, ulcerative colitis), inflammatory pain, neuropathic pain, osteoarthritic pain, autoimmune thyroid disease, immune-mediated (also known as type I) diabetes, lupus, post-operative adhesions, vestibular disorders and cancer.

Background Art

[2] Histamine, which is a biogenic amine, plays a central role in the immune and inflammatory response and is also a neurotransmitter. For example, histamine controls various functions of antigen-presenting cells (dendritic cells and macrophages), T cells, B cells, epithelial and endothelial cells, and proliferation of T cells or cytokine secretion in dendritic cells and mast cells (JDDG, 2010, 8, 495-504). There are 4 histamine receptors (histamine 1 receptor, histamine 2 receptor, histamine 3 receptor and histamine 4 receptor) (Br. J. Pharm 2006, *147*, S127-S135). An acute allergic reaction is controlled by the histamine 1 receptor which is distributed ubiquitously in the body (Br. J. Pharmac. Chemother. 1966, *27*, 427-439) and a gastric acid secretion is controlled by the histamine 2 receptor which also are distributed ubiquitously in the body like histamine 1 receptor (Nature 1972, *236*, 385-390). It is well known that the neurotransmitter secretion in the central nervous system is controlled by the histamine 3 receptor which is expressed in neurons (Nature 1983, *302*, 832-837). The histamine 4 receptor further explains physiological functions of many signaling processes which are not explained only by the histamine 1 receptor, histamine 2 receptor and histamine 3 receptor. The histamine 4 receptor was reported for the first time in 1994 and its cloning was performed only since 2000. The histamine 4 receptor, which is a G-protein coupled receptor, consists of 390 amino acids and is activated by binding with Gi/o protein to increase calcium concentration or suppress cyclic adenosine monophosphate

(cAMP) (The Open Immunology Journal, 2009, *2*, 9-41). The histamine 4 receptor is mainly expressed in bone marrow or eosinophils, basophils, T cells, mast cells, monocytes and dendritic cells, and is also observed in the spleen, thymus, lung, heart and intestines (Nat. Rev. Drug Discov. 2008, *7*, 41-53; Biochem. Biophys. Res. Commun. 2000, *279*, 615-620). The histamine 4 receptor not only plays a central role in the immune response but also has effects on the activation and migration of various immunocytes, and the production of cytokines and chemokines (J. Immunol. 2005, *174* , 5224-5232; J. Pharmacol. Exp. Ther. 2003, *305*, 1212-1221; J. Allergy Clin. Immnol. 2007, *120*, 300-307; J. Recept. Signal Transduct. Res. 2002, *22*, 431-448).

[3]

[4] In various *in vivo* experiments, it is well known that the histamine 4 receptor plays an important role in inflammation and itch (J. Allergy Clin. Immnol. 2007, *119*, 176-183; J. Pharmacol. Exp. Ther. 2004, *309*, 404-413). Especially, as results of researches, it has been found in an allergic mouse asthma model that the histamine 4 antagonists alleviate lung inflammation by controlling Th2 (T helper type 2) reaction, and confirmed that histamine 4 antagonists effectively suppress histamine-induced itch. Such a dual effect against allergic inflammation and itch is a basis for the fact that the histamine 4 receptor may be a good target for treating allergic skin diseases such as atopic dermatitis (J. Invest. Dermatol. 2010, 130(4), 1023-1033).

[5]

[6] In such an immunocyte, antagonism against the various functions of the histamine 4 receptor is a key focus of study of inflammatory diseases, pruritus, pain, allergic rhinitis, asthma, rheumatoid arthritis, atopic dermatitis, idiopathic chronic urticaria, inflammatory pain, neuropathic pain and osteoarthritic pain. In addition, a recent study related to effectiveness of the histamine 4 receptor against cancer has been announced, and thereby its development as an anti-cancer drug is expected.

[7]

[8] Recently, it has been reported in WO2010/030785 that quinoxaline-based derivatives show activity on the histamine 4 receptor. However, they did not show a sufficient pharmacological *in vivo* activity in animal model because their solubility and metabolic stability are not high.

Disclosure of Invention

Technical Problem

[9] The heterocyclic compounds of the present invention including pyridopyrazine, pyridopyrimidine and naphthyridine exhibit the same or a stronger histamine 4 receptor inhibitory activity, as compared with conventional human histamine 4 receptor (hH4R) inhibitors such as those disclosed in WO2010/030785; show a selectivity for each of

the subtype receptors of histamine and receptors, transporters and ion channels on a membrane; have higher solubility, metabolic stability and accordingly effective pharmacokinetics so as to be used for treatment with lower dosage and fewer administration times; show the suppressive effect against the histamine-induced infiltration of inflammatory cells such as mast cells and eosinophils, and thus have strong anti-inflammatory and anti-itching effects in an atopic dermatitis model; and have a selectivity for the serotonin 3 receptor to prevent side effects such as diarrhea or constipation (Clinical and Experimental Immunology, 2010, *161*, 19-27; Pharmacology & Therapeutics, 2010, *128*, 146-169) because of the high structural similarity between the histamine 4 receptor (hH4R) ligands and the serotonin 3 receptor ligands (BMCL, 2011, *21*, 5460-5464). Thus, the purpose of the present invention is to provide such novel heterocyclic compounds and pharmaceutical compositions comprising the same.

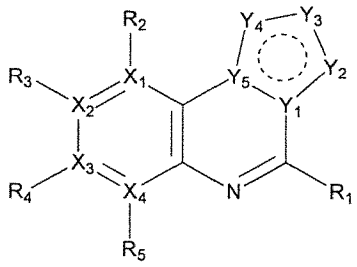
[10]

[11] As novel heterocyclic compounds according to the present invention and pharmaceutical compositions comprising the same show strong human histamine 4 receptor (hH4R) inhibitory activity, they are useful in treating or preventing inflammatory diseases, allergy, pain, nasal polyps, rhinitis, chronic sinusitis, nasal congestion, nasal itch, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis, eczema, pruritus, itchy skin, urticaria, idiopathic chronic urticaria, scleroderma, conjunctivitis, keratoconjunctivitis, ocular inflammation, dry eye, cardiac dysfunction, arrhythmia, atherosclerosis, multiple sclerosis, inflammatory bowel disease (including colitis, Crohn's disease, ulcerative colitis), inflammatory pain, neuropathic pain, osteoarthritic pain, autoimmune thyroid disease, immune-mediated (also known as type I) diabetes, lupus, post-operative adhesions, vestibular disorders and cancer.

Solution to Problem

[12] The present invention provides a heterocyclic compound of formula 1

[13] [Formula 1]

[14] 

[15] or a racemate, isomer or pharmaceutically acceptable salt thereof:

[16] wherein

[17] each of X_1, X_2, X_3 and X_4 is independently C or N, provided that at least one of X_1, X

$_2$, X_3 and X_4 is N,

[18] R_1 is a saturated or unsaturated 3-12 membered mono- or poly-heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S), where R_1 is unsubstituted or substituted with 1-3 substituents selected from $-NR_6R_7$, $-C_1$-C_6 alkyl-NR_6R_7 and R_8; or R_1 is selected from -H, $-NR_6R_7$ and R_8,

[19] R_2, R_3, R_4 and R_5 may be the same or different; and each of them is independently selected from -H; $-C_1$-C_6alkyl; $-C_1$-C_6haloalkyl; $-C_1$-C_6perhaloalkyl; -amino-C_1-C_6alkyl; $-C_3$-C_8cycloalkyl; -halogen (-F, -Cl, -Br, -I); -CN; $-C_1$-C_6alkoxy; $-C_1$-C_6haloalkoxy; $-C_1$-C_6perhaloalkoxy; $-C_2$-C_7alkenyl; $-C_2$-C_8alkynyl; -amino; -amido; $-C_1$-C_6alkylcarboxyl; -carboxyl (-COOH); $-C_1$-C_6acyl; -OH; -nitro ($-NO_2$); $-C_6$-C_{10}aryl; -heterocyclyl; and -O-C_1-C_6alkyl-heterocyclyl, where the heterocyclyl is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S),

[20] provided that when X_1 is N, R_2 does not exist; when X_2 is N, R_3 does not exist; when X_3 is N, R_4 does not exist; and when X_4 is N, R_5 does not exist,

[21] each of Y_1, Y_2, Y_3, Y_4 and Y_5 is independently C or a heteroatom (preferably a heteroatom independently selected from N, O and S), provided that at least one of Y_1, Y_2, Y_3, Y_4 and Y_5 is a heteroatom independently selected from N, O and S,

[22] each of Y_2 and Y_3 may be independently substituted with R_9,

[23] Y_4 may be substituted with -H or $-C_1$-C_6alkyl,

[24] each of R_6 and R_7 is independently selected from -H; $-C_1$-C_6alkyl; $-C_3$-C_8cycloalkyl; -heterocyclyl; -amino-C_1-C_6mono- or di-alkyl; $-C_1$-C_6alkyl-amino-C_1-C_6mono- or di-alkyl; $-C_1$-C_6alkyl-heterocyclyl; $-C_1$-C_6alkylcarboxyl; -carboxyl (-COOH); and phenyl, where the heterocyclyl is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S),

[25] R_8 is $-C_1$-C_6alkyl; $-C_1$-C_6alkoxy; -OH; -amino; $-C_1$-C_6alkyl-amino; $-C_3$-C_8cycloalkyl; -S-C_1-C_6alkyl-amino-C_1-C_6mono- or di-alkyl; -S-C_1-C_6alkyl-heterocyclyl; -O-heterocyclyl; or -O-C_1-C_6alkyl-heterocyclyl, where the heterocyclyl is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S), and

[26] R_9 is selected from -H; -OH; $-C_1$-C_6alkyl; $-C_1$-C_6haloalkyl; $-C_1$-C_6perhaloalkyl; -amino-C_1-C_6mono- or di-alkyl; $-C_3$-C_7cycloalkyl; -heterocyclyl; $-C_6$-C_{10}aryl; 5-12 membered heteroaryl; $-C_1$-C_6alkoxy; $-C_1$-C_6haloalkoxy; -halogen (-F, -Cl, -Br, -I); -amino; -amido; $-C_1$-C_6acyl; -CN; -carboxyl (-COOH); $-C_1$-C_6alkylcarboxyl; and -nitro ($-NO_2$), with proviso that when Y_4 is N and Y_1, Y_2, Y_3 and Y_5 is C, Y_3 is not substituted with a substituent having -C(=O)- moiety,

[27] wherein each of the alkyl, cycloalkyl, heterocyclyl, alkoxy, alkenyl, alkynyl, acyl and aryl groups may be independently unsubstituted or substituted with one or more sub-

stituents (for example, 1-3 substituents) selected from the group consisting of -C_1-C_4 alkyl, -halogen (-F, -Cl, -Br, -I), -CN, -C_1-C_4alkoxy, -amino, -amido, -carboxyl (-COOH), -C_1-C_6acyl, -OH, -nitro (-NO_2), heterocyclyl and phenyl, where the heterocyclyl is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably, heteroatoms selected from N, O and S).

[28]

[29] According to a preferred embodiment of the present invention, in the above formula 1, each of X_1, X_2 and X_3 is independently C or N, and X_4 is N.

[30]

[31] According to another preferred embodiment of the present invention, in the above formula 1, each of Y_1, Y_2, Y_3, Y_4 and Y_5 is independently C or a heteroatom (preferably a heteroatom independently selected from N, O and S), provided that at least three of Y_1, Y_2, Y_3, Y_4 and Y_5 are N.

[32]

[33] According to another preferred embodiment of the present invention, in the above formula 1, R_1 is a saturated or unsaturated 3-8 membered mono- or poly-heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S), where R_1 is unsubstituted or substituted with 1-3 substituents selected from NR_6R_7, C_1-C_6 alkyl-NR_6R_7 and R_8.

[34]

[35] According to another preferred embodiment of the present invention, in the above formula 1, R_3 is selected from -H; -C_1-C_6alkyl; -C_1-C_6haloalkyl; -C_1-C_6perhaloalkyl; -halogen (-F, Cl, -Br, -I); -CN; -C_1-C_6alkoxy; -C_1-C_6haloalkoxy; -C_1-C_6perhaloalkoxy; -C_2-C_7alkenyl; -C_2-C_8alkynyl and -OH.

[36]

[37] According to another preferred embodiment of the present invention, in the above formula 1,

[38] each of X_1, X_2, X_3 and X_4 is independently C or N, provided that at least one of X_1, X_2, X_3 and X_4 is N,

[39] R_1 is a saturated or unsaturated 3-12 membered mono- or poly-heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S), where R_1 is unsubstituted or substituted with 1-3 substituents selected from -NR_6R_7, -C_1-C_6 alkyl-NR_6R_7 and R_8; or R_1 is selected from -NR_6R_7 and R_8,

[40] R_2, R_3, R_4 and R_5 may be the same or different; and each of them is independently selected from -H; -C_1-C_6alkyl; -C_1-C_6haloalkyl; -C_1-C_6perhaloalkyl; -halogen (-F, -Cl, -Br, -I); -CN; -C_1-C_6alkoxy; -C_1-C_6haloalkoxy; -C_1-C_6perhaloalkoxy; -C_2-C_7alkenyl; -C_2-C_8alkynyl; and -OH,

[41] provided that when X_1 is N, R_2 does not exist; when X_2 is N, R_3 does not exist; when

X_3 is N, R_4 does not exist; and when X_4 is N, R_5 does not exist,

[42] each of Y_1, Y_2, Y_3, Y_4 and Y_5 is independently C or a heteroatom (preferably a heteroatom independently selected from N, O and S), provided that at least two of Y_1, Y_2, Y_3, Y_4 and Y_5 are heteroatoms independently selected from N, O and S,

[43] each of Y_2 and Y_3 may be independently substituted with R_9,

[44] Y_4 may be substituted with -H or -C_1-C_6alkyl,

[45] each of R_6 and R_7 is independently selected from -H; -C_1-C_6alkyl; and -carboxyl (-COOH),

[46] R_8 is selected from -C_1-C_6alkyl; and -C_3-C_8cycloalkyl, and

[47] R_9 is selected from -H; -C_1-C_6alkyl; and -C_3-C_7cycloalkyl,

[48] wherein each of the alkyl, cycloalkyl, heterocyclyl, alkoxy, alkenyl and alkynyl groups may be independently unsubstituted or substituted with one or more substituents selected from the group consisting of -C_1-C_4alkyl, -OH and -C_1-C_4alkoxy, where the heterocyclyl is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S).

[49]

[50] According to another preferred embodiment of the present invention, in the above formula 1,

[51] each of X_1, X_2, X_3 and X_4 is independently C or N, provided that at least one of X_1, X_2, X_3 and X_4 is N,

[52] R_1 is a saturated or unsaturated 3-12 membered mono- or poly-heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S), where R_1 is unsubstituted or substituted with 1-3 substituents selected from -NR_6R_7 and R_8,

[53] R_2, R_3, R_4 and R_5 may be the same or different; and each of them is independently selected from -H; -C_1-C_6alkyl; -C_1-C_6haloalkyl; -halogen (-F, -Cl, -Br, -I); -CN; -C_1-C_6 alkoxy; -C_1-C_6haloalkoxy; -C_2-C_7alkenyl; and -C_2-C_8alkynyl,

[54] provided that when X_1 is N, R_2 does not exist; when X_2 is N, R_3 does not exist; when X_3 is N, R_4 does not exist; and when X_4 is N, R_5 does not exist,

[55] each of Y_1, Y_2, Y_3, Y_4 and Y_5 is independently selected from C, N and O, provided that at least two of Y_1, Y_2, Y_3, Y_4 and Y_5 are N or O,

[56] each of Y_2 and Y_3 may be independently substituted with R_9,

[57] each of R_6 and R_7 is independently selected from -H and -C_1-C_6alkyl,

[58] R_8 is selected from -C_1-C_6alkyl, and

[59] R_9 is selected from -H, -C_1-C_6alkyl and -C_3-C_7cycloalkyl,

[60] wherein each of the alkyl, cycloalkyl, heterocyclyl, alkoxy, alkenyl and alkynyl groups may be independently unsubstituted or substituted with one or more substituents selected from the group consisting of -C_1-C_4alkyl, -OH and -C_1-C_4alkoxy, where the heterocyclyl is a saturated or unsaturated 3-6 membered heterocyclyl

containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S).

[61]

[62] According to another preferred embodiment of the present invention, in the above formula 1,

[63] each of X_1, X_2, X_3 and X_4 is independently C or N, provided that at least one of X_1, X_2, X_3 and X_4 is N,

[64] R_1 is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S), where R_1 is unsubstituted or substituted with $-NR_6R_7$,

[65] R_2, R_3, R_4 and R_5 may be the same or different; and each of them is independently selected from -H; $-C_1$-C_6alkyl; $-C_1$-C_6haloalkyl; -halogen (-F, Cl, -Br, -I); -CN; $-C_1$-C_6 alkoxy; $-C_1$-C_6haloalkoxy; $-C_2$-C_7alkenyl; and $-C_2$-C_8alkynyl,

[66] provided that when X_1 is N, R_2 does not exist; when X_2 is N, R_3 does not exist; when X_3 is N, R_4 does not exist; and when X_4 is N, R_5 does not exist,

[67] each of Y_1, Y_2, Y_3, Y_4 and Y_5 is independently selected from C, N and O, provided that at least two of Y_1, Y_2, Y_3, Y_4 and Y_5 are N,

[68] each of Y_2 and Y_3 may be independently substituted with R_9,

[69] each of R_6 and R_7 is independently selected from -H and $-C_1$-C_6alkyl, and

[70] R_9 is selected from -H, $-C_1$-C_6alkyl and $-C_3$-C_7cycloalkyl,

[71] wherein each of the alkyl, cycloalkyl, heterocyclyl, alkoxy, alkenyl and alkynyl groups may be independently unsubstituted or substituted with one or more substituents selected from the group consisting of $-C_1$-C_4alkyl, -OH and $-C_1$-C_4alkoxy, where the heterocyclyl is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S).

[72]

[73] According to another preferred embodiment of the present invention, in the above formula 1,

[74] each of X_1, X_2, X_3 and X_4 is independently C or N, provided that at least one of X_1, X_2, X_3 and X_4 is N,

[75] R_1 is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S), where R_1 is unsubstituted or substituted with $-NR_6R_7$,

[76] R_2, R_3, R_4 and R_5 may be the same or different; and each of them is independently selected from -H; $-C_1$-C_6alkyl; $-C_1$-C_6haloalkyl; and -halogen (-F, -Cl, -Br, -I),

[77] provided that when X_1 is N, R_2 does not exist; when X_2 is N, R_3 does not exist; when X_3 is N, R_4 does not exist; and when X_4 is N, R_5 does not exist,

[78] each of Y_1, Y_2, Y_3, Y_4 and Y_5 is independently selected from C, N and O, provided that at least two of Y_1, Y_2, Y_3, Y_4 and Y_5 are N,

[79] each of Y_2 and Y_3 may be independently substituted with R_9,

[80] each of R_6 and R_7 is independently selected from -H and -C_1-C_6alkyl, and

[81] R_9 is selected from -H and -C_1-C_6alkyl,

[82] wherein each of the alkyl and heterocyclyl groups may be independently unsubstituted or substituted with one or more substituents selected from the group consisting of -C_1-C_4alkyl, -OH and -C_1-C_4alkoxy, where the heterocyclyl is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S.

[83]

[84] The compound of the present invention is a human histamine 4 receptor (hH4R) inhibitor and is useful for treating or preventing inflammatory diseases, allergy, pain, nasal polyps, rhinitis, chronic sinusitis, nasal congestion, nasal itch, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis, eczema, pruritus, itchy skin, urticaria, idiopathic chronic urticaria, scleroderma, conjunctivitis, keratoconjunctivitis, ocular inflammation, dry eye, cardiac dysfuction, arrhythmia, atherosclerosis, multiple sclerosis, inflammatory bowel disease (including colitis, Crohn's disease, ulcerative colitis), inflammatory pain, neuropathic pain, osteoarthritic pain, autoimmune thyroid disease, immune-mediated (also known as type I) diabetes, lupus, post-operative adhesions, vestibular disorders and cancer, and especially useful as an agent for treating atopic dermatitis.

[85]

[86] Unless mentioned otherwise, alkyl substituent as described herein and alkyl residue in other substituents (for example, alkoxy) as described herein may be linear or branched. Also, halogen includes fluorine (F), chlorine (Cl), bromine (Br) and iodine (I).

[87]

[88] As representative examples of the compound of formula 1 according to the present invention, the following compounds may be mentioned:

[89]

[90] 3-Methyl-6-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine (compound 1);

[91] 8-Methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 2);

[92] 4-(4-Methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 3);

[93] 8-Chloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 4);

[94] 3-Chloro-6-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine (compound 5);

[95] 6-(4-Methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine (compound 6);

[96] 8-Chloro-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 7);

[97] 1-(8-Chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine (compound 8);

[98] (R)-1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*,*N*-dimethylpyrrolidin-3-amine (compound 9);

[99] (R)-1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylpyrrolidin-3-amine (compound 10);

[100] (R)-1-(3-chloropyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazin-6-yl)-*N*-methylpyrrolidin-3-amine (compound 11);

[101] 8-Bromo-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 12);

[102] 4-(4-Methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-carbonitrile (compound 13);

[103] 8-Chloro-1-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 14);

[104] 8-Chloro-1-methyl-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 15);

[105] 8-Bromo-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 16);

[106] 7,8-Dichloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 17);

[107] 1-(8-Chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 18);

[108] (S)-8-chloro-4-(3-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 19);

[109] (S)-8-chloro-4-(3,4-dimethylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 20);

[110] 8-Chloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-7-carbonitrile (compound 21);

[111] 8-Chloro-4-(3,4,5-trimethylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 22);

[112] 8-Chloro-7-ethoxy-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 23);

[113] 1-(8-Bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 24);

[114] 4-(3-(Methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-carbon

itrile (compound 25);

[115] 4-(Piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-carbonitrile (compound 26);

[116] 1-(7,8-Dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 27);

[117] 8-Chloro-4-(3-(methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-7-carbonitrile (compound 28);

[118] 8-Chloro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 29);

[119] (R)-1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)pyrrolidin-3-amine (compound 30);

[120] 9-Chloro-2-methyl-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (compound 31);

[121] 9-Chloro-2-methyl-5-(piperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (compound 32);

[122] 1-(9-Chloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-yl)-*N*-methylazetidin-3-amine (compound 33);

[123] 9-Chloro-2-cyclopropyl-*N*,*N*-diethylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amine (compound 34);

[124] 9-Chloro-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (compound 35);

[125] 1-(9-Chloropyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-yl)-*N*-methylazetidin-3-amine (compound 36);

[126] 9-Chloro-5-(piperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (compound 37);

[127] 9-Chloro-2-cyclopropyl-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (compound 38);

[128] 9-Chloro-2-cyclopropyl-5-(piperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (compound 39);

[129] 9-Chloro-2-(methoxymethyl)-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (compound 40);

[130] 9-Chloro-2-ethyl-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (compound 41);

[131] 9-Chloro-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (compound 42);

[132] 8-Chloro-2-methyl-4-(4-methylpiperazin-1-yl)-2H-pyrazolo[3,4-c][1,8]naphthylidine (compound 43);

[133] 1-(8-Chloro-2-methyl-2H-pyrazolo[3,4-c][1,8]naphthylidine-4-yl)-*N*-methylazetidin-

3-amine (compound 44);

[134] 8-Chloro-2-methyl-4-(piperazin-1-yl)-2H-pyrazolo[3,4-c][1,8]naphthylidine (compound 45);

[135] 8-Chloro-4-(4-methylpiperazin-1-yl)imidazo[1,2-a]pyrido[2,3-e]pyrazine (compound 46);

[136] 8-Chloro-4-(piperazin-1-yl)imidazo[1,2-a]pyrido[2,3-e]pyrazine (compound 47).

[137] 1-(8-Iodopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 48);

[138] 8-Iodo-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 49);

[139] *N*-Methyl-1-(8-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine (compound 50);

[140] 1-(8-(Difluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 51);

[141] *N*-Methyl-1-(8-(trifluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine (compound 52);

[142] 4-(4-Methylpiperazin-1-yl)-8-(trifluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 53);

[143] 1-(8-Ethynylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 54);

[144] *N*-Methyl-1-(8-vinylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine (compound 55);

[145] 1-(8-Ethylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 56);

[146] 4-(3-(Methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-ol (compound 57);

[147] 1-(8-Methoxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 58);

[148] 1-(8-(Difluoromethoxy)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 59);

[149] 8-Chloro-7-methoxy-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 60);

[150] 8-Chloro-7-methoxy-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 61);

[151] 7,8-Dichloro-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 62);

[152] 8-Chloro-7-ethoxy-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 63);

[153] 8-Chloro-4-(4-methylpiperazin-1-yl)-7-(2,2,2-trifluoroethoxy)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 64);

[154] 1-(8-Bromo-9-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 65);

[155] 8-Bromo-9-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 66);

[156] 1-(8,9-Dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 67);

[157] 1-(8-Bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine hydrochloride (compound 68);

[158] 1-(8-Bromopyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine hydrochloride (compound 69);

[159] 8-Chloro-4-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 70);

[160] 8-Bromo-4-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 71);

[161] 1-(8-Bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-3-methylazetidin-3-amine (compound 72);

[162] 1-(8-Bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*,3-dimethylazetidin-3-amine (compound 73);

[163] 8-Bromo-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 74);

[164] 4-(Hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-8-iodopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 75);

[165] 8-Chloro-4-(4-cyclopropylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 76);

[166] 4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 77);

[167] 8-Chloro-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 78);

[168] 8-Chloro-4-(1,4-diazepan-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 79);

[169] 8-Chloro-4-(4-methyl-1,4-diazepan-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 80);

[170] (R)-1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylpyrrolidin-3-amine (compound 81);

[171] 8-Chloro-4-(hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 82);

[172] 8-Chloro-4-(1-methylhexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 83);

[173] 1-(8-Chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*,*N*-dimethylazetidin-3-amine (compound 84);

[174] 1-(8-Bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*,*N*-dimethylazetidin-3-amine (compound 85);

[175] (1-(8-Bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamic acid (compound 86);

[176] 2-((8-Chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)amino)ethanol (compound 87);

[177] 1-(8-Chloroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 88);

[178] 1-(8-Bromoimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 89);

[179] *tert*-Butyl (1-(8-chloro-2-methyloxazolo[4,5-c][1,8]naphthylidine-4-yl)azetidin-3-yl)(methyl)carbamate (compound 90);

[180] 1-(8-Chloro-2-methyloxazolo[4,5-c][1,8]naphthylidine-4-yl)-*N*-methylazetidin-3-amine (compound 91);

[181] 8-Chloro-2-methyl-4-(4-methylpiperazin-1-yl)oxazolo[4,5-c][1,8]naphthylidine (compound 92);

[182] 1-(8-Chloropyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 93);

[183] 8-Chloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e]tetrazolo[1,5-a]pyrazine (compound 94);

[184] 1-(8-Bromopyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 95);

[185] 8-Bromo-4-(4-methylpiperazin-1-yl)pyrido[2,3-e]tetrazolo[1,5-a]pyrazine (compound 96);

[186] 1-(8-Chloro-2-methylpyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 97);

[187] 8-Chloro-2-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazine (compound 98);

[188] 1-(8-bromo-7-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 99);

[189] 8-bromo-7-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 100);

[190] 8-chloro-4-(3-(methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-

7-ol HCl salt (compound 101);

[191] *N*-(1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)-*N*-methylhydroxylamine (compound 102);

[192] 1-(2-bromopyrido[3,2-e]pyrrolo[1,2-c]pyrimidin-6-yl)-*N*-methylazetidin-3-amine (compound 103);

[193] 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine 2,2,2-trifluoroacetate (compound 104);

[194] (S)-1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 105);

[195] (R)-1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 106);

[196] 1-(8-bromo-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 107);

[197] 1-(8-bromo-2-methylimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 108);

[198] 1-(9-bromo-2-methylpyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-yl)-*N*-methylazetidin-3-amine (compound 109);

[199] 1-(9-bromopyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-yl)-*N*-methylazetidin-3-amine (compound 110);

[200] *N*-methyl-1-(8-nitropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine (compound 111);

[201] 4-(3-(methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-amine (compound 112);

[202] N-methyl-1-(8-phenylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine

[203] (compound 113);

[204] 1-(8-(furan-2-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine

[205] (compound 114);

[206] 1-(2-bromopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6-yl)-N-methylazetidin-3-amine (compound 115);

[207] 1-(2-chloropyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazin-6-yl)-N-methylazetidin-3-amine (compound 116);

[208] 1-(8-chloropyrido[3,4-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (compound 117);

[209] 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine methanesulfonic acid salt (compound 118);

[210] 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amin

e maleic acid salt (compound 119);

[211] 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine 2-hydroxypropane-1,2,3-tricarboxylic acid salt (compound 120);

[212] 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine nitric acid salt (compound 121);

[213] 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine hydroiodic acid salt (compound 122);

[214] 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine phosphoric acid salt (compound 123);

[215] 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine 4,4'-methylenebis(3-hydroxy-2-naphthoic acid) salt (compound 124);

[216] 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine hydrobromic acid salt (compound 125);

[217] 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine sulfuric acid salt (compound 126);

[218] 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (2R,3R)-2,3-dihydroxysuccinic acid salt (compound 127);

[219] 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (1S)-(+)-10-Camphorsulfonic acid salt (compound 128);

[220] 8-bromo-N-(1-methylpyrrolidin-3-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-amine (compound 129);

[221] 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (S)-2-hydroxypropanoic acid salt (compound 130);

[222] N-(azetidin-3-ylmethyl)-8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-amine trifluoroacetic acid salt (compound 131); and

[223] 4-(azetidin-3-ylmethoxy)-8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine hydrochloric acid salt (compound 132).

[224]

[225] The above-listed names of the compounds are described in accordance with the nomenclature method provided by ChemBioDraw Ultra software (Version 12.02.1076) of CambridgeSoft.

[226]

[227] In case of the compound of formula 1 according to the present invention being a racemate, the racemate may be separated into its respective isomers by using a conventional separation method, for example, such as a general column chromatography packed with normal-phase silica gel (Isu Chemical Co., particle diameter: 0.040~0.063 mm and 0.063~0.200 mm), a general column chromatography packed with amine silica gel (Isu Chemical Co., particle diameter: 0.040~0.075 mm), or a pressurized

fractionating column chromatography packed in reverse phase (Yamazen, W-Prep 2XY), and employing the corresponding solvent, preferably a solvent mixture of hexane, ethyl acetate, dichloromethane and methanol in normal-phase and a solvent mixture of water and acetonitrile in reverse-phase.

[228]

[229] The compound of formula 1 according to the present invention may also form a pharmaceutically acceptable salt. Representative acids useful in preparing such a pharmaceutically acceptable salt (for example, acid addition salts) include, but not limited to, hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrobromic acid, hydroiodic acid, formic acid, citric acid, acetic acid, trichloroacetic acid or trifluoroacetic acid, benzoic acid, fumaric acid, maleic acid, methane sulfonic acid, benzene sulfonic acid, p-toluene sulfonic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, 4-acetamidobenzoic acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphorsulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, cyclamic acid, dodecyl sulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, galactaric acid, gentisic acid, glucoheptanoic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid, α-oxo-glutaric acid, glycolic acid, hippuric acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methane sulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, undecylenic acid and the like. In addition, other acid salts that are known and used in the art of amine derivatives may be included. They may be prepared by conventionally known processes.

[230]

[231] The compound of formula 1 as defined above according to the present invention may be prepared by, but not limited to, the methods described in the following embodiments.

[232]

[233] The heterocyclic compound having a structure of formula 1, or a racemate, isomer or pharmaceutically acceptable salt thereof may be prepared by a method comprising the steps of:

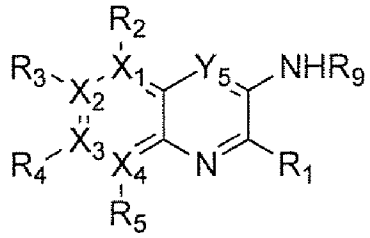
[234] (a) preparing a compound of formula 3 via arylation of a compound of formula 4 with a compound of formula R_1-H (except that R_1 is -H);

[235] (b) preparing a compound of formula 2 via arylation of the prepared compound of formula 3; and

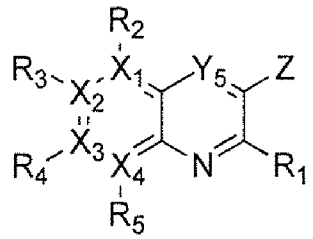
[236] (c) cyclizing the prepared compound of formula 2 (or, a step of deprotecting R_1 may be comprised):

[237]

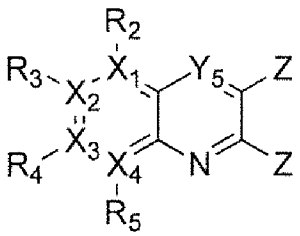
[238] [Formula 2]

[239] 

[240] [Formula 3]

[241] 

[242] [Formula 4]

[243] 

[244]

[245] wherein, in formulas 2 to 4, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5, R_9 and Y_5 are the same as defined in formula 1; and Z represents a reactive leaving group such as halogen (-F, -Cl, -Br).

[246]

[247] The heterocyclic compound having a structure of formula 5 which is formula 1 as defined above wherein Y_1, Y_2 and Y_4 are N, or a racemate, isomer or pharmaceutically acceptable salt thereof may be prepared by a method comprising the steps of:

[248] (a) preparing a compound of formula 9 via halogenation of a compound of formula 10;

[249] (b) preparing a compound of formula 8 via cyanation of the prepared compound of formula 9;

[250] (c) preparing a compound of formula 7 via acylation of the prepared compound of formula 8;

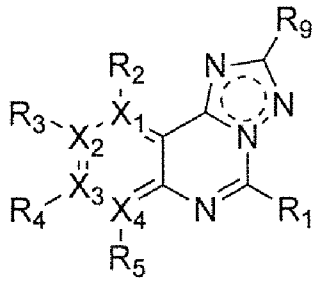
[251] (d) preparing a compound of formula 6 via cyclization of the prepared compound of formula 7 followed by halogenation; and

[252] (e) conducting arylation of the prepared compound of formula 6 with a compound of formula R_1-H (except that R_1 is -H) (or, a step of deprotecting R_1 may be comprised):

[253]

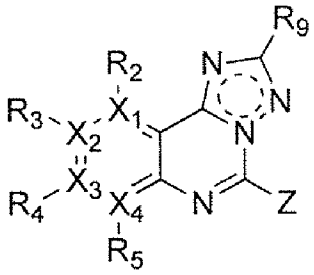
[254] [Formula 5]

[255]



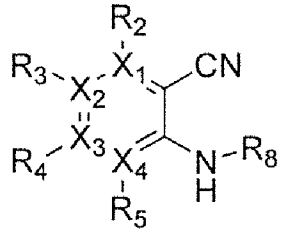
[256] [Formula 6]

[257]



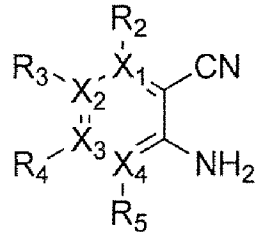
[258] [Formula 7]

[259]



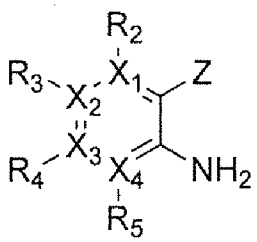
[260] [Formula 8]

[261]

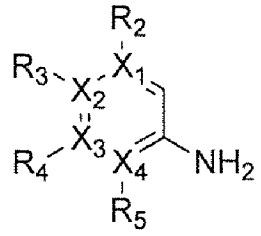


[262] [Formula 9]

[263]



[264] [Formula 10]

[265] 

[266]

[267] wherein, in formulas 5 to 10, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5, R_8 and R_9 are the same as defined in formula 1; and Z represents a reactive leaving group such as halogen (-F, -Cl, -Br), methanesulfonate, triflate, and tosylate.

[268]

[269] The heterocyclic compound having a structure of formula 11 which is formula 1 as defined above wherein Y_2, Y_4 and Y_5 are N, or a racemate, isomer or pharmaceutically acceptable salt thereof may be prepared by a method comprising the steps of:

[270] (a) preparing a compound of formula 16 via arylation of a compound of formula 17;

[271] (b) preparing a compound of formula 15 via imidation of the prepared compound of formula 16;

[272] (c) preparing a compound of formula 14 via acylation of the prepared compound of formula 15;

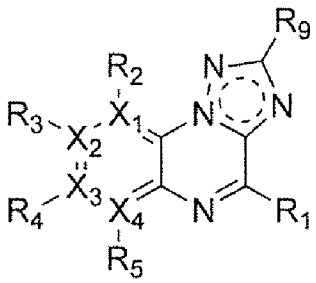
[273] (d) preparing a compound of formula 13 via cyclization of the prepared compound of formula 14;

[274] (e) preparing a compound of formula 12 via reduction of the prepared compound of formula 13 followed by halogenation; and

[275] (f) conducting arylation of the prepared compound of formula 12 with a compound of formula R_1-H (except that R_1 is -H) (or, a step of deprotecting R_1 may be comprised):

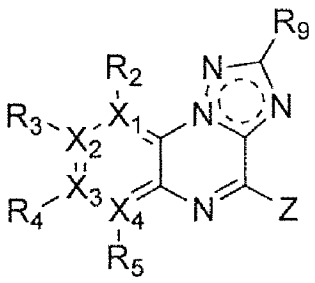
[276]

[277] [Formula 11]

[278] 

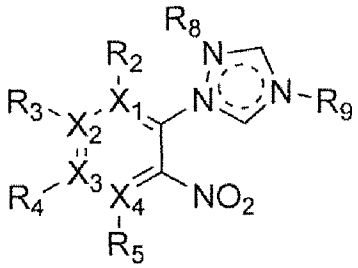
[279] [Formula 12]

[280]



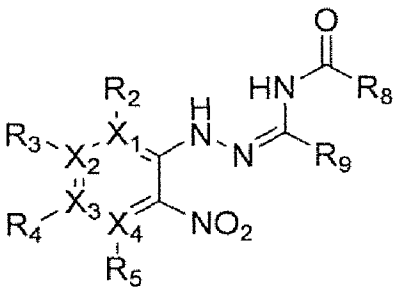
[281] [Formula 13]

[282]



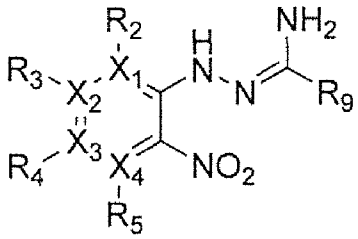
[283] [Formula 14]

[284]



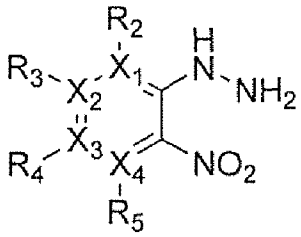
[285] [Formula 15]

[286]



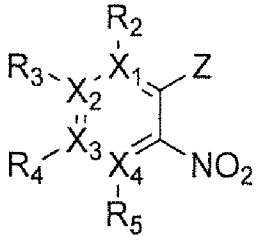
[287] [Formula 16]

[288]



[289] [Formula 17]

[290]



[291] wherein, in formulas 11 to 17, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5, R_8 and R_9 are the same as defined in formula 1; and Z represents a reactive leaving group such as halogen (-F, -Cl, -Br).

[292]

[293] The heterocyclic compound having a structure of formula 18 which is formula 1 as defined above wherein Y_2 and Y_3 are N, or a racemate, isomer or pharmaceutically acceptable salt thereof may be prepared by a method comprising the steps of:

[294] (a) preparing a compound of formula 21 via Friedel-Craft reaction of a compound of formula 23 with a compound of formula 22;

[295] (b) preparing a compound of formula 20 via cyclization of the prepared compound of formula 21;

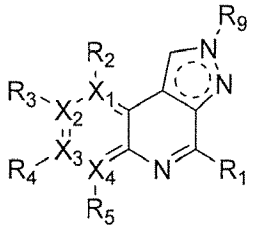
[296] (c) preparing a compound of formula 19 via halogenation of the prepared compound of formula 20; and

[297] (d) conducting arylation of the prepared compound of formula 19 with a compound of formula R_1-H (except that R_1 is -H) (or, a step of deprotecting R_1 may be comprised):

[298]

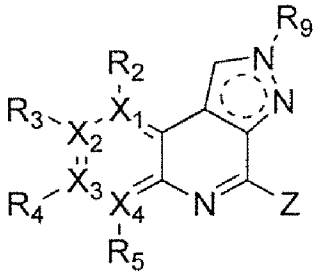
[299] [Formula 18]

[300]

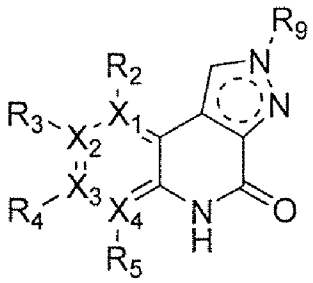


[301] [Formula 19]

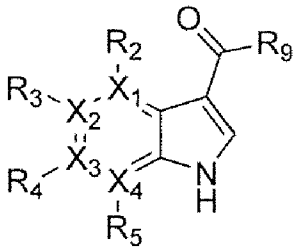
[302]



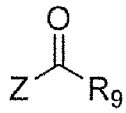
[303] [Formula 20]

[304] 

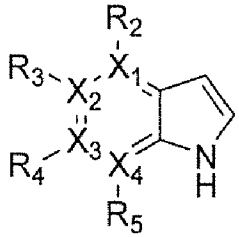
[305] [Formula 21]

[306] 

[307] [Formula 22]

[308] 

[309] [Formula 23]

[310] 

[311] wherein, in formulas 18 to 23, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5 and R_9 are the same as defined in formula 1; and Z represents a reactive leaving group such as halogen (-F, -Cl, -Br).

[312]

[313] The heterocyclic compound having a structure of formula 24 which is formula 1 as defined above wherein Y_1, Y_3 and Y_4 are N, or a racemate, isomer or pharmaceutically acceptable salt thereof may be prepared by a method comprising the steps of:

[314] (a) preparing a compound of formula 28 via cyclization of a compound of formula 29;

[315] (b) preparing a compound of formula 27 via halogenation of the prepared compound of formula 28 followed by hydroxylation;

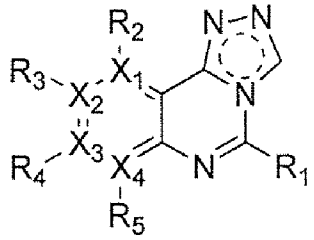
[316] (c) preparing a compound of formula 26 via arylation of the prepared compound of formula 27 with a compound of formula R_1-H (except that R_1 is -H) followed by halogenation;

[317] (d) preparing a compound of formula 25 via arylation of the prepared compound of formula 26; and

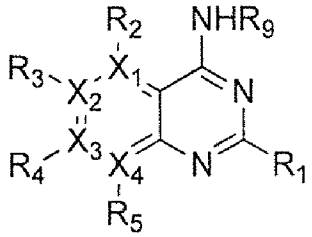
[318] (e) cyclizing the prepared compound of formula 25 (or, a step of deprotecting R_1 may be comprised):

[319]

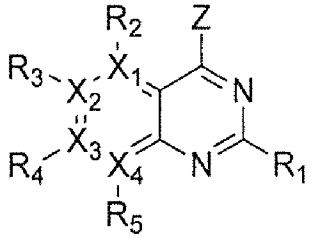
[320] [Formula 24]

[321] 

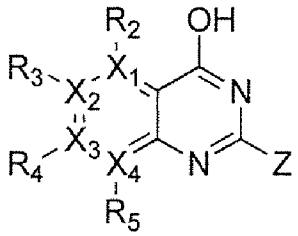
[322] [Formula 25]

[323] 

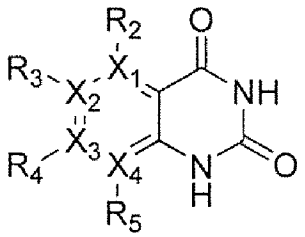
[324] [Formula 26]

[325] 

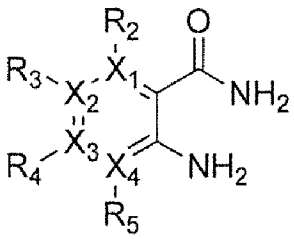
[326] [Formula 27]

[327] 

[328] [Formula 28]

[329] 

[330] [Formula 29]

[331] 

[332] wherein, in formulas 24 to 29, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5 and R_9 are the same as defined in formula 1; and Z represents a reactive leaving group such as halogen (-F, -Cl, -Br).

[333]

[334] The heterocyclic compound having a structure of formula 30 which is formula 1 as defined above wherein Y_2 is N and Y_4 is O, or a racemate, isomer or pharmaceutically acceptable salt thereof may be prepared by a method comprising the steps of:

[335] (a) preparing a compound of formula 36 via esterification of a compound of formula 37;

[336] (b) preparing a compound of formula 35 via arylation of the prepared compound of formula 36;

[337] (c) preparing a compound of formula 34 via cyclization of the prepared compound of formula 35;

[338] (d) preparing a compound of formula 33 via enolate addition reaction of the prepared compound of formula 34;

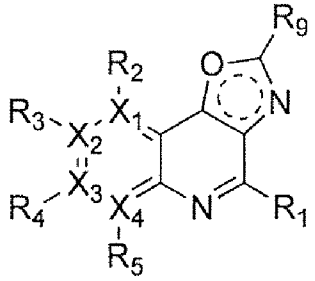
[339] (e) preparing a compound of formula 32 via cyclization of the prepared compound of formula 33;

[340] (f) preparing a compound of formula 31 via halogenation of the prepared compound of formula 32; and

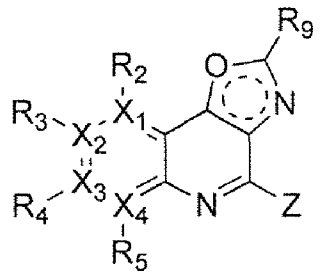
[341] (g) conducting arylation of the prepared compound of formula 31 with a compound of formula R_1-H (except that R_1 is -H) (or, a step of deprotecting R_1 may be comprised):

[342]

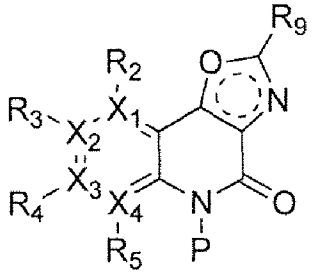
[343] [Formula 30]

[344] 

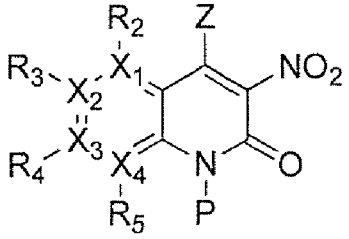
[345] [Formula 31]

[346] 

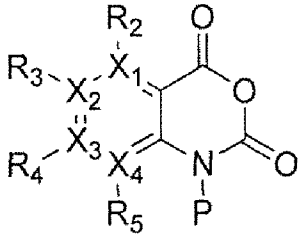
[347] [Formula 32]

[348] 

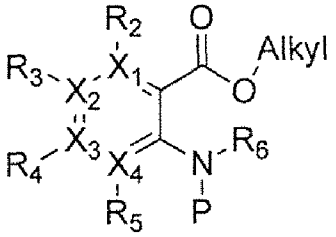
[349] [Formula 33]

[350] 

[351] [Formula 34]

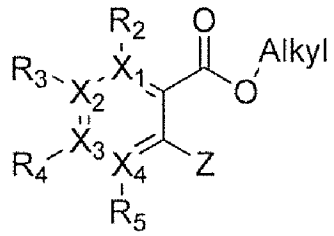
[352] 

[353] [Formula 35]

[354] 

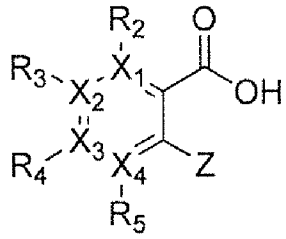
[355] [Formula 36]

[356]



[357] [Formula 37]

[358]



[359] wherein, in formulas 30 to 37, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5, R_6 and R_9 are the same as defined in formula 1; P represents a protecting group such as *para* -methoxybenzyl, 3',5'-dimethoxybenzyl, tri-methoxybenzyl; and Z represents a reactive leaving group such as halogen (-F, -Cl, -Br).

[360]

[361] The heterocyclic compound having a structure of formula 38 which is formula 1 as defined above wherein Y_1 is N and each of Y_2 and Y_3 is independently C or N, or a racemate, isomer or pharmaceutically acceptable salt thereof may be prepared by a method comprising the steps of:

[362] (a) preparing a compound of formula 40 via the Suzuki coupling reaction of a compound of formula 42 with a compound of formula 41;

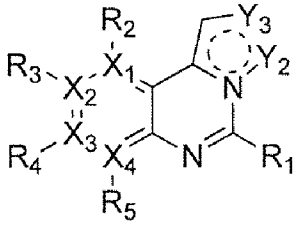
[363] (b) preparing a compound of formula 39 via halogenation of the prepared compound of formula 40; and

[364] (c) conducting arylation of the prepared compound of formula 39 with a compound of formula R_1-H (except that R_1 is -H) (or, a step of deprotecting R_1 may be comprised):

[365]

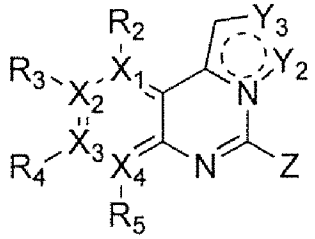
[366] [Formula 38]

[367]

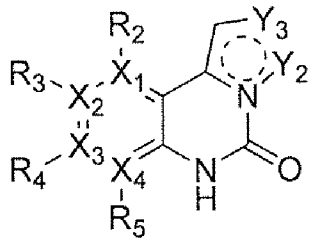


[368] [Formula 39]

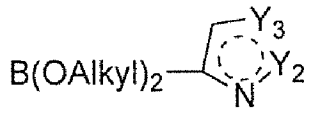
[369]



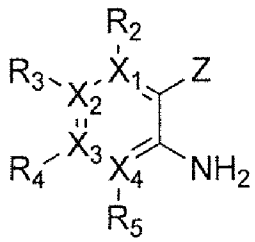
[370] [Formula 40]

[371] 

[372] [Formula 41]

[373] 

[374] [Formula 42]

[375] 

[376] wherein, in formulas 38 to 42, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4 and R_5 are the same as defined in formula 1; and Z represents a reactive leaving group such as halogen (-F, -Cl, -Br).

[377]

[378] The heterocyclic compound having a structure of formula 43 which is formula 1 as defined above wherein Y_5 is N, or a racemate, isomer or pharmaceutically acceptable salt thereof may be prepared by a method comprising the steps of:

[379] (a) preparing a compound of formula 46 via pyrrolation of a compound of formula 47;

[380] (b) preparing a compound of formula 45 via cyclization of the prepared compound of formula 46;

[381] (c) preparing a compound of formula 44 via halogenation of the prepared compound of formula 45; and

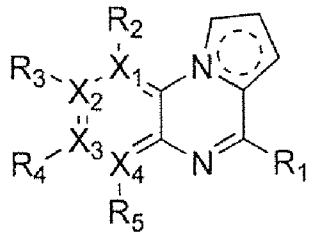
[382] (d) conducting arylation of the prepared compound of formula 44 with a compound of formula R_1-H (except that R_1 is -H) (or, a step of deprotecting R_1 may be

comprised):

[383]

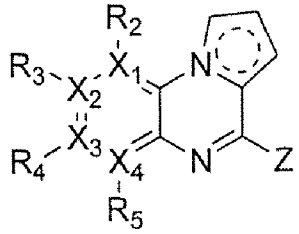
[384] [Formula 43]

[385]



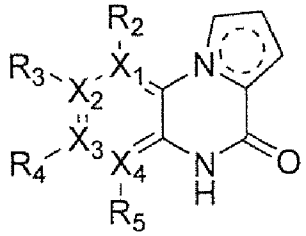
[386] [Formula 44]

[387]



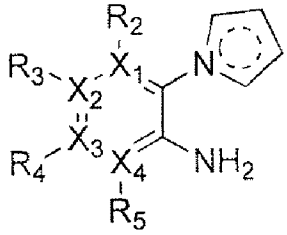
[388] [Formula 45]

[389]



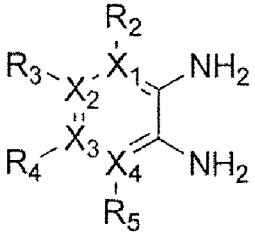
[390] [Formula 46]

[391]



[392] [Formula 47]

[393]



[394] wherein, in formulas 43 to 47, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4 and R_5 are the same as defined in formula 1; and Z represents a reactive leaving group such as halogen (-F, -Cl, -Br).

[395]

[396] The compound of formula 1 according to the present invention has an excellent human histamine 4 receptor (hH4R) inhibitory activity. Therefore, the present invention also provides a pharmaceutical composition comprising an effective amount of a compound of formula 1, or a racemate, isomer or pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

[397]

[398] A pharmaceutical composition according to the present invention can be prepared by mixing an effective amount of a compound of formula 1, or a racemate, isomer or pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable carrier, binder, stabilizer and/or diluent. In addition, when the pharmaceutical composition according to the present invention is prepared in an injection liquid form, a pharmaceutically acceptable buffer, dissolution adjuvant and/or isotonic agent may be mixed with the compound of formula 1, or a racemate, isomer or pharmaceutically acceptable salt thereof.

[399]

[400] Since the pharmaceutical composition according to the present invention shows a strong human histamine 4 receptor (hH4R) inhibitory activity, it is useful for treating or preventing inflammatory diseases, allergy, pain, nasal polyps, rhinitis, chronic sinusitis, nasal congestion, nasal itch, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis, eczema, pruritus, itchy skin, urticaria, idiopathic chronic urticaria, scleroderma, conjunctivitis, keratoconjunctivitis, ocular inflammation, dry eye, cardiac dysfunction, arrhythmia, atherosclerosis, multiple sclerosis, inflammatory bowel disease (including colitis, Crohn's disease, ulcerative colitis), inflammatory pain, neuropathic pain, osteoarthritic pain, autoimmune thyroid disease, immune-mediated (also known as type I) diabetes, lupus, post-operative adhesions, vestibular disorders and cancer.

[401]

[402] The pharmaceutical composition according to the prevent invention may be prepared in a delivery form of a pharmaceutical composition comprising one or more dosage units of pharmaceutical agent by using a preparation technique known or available to a skilled artisan, and a suitable pharmaceutical excipient. In a method of the present invention, the composition may be administered via suitable delivery route, for example, such as oral or parenteral, percutaneous, rectal, topical or ocular administration, or by inhalation. The pharmaceutical formulation may be in a form of tablet, capsule, sachet, sugar-coated pill, powder, granule, lozenge, powder for reconstitution, liquid preparation or suppository. For example, the composition may be formulated in a form for intravenous injection, spray, topical or oral administration.

[403]

[404] In case of preparing a formulation in oral dosage form, any conventional pharmaceutical carriers may be used. For example, water, glycols, oils, alcohols and the like may be used as a carrier in case of oral liquid formulations such as suspensions, syrups, elixirs and solutions; and starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like may be used as a carrier in case of solid formulations such as powders, pills, capsules and tablets. Because of the easiness of administration, tablets and capsules are the most convenient dose forms, and tablets and pills are preferably prepared as enteric coating formulations.

[405]

[406] In case of parenteral formulations, sterilized water is used usually and other ingredient(s) such as a dissolution adjuvant may also be comprised. Injection formulations, for example, sterilized aqueous- or oil-based suspension for injection may be prepared according to known techniques by using appropriate dispersing agent, wetting agent or suspending agent. The solvents useful for this purpose include water, ringer solution and isotonic NaCl solution, and sterilized, immobilized oils are also used as a solvent or a suspending medium conventionally. Any non-irritant immobilized oils including mono- and di-glycerides may be used for this purpose, and fatty acids such as an oleic acid may be used for an injection formulation.

[407]

[408] In case of percutaneous formulations, a penetration-enhancing agent and/or a suitable wetting agent may be used as a carrier, optionally in combination with suitable non-irritant additive(s) to the skin. As such additives, those helpful in enhancing the administration through the skin and/or preparing the desired composition may be selected. The percutaneous formulation may be administered in various ways, for example, such as a transdermal patch, a spot-on treatment or an ointment.

[409]

[410] The administration time and dosage of the pharmaceutical composition according to the present invention may be suitably determined according to the patient's disease, condition, age, body weight and administration form. In case of adults, the pharmaceutical composition may be administered in an amount of 0.1~2,000mg, preferably 1~200mg per day, in a single dose or multiple doses, but not limited thereto.

[411]

[412] Since the pharmaceutical composition according to the present invention shows a strong human histamine 4 receptor (hH4R) inhibitory activity, it is useful for treating or preventing inflammatory diseases, allergy, pain, nasal polyps, rhinitis, chronic sinusitis, nasal congestion, nasal itch, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis, eczema, pruritus, itchy skin, urticaria, idiopathic chronic urticaria, scleroderma, conjunctivitis, keratoconjunctivitis, ocular in-

flammation, dry eye, cardiac dysfunction, arrhythmia, atherosclerosis, multiple sclerosis, inflammatory bowel disease (including colitis, Crohn's disease, ulcerative colitis), inflammatory pain, neuropathic pain, osteoarthritic pain, autoimmune thyroid disease, immune-mediated (also known as type I) diabetes, lupus, post-operative adhesions, vestibular disorders and cancer.

[413]

[414] Unless stated otherwise, alkyl moiety and alkyl moiety of other groups (for example, alkoxy group) described in the present invention may be of the linear or branched species. In addition, halogen includes fluorine, chlorine, bromine and iodine.

[415]

[416] The compound of formula 1 according to the present invention may be a racemate. The racemate may be separated to its respective isomer by using a conventional separation method - for example, normal column chromatography packed with normal-phase silica gel (Merck, 0.040~0.063 mm and 0.063~0.200 mm), normal column chromatography packed with amine silica gel (chromatorex, 100~200 mesh), or preparative pressure reverse-phase column chromatography (Yonglin, SDV 30 plus), employing the corresponding solvent, preferably a solvent mixture of hexane, ethyl acetate, dichloromethane and methanol in normal phase and a solvent mixture of water and acetonitrile in reverse phase.

[417]

[418] The compound of formula 1 according to the present invention may also form a pharmaceutically acceptable salt. Such a pharmaceutically acceptable salt includes acid addition salts derived from acids which form non-toxic addition salts containing pharmaceutically acceptable anions - for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrobromic acid, hydroiodic acid, organic acids such as tartaric acid, formic acid, citric acid, acetic acid, trichloroacetic acid or trifluoroacetic acid, gluconic acid, benzoic acid, lactic acid, fumaric acid, maleic acid, sulfonic acids such as methane sulfonic acid, benzene sulfonic acid, p-toluene sulfonic acid, naphthalene sulfonic acid; and salts of alkali metal such as sodium, potassium, etc. In addition, acid or alkali salts known and used in the art of aromatic amidine derivatives and lactam derivatives may be included. Conventional processes may be used to make the salts.

[419]

[420] The compound of formula 1 according to the present invention may be prepared by the following process. Accordingly, the present invention also provides a method for preparing the compound of formula 1.

[421]

[422] More specifically, the compound of formula 1 may be prepared by, but not limited

to, each of Methods 1 to 8 described in the following.

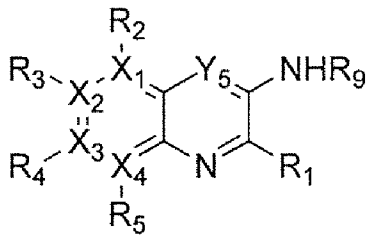
[423]

[424] Method 1

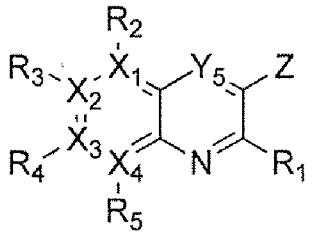
[425] A compound having a structure of the following formula 2, which is formula 1 as defined above wherein Y_2 and Y_5 are N, may be prepared by a method comprising the steps of: preparing a compound of formula 3 via arylation of a compound of formula 4 with a compound of formula R_1-H (except that R_1 is -H); preparing a compound of formula 2 via arylation of the prepared compound of formula 3; and cyclizing the prepared compound of formula 2:

[426]

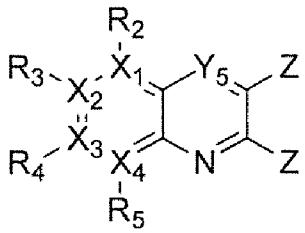
[427] [Formula 2]

[428] 

[429] [Formula 3]

[430] 

[431] [Formula 4]

[432] 

[433] wherein, in formulas 2 to 4, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are the same as defined in formula 1; and Z represents a reactive leaving group, preferably a halogen atom (-F, -Cl, -Br).

[434]

[435] Method 1 is more specifically described in the following.

[436]

[437] Compounds of formulas 2, 3 and 4 used as starting material may be prepared according to the known methods in the art (for example, J. Med. Chem. 1990, 33, 2240-2254, J. Med. Chem. 1997, 40, 2053-2063).

[438]

[439] Preparing a compound of formula 3 via arylation of a compound of formula 4 with a compound of formula R_1-H (except that R_1 is -H) is carried out according to a conventional method in the presence of suitable solvent and base.

[440] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N*,*N* -dimethyl formamide, *N*,*N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is dichloromethane.

[441]

[442] The next step for preparing a compound of formula 2 via arylation of the prepared compound of formula 3 is carried out according to a conventional method in the presence of a suitable solvent.

[443] Generally, conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N*,*N*-dimethyl formamide, *N*,*N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is ethanol.

[444]

[445] The next step for preparing a compound of formula 1 via cyclization of the prepared compound of formula 2 is carried out according to a conventional method in the presence of a suitable solvent.

[446] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene,

etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N,N* -dimethyl formamide, *N,N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is ethanol.

[447] The cyclization reaction is carried out at 50~200℃ for 0.1 to 24 hours, preferably under the conditions of 80℃ and 1 hour with trimethyl orthoformate or triethyl orthoformate.

[448]

[449] The above method for making a compound of formula 2 is more specifically described in the following example.

[450]

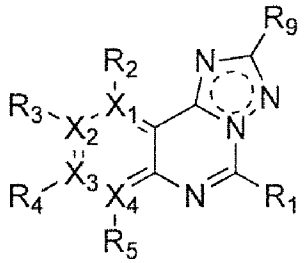
[451] Method 2

[452] A compound having a structure of the following formula 5, which is formula 1 as defined above wherein Y_1, Y_2 and Y_4 are N, may be prepared by a method comprising the steps of: preparing a compound of formula 9 via halogenation of a compound of the following formula 10; preparing a compound of formula 8 via cyanation of the prepared compound of formula 9; preparing a compound of formula 7 via acylation of the prepared compound of formula 8; preparing a compound of formula 6 via cyclization of the prepared compound of formula 7 followed by halogenation; and conducting arylation of the prepared compound of formula 6 with a compound of formula R_1-H (except that R_1 is -H):

[453]

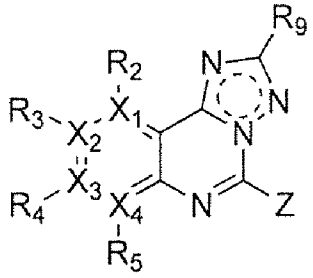
[454] [Formula 5]

[455]



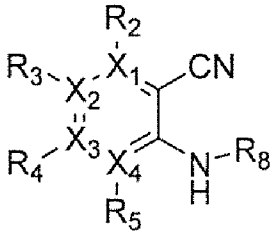
[456] [Formula 6]

[457]



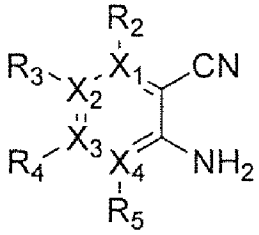
[458] [Formula 7]

[459]



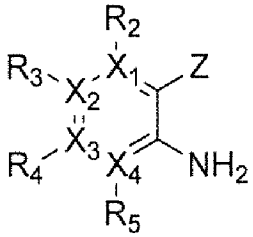
[460] [Formula 8]

[461]



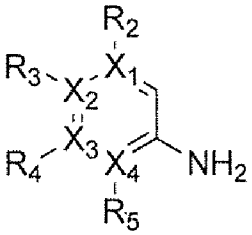
[462] [Formula 9]

[463]



[464] [Formula 10]

[465]



[466] wherein, in formulas 5 to 10, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_9 are the same as defined in formula 1; and Z represents a reactive leaving group, preferably a halogen atom (-F, -Cl, -Br), methanesulfonate, triflate and tosylate.

[467]

[468] Method 2 is more specifically described in the following.

[469]

[470] Compounds of formulas 5, 6, 7, 8, 9 and 10 used as starting material may be prepared according to known methods in the art.

[471]

[472] Preparing a compound of formula 9 via halogenation of a compound of formula 10 is carried out according to a conventional method in the presence of a suitable solvent.

[473] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N*,*N* -dimethyl formamide, *N*,*N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is chloroform.

[474] Exemplary halogenating agents for the reaction include bromine, phosphorous trichloride, phosphoryl chloride, phosphorous oxybromide, phenylphosphonyl chloride and phosphorous pentachloride. Preferred is bromine. The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[475]

[476] The next step for preparing a compound of formula 8 via cyanation of the prepared compound of formula 9 is carried out according to a conventional method in the presence of suitable solvent and cyanating agent.

[477] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N*,*N* -dimethyl formamide, *N*,*N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is *N*-methylpyrrolidone.

[478] Exemplary cyanating agents for the reaction include KCN, NaCN, $Zn(CN)_2$, CuCN, $(CH_3)_2C(OH)CN$ and TMSCN. Preferred is $Zn(CN)_2$. The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[479]

[480] The next step for preparing a compound of formula 7 via acylation of the prepared compound of formula 8 is carried out according to a conventional method in the presence of a suitable solvent.

[481] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1.2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N*,*N* - dimethyl formamide, *N*,*N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is 2-butanone.

[482]

[483] The next step for preparing a compound of formula 6 via cyclization of the prepared compound of formula 7 followed by halogenation is carried out according to a conventional method in the presence of a suitable solvent.

[484] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N*,*N* - dimethyl formamide, *N*,*N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is diphenyl ether.

[485] Exemplary halogenating agents for the reaction include phosphorous trichloride, phosphoryl chloride, phosphorous oxybromide, phenylphosphonyl chloride and phosphorous pentachloride. Preferred is phosphoryl chloride. The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[486]

[487] The next step for preparing a compound of formula 5 via arylation of the prepared compound of formula 6 with a compound of formula R_1-H (except that R_1 is -H) is carried out according to a conventional method in the presence of suitable solvent and

base.

[488] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N,N* -dimethyl formamide, *N,N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is *N,N*-dimethyl formamide.

[489]

[490] The above method for making a compound of formula 5 is more specifically described in the following example.

[491]

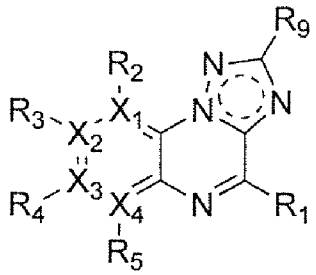
[492] Method 3

[493] A compound having a structure of the following formula 11, which is formula 1 as defined above wherein Y_2, Y_4 and Y_5 are N, may be prepared by a method comprising the steps of: preparing a compound of formula 16 via arylation of a compound of formula 17; preparing a compound of formula 15 via imidation of the prepared compound of formula 16; preparing a compound of formula 14 via acylation of the prepared compound of formula 15; preparing a compound of formula 13 via cyclization of the prepared compound of formula 14; preparing a compound of formula 12 via reduction of the prepared compound of formula 13 followed by halogenation; and conducting arylation of the prepared compound of formula 12 with a compound of formula R_1-H (except that R_1 is -H):

[494]

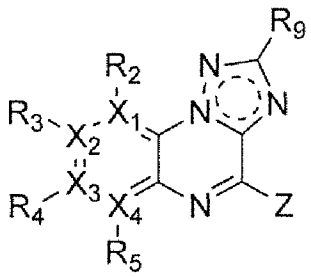
[495] [Formula 11]

[496]



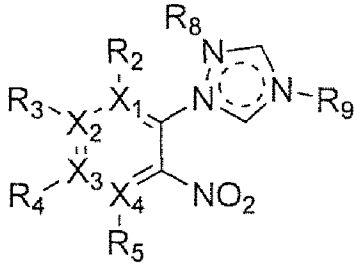
[497] [Formula 12]

[498]



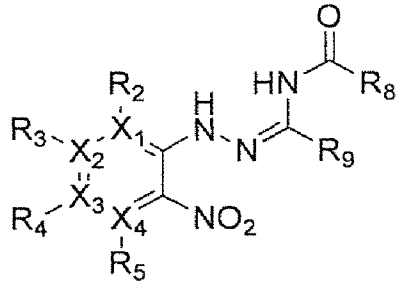
[499] [Formula 13]

[500]



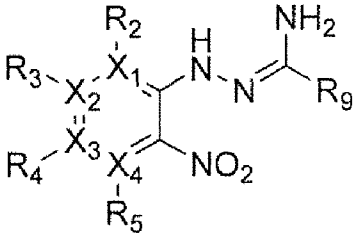
[501] [Formula 14]

[502]



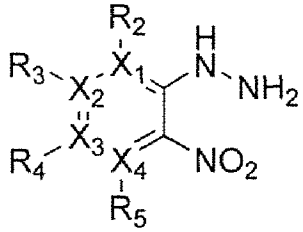
[503] [Formula 15]

[504]



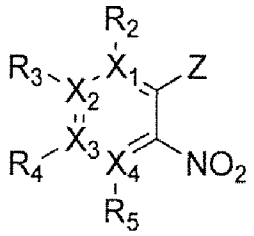
[505] [Formula 16]

[506]



[507] [Formula 17]

[508]



[509] wherein, in formulas 11 to 17, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_9 are the same as defined in formula 1; and Z represents a reactive leaving group, preferably a halogen atom (-F, -Cl, -Br).

[510]

[511] Method 3 is more specifically described in the following.

[512]

[513] Compounds of formulas 11, 12, 13, 14, 15, 16 and 17 used as starting material may be prepared according to the known methods in the art.

[514]

[515] Preparing a compound of formula 16 via arylation of a compound of formula 17 is carried out according to a conventional method in the presence of a suitable solvent.

[516] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N*,*N* -dimethyl formamide, *N*,*N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is ethanol.

[517]

[518] The next step for preparing a compound of formula 15 via imidation of the prepared compound of formula 16 is carried out according to a conventional method in the presence of a suitable solvent.

[519] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol,

ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N,N* - dimethyl formamide, *N,N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is pyridine.

[520]

[521] The next step for preparing a compound of formula 14 via acylation of the prepared compound of formula 15 is carried out according to a conventional method in the presence of a suitable solvent.

[522] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N,N* - dimethyl formamide, *N,N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is diethyl ether.

[523]

[524] The next step for preparing a compound of formula 13 via cyclization of the prepared compound of formula 14 is carried out according to a conventional method in the presence of a suitable solvent.

[525] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N,N* - dimethyl formamide, *N,N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is toluene.

[526] The reaction may be conducted at, but not limited to, 50 to 200°C for about 0.1 to 24 hours.

[527]

[528] The next step for preparing a compound of formula 12 via reduction of the prepared compound of formula 13 followed by halogenation is carried out according to a conventional method in the presence of a suitable solvent, reducing agent and halogenating agent.

[529] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N,N* -dimethyl formamide, *N,N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is acetic acid.

[530] Exemplary reducing agents for the reaction include palladium on carbon catalyst (5% w/w), palladium on carbon catalyst (10% w/w), raney nickel, zinc and iron. Particularly preferred is iron. The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[531] In addition, exemplary halogenating agents for the reaction include phosphorous trichloride, phosphoryl chloride, phosphorous oxybromide, phenylphosphonyl chloride and phosphorous pentachloride. Preferred is phosphoryl chloride. The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[532]

[533] The next step for preparing a compound of formula 11 via arylation of the prepared compound of formula 12 with a compound of formula R_1-H (except that R_1 is -H) is carried out according to a conventional method in the presence of a suitable solvent and base.

[534] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N,N* -dimethyl formamide, *N,N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable

solvent for the reaction is *N*,*N*-dimethyl formamide.

[535]

[536] The above method for making a compound of formula 11 is more specifically described in the following example.

[537]

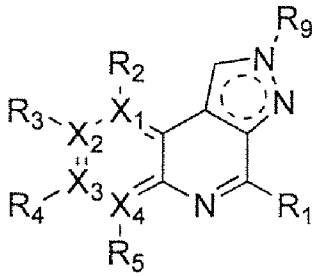
[538] Method 4

[539] A compound having a structure of the following formula 18, which is formula 1 as defined above wherein Y_2 and Y_3 are N, may be prepared by a method comprising the steps of: preparing a compound of the following formula 21 via Friedel-Craft reaction of a compound of the following formula 23 with a compound of the following formula 22; preparing a compound of formula 20 via cyclization of the prepared compound of formula 21; preparing a compound of formula 19 via halogenation of the prepared compound of formula 20; and conducting arylation of the prepared compound of formula 19 with a compound of formula R_1-H (except that R_1 is -H):

[540]

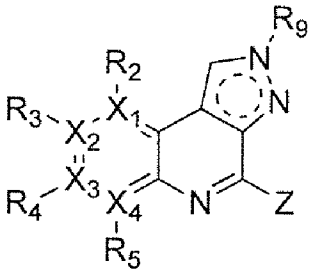
[541] [Formula 18]

[542]



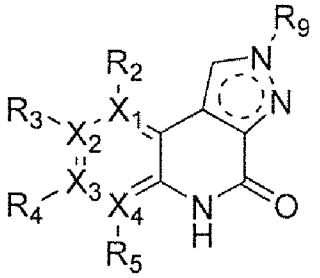
[543] [Formula 19]

[544]

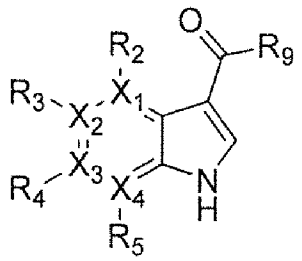


[545] [Formula 20]

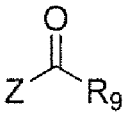
[546]



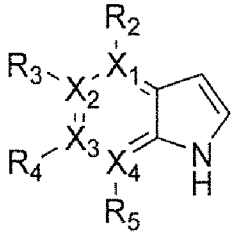
[547] [Formula 21]

[548] 

[549] [Formula 22]

[550] 

[551] [Formula 23]

[552] 

[553] wherein, in formulas 18 to 23, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_9 are the same as defined in formula 1; and Z represents a reactive leaving group, preferably a halogen atom (-F, -Cl, -Br).

[554]

[555] Method 4 is more specifically described in the following.

[556]

[557] Compounds of formulas 18, 19, 20, 21, 22 and 23 used as starting material may be prepared according to known methods in the art.

[558]

[559] Preparing a compound of formula 21 via Friedel-Craft reaction of a compound of formula 23 with a compound of formula 22 is carried out according to a conventional method in the presence of a suitable solvent.

[560] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N,N* -dimethyl formamide, *N,N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable

solvent for the reaction is dichloromethane.

[561]

[562] The next step for preparing a compound of formula 20 via cyclization of the prepared compound of formula 21 is carried out according to a conventional method in the presence of a suitable solvent.

[563] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N*,*N* -dimethyl formamide, *N*,*N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is ethanol.

[564] The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[565]

[566] The next step for preparing a compound of formula 19 via halogenation of the prepared compound of formula 20 is carried out according to a conventional method in the presence of a suitable solvent and halogenating agent.

[567] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N*,*N* -dimethyl formamide, *N*,*N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is toluene. A solvent may not be used in the present reaction.

[568] Exemplary halogenating agents for the reaction include phosphorous trichloride, phosphoryl chloride, phosphorous oxybromide, phenylphosphonyl chloride and phosphorous pentachloride. Preferred is phosphoryl chloride. The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[569]

[570] The next step for preparing a compound of formula 18 via arylation of the prepared compound of formula 19 with a compound of formula R_1-H (except that R_1 is -H) is carried out according to a conventional method in the presence of a suitable solvent and base.

[571] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N*,*N* -dimethyl formamide, *N*,*N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is *N*,*N*-dimethyl formamide.

[572]

[573] The above method for making a compound of formula 18 is more specifically described in the following example.

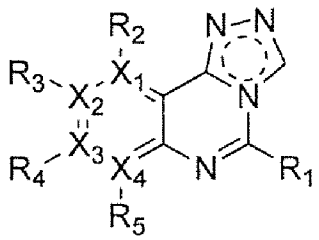
[574]

[575] Method 5

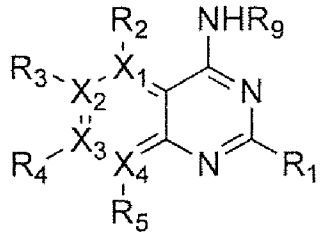
[576] A compound having a structure of the following formula 24, which is formula 1 as defined above wherein Y_1, Y_3 and Y_4 are N, may be prepared by a method comprising the steps of: preparing a compound of the following formula 28 via cyclization of a compound of the following formula 29; preparing a compound of formula 27 via halogenation of the prepared compound of formula 28 followed by hydroxylation; preparing a compound of formula 26 via arylation of the prepared compound of formula 27 with a compound of formula R_1-H (except that R_1 is -H) followed by halogenation; preparing a compound of formula 25 via arylation of the prepared compound of formula 26; and cyclizing the prepared compound of formula 25:

[577]

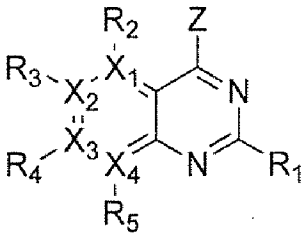
[578] [Formula 24]

[579] 

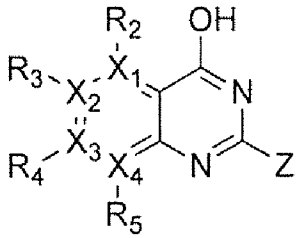
[580] [Formula 25]

[581] 

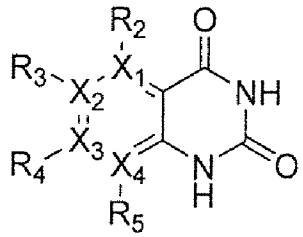
[582] [Formula 26]

[583] 

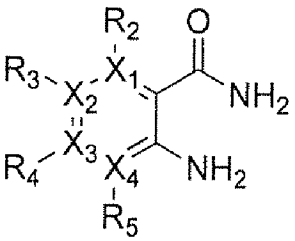
[584] [Formula 27]

[585] 

[586] [Formula 28]

[587] 

[588] [Formula 29]

[589] 

[590] wherein, in formulas 24 to 29, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are the same as defined in formula 1; and Z represents a reactive leaving group, preferably a halogen atom (-F, -Cl, -Br).

[591]

[592] Method 5 is more specifically described in the following.

[593]

[594] Compounds of formulas 24, 25, 26, 27, 28 and 29 used as starting material may be

prepared according to known methods in the art.

[595]

[596] Preparing a compound of formula 28 via cyclization of a compound of formula 29 is carried out according to a conventional method in the presence of suitable solvent and cyclizing agent.

[597] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N*,*N* -dimethyl formamide, *N*,*N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is dioxane.

[598] Exemplary cyclizing agents for the reaction include diphosgene and triphosgene. Preferred is diphosgene. The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[599]

[600] The next step for preparing a compound of formula 27 via halogenation of the prepared compound of formula 28 followed by hydroxylation is carried out according to a conventional method in the presence of a suitable solvent, halogenating agent and hydroxylating agent.

[601] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N*,*N* -dimethyl formamide, *N*,*N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is *n*-butanol.

[602] Exemplary halogenating agents for the reaction include phosphorous trichloride, phosphoryl chloride, phosphorous oxybromide, phenylphosphonyl chloride and phosphorous pentachloride. Preferred is phosphoryl chloride. The reaction may be

conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[603] Exemplary hydroxylating agents for the reaction include lithium hydroxide, sodium hydroxide, potassium hydroxide, calcium hydroxide and magnesium hydroxide. Preferred is sodium hydroxide. The reaction may be conducted at, but not limited to, room temperature for about 0.1 to 24 hours.

[604]

[605] The next step for preparing a compound of formula 26 via arylation of the prepared compound of formula 27 with a compound of formula R_1-H (except that R_1 is -H) followed by halogenation is carried out according to a conventional method in the presence of a suitable solvent and halogenating agent.

[606] Conventional solvents which have no adverse effects on the reaction may be used in the arylation reaction. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N*,*N*-dimethyl formamide, *N*,*N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is ethanol.

[607] Exemplary halogenating agents for the reaction include phosphorous trichloride, phosphoryl chloride, phosphorous oxybromide, phenylphosphonyl chloride and phosphorous pentachloride. Preferred is phosphoryl chloride. The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[608]

[609] The next step for preparing a compound of formula 25 via arylation of the prepared compound of formula 26 is carried out according to a conventional method in the presence of a suitable solvent.

[610] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N*,*N* -dimethyl formamide, *N*,*N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl

sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is ethanol.

[611]

[612] The next step for preparing a compound of formula 24 via cyclization of the prepared compound of formula 25 is carried out according to a conventional method in the presence of a suitable solvent and cyclizing agent.

[613] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N*,*N* -dimethyl formamide, *N*,*N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is ethanol.

[614] Exemplary preferred cyclizing agents for the reaction include trimethyl orthoformate and triethyl orthoformate. The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[615]

[616] The above method for making a compound of formula 24 is more specifically described in the following example.

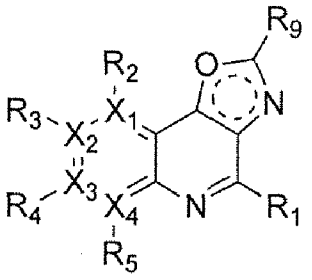
[617]

[618] Method 6

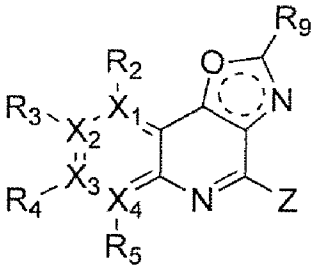
[619] A compound having a structure of the following formula 30, which is formula 1 as defined above wherein Y_2 is N and Y_4 is O, may be prepared by a method comprising the steps of: preparing a compound of the following formula 36 via esterification of a compound of the following formula 37; preparing a compound of formula 35 via arylation of the prepared compound of formula 36; preparing a compound of formula 34 via cyclization of the prepared compound of formula 35; preparing a compound of formula 33 via enolate addition reaction of the prepared compound of formula 34; preparing a compound of formula 32 via cyclization of the prepared compound of formula 33; preparing a compound of formula 31 via halogenation of the prepared compound of formula 32; and conducting arylation of the prepared compound of formula 31 with a compound of formula R_1-H (except that R_1 is -H):

[620]

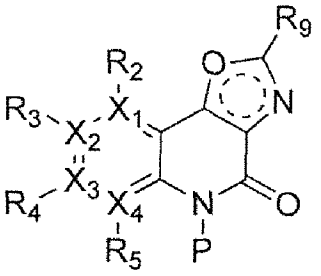
[621] [Formula 30]

[622] 

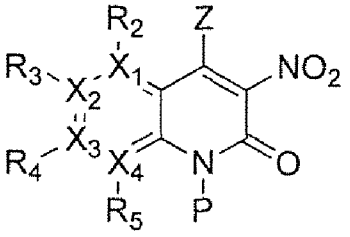
[623] [Formula 31]

[624] 

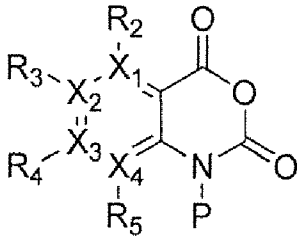
[625] [Formula 32]

[626] 

[627] [Formula 33]

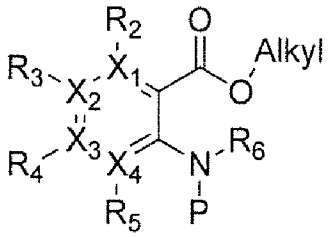
[628] 

[629] [Formula 34]

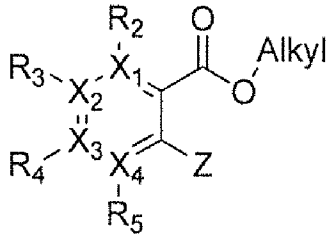
[630] 

[631] [Formula 35]

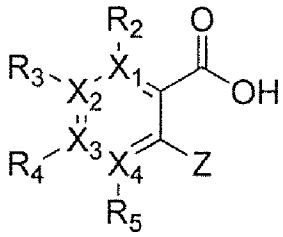
[632]



[633] [Formula 36]

[634] 

[635] [Formula 37]

[636] 

[637] wherein, in formulas 30 to 37, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are the same as defined in formula 1; Z represents a reactive leaving group, preferably a halogen atom (-F, -Cl, -Br); and P represents a protecting group, preferably para-methoxybenzyl, 3',5'-dimethoxybenzyl and tri-methoxybenzyl.

[638]

[639] Method 6 is more specifically described in the following.

[640]

[641] Compounds of formulas 30, 31, 32, 33, 34, 35, 36 and 37 used as starting material may be prepared according to known methods in the art.

[642]

[643] Preparing a compound of the following formula 36 via esterification of a compound of the following formula 37 is carried out according to a conventional method in the presence of a suitable solvent and esterification agent.

[644] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl

acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N,N* -dimethyl formamide, *N,N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvents for the reaction are dichloromethane and methanol.

[645]

[646] The next step for preparing a compound of formula 35 via arylation of the prepared compound of formula 36 is carried out according to a conventional method in the presence of a suitable solvent.

[647] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N,N* -dimethyl formamide, *N,N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is ethanol.

[648]

[649] The next step for preparing a compound of formula 34 via cyclization of the prepared compound of formula 35 is carried out according to a conventional method in the presence of a suitable solvent and cyclizing agent.

[650] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N,N* -dimethyl formamide, *N,N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is dioxane.

[651] Exemplary cyclizing agents for the reaction include diphosgene and triphosgene. Preferred is diphosgene. The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[652]

[653] The next step for preparing a compound of formula 33 via enolate addition reaction of the prepared compound of formula 34 is carried out according to a conventional method in the presence of a suitable solvent.

[654] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N,N* -dimethyl formamide, *N,N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is tetrahydrofuran.

[655] The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[656]

[657] The next step for preparing a compound of formula 32 via cyclization of the prepared compound of formula 33 is carried out according to a conventional method in the presence of a suitable solvent.

[658] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N,N* -dimethyl formamide, *N,N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is acetic acid.

[659] The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[660]

[661] The next step for preparing a compound of formula 31 via halogenation of the prepared compound of formula 32 is carried out according to a conventional method in the presence of a suitable halogenating agent.

[662] Exemplary halogenating agents for the reaction include phosphorous trichloride,

phosphoryl chloride, phosphorous oxybromide, phenylphosphonyl chloride and phosphorous pentachloride. Preferred is phosphoryl chloride. The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[663]

[664] The next step for preparing a compound of formula 30 via arylation of the prepared compound of formula 31 with a compound of formula R_1-H (except that R_1 is -H) is carried out according to a conventional method in the presence of a suitable solvent and base.

[665] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N,N* -dimethyl formamide, *N,N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is *N,N*-dimethyl formamide.

[666]

[667] The above method for making a compound of formula 30 is more specifically described in the following example.

[668]

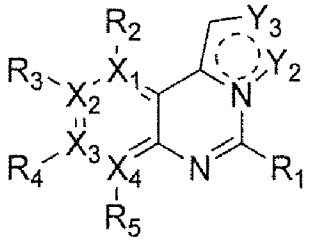
[669] Method 7

[670] A compound having a structure of the following formula 38, which is formula 1 as defined above wherein Y_1 is N, each of Y_2 and Y_3 is independently C or N and at least one of Y_1, Y_2 and Y_3 is N, may be prepared by a method comprising the steps of: preparing a compound of the following formula 40 via the Suzuki coupling reaction of a compound of the following formula 42 with a compound of the following formula 41; preparing a compound of formula 39 via halogenation of the prepared compound of formula 40; and conducting arylation of the prepared compound of formula 39 with a compound of formula R_1-H (except that R_1 is -H):

[671]

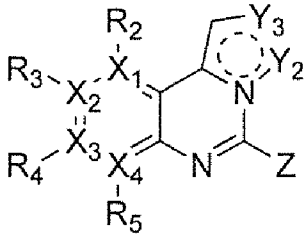
[672] [Formula 38]

[673]



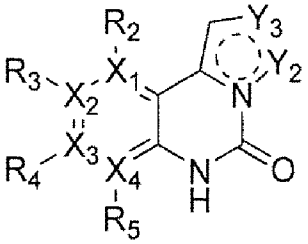
[674] [Formula 39]

[675]



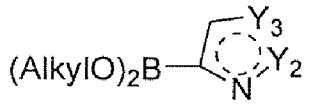
[676] [Formula 40]

[677]



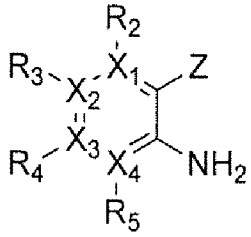
[678] [Formula 41]

[679]



[680] [Formula 42]

[681]



[682] wherein, in formulas 38 to 42, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are the same as defined in formula 1; and Z represents a reactive leaving group, preferably a halogen atom (-F, -Cl, -Br).

[683]

[684] Method 7 is more specifically described in the following.

[685]

[686] Compounds of formulas 38, 39, 40, 41 and 42 used as starting material may be prepared according to known methods in the art.

[687]

[688] Preparing a compound of formula 40 via the Suzuki coupling reaction of a compound of formula 42 with a compound of formula 41 is carried out according to a conventional method in the presence of a suitable solvent and catalyst.

[689] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N,N* -dimethyl formamide, *N,N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvents for the reaction are *N,N*-dimethyl formamide and water.

[690] Exemplary catalysts for the reaction include tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$), palladium(II)acetate ($Pd(OAc)_2$), bis(triphenylphosphine)palladium(II)dichloride ($PdCl_2(PPh_3)_2$), [1,1-bis(diphenylphosphino)ferrocene]dichloro-palladium(II) ($PdCl_2(dppf)$), (dibenzylideneacetone)dipalladium(0) ($Pd(dba)_2$) and palladium(II)chloride ($PdCl_2$). Preferred is tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$). The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[691]

[692] The next step for preparing a compound of formula 39 via halogenation of the prepared compound of formula 40 is carried out according to a conventional method in the presence of a suitable halogenating agent.

[693] Exemplary halogenating agents for the reaction include phosphorous trichloride, phosphoryl chloride, phosphorous oxybromide, phenylphosphonyl chloride and phosphorous pentachloride. Preferred is phosphoryl chloride. The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[694]

[695] The next step for preparing a compound of formula 38 via arylation of the prepared compound of formula 39 with a compound of formula R_1-H (except that R_1 is -H) is carried out according to a conventional method in the presence of suitable solvent and base.

[696] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene,

etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N,N* -dimethyl formamide, *N,N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is dichloromethane.

[697]

[698] The above method for making a compound of formula 5 is more specifically described in the following example.

[699]

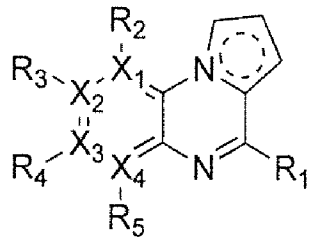
[700] Method 8

[701] A compound having a structure of the following formula 43, which is formula 1 as defined above wherein Y_5 is N, may be prepared by a method comprising the steps of: preparing a compound of the following formula 46 via pyrrolation of a compound of the following formula 47; preparing a compound of formula 45 via cyclization of the prepared compound of formula 46; preparing a compound of formula 44 via halogenation of the prepared compound of formula 45; and conducting arylation of the prepared compound of formula 44 with a compound of formula R_1-H (except that R_1 is -H):

[702]

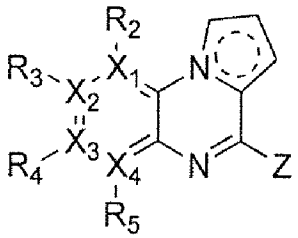
[703] [Formula 43]

[704]



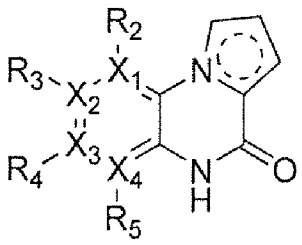
[705] [Formula 44]

[706]



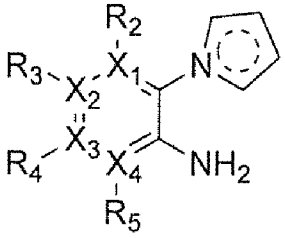
[707] [Formula 45]

[708]



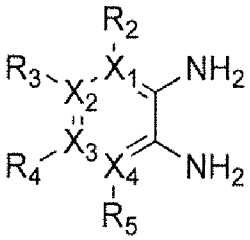
[709] [Formula 46]

[710]



[711] [Formula 47]

[712]



[713] wherein, in formulas 43 to 47, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are the same as defined in formula 1; and Z represents a reactive leaving group, preferably a halogen atom (-F, -Cl, -Br).

[714]

[715] Method 8 is more specifically described in the following.

[716]

[717] Compounds of formulas 43, 44, 45, 46 and 47 used as starting material may be prepared according to known methods in the art.

[718]

[719] Preparing a compound of formula 46 via pyrrolation of a compound of formula 47 is carried out according to a conventional method in the presence of a suitable solvent.

[720] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N,N* -

dimethyl formamide, *N*,*N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is acetic acid. The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[721]

[722] The next step for preparing a compound of formula 45 via cyclization of the prepared compound of formula 46 is carried out according to a conventional method in the presence of suitable solvent and cyclizing agent.

[723] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme, etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N*,*N* -dimethyl formamide, *N*,*N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is toluene.

[724] Exemplary cyclizing agents for the reaction include diphosgene and triphosgene. Preferred is triphosgene. The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[725]

[726] The next step for preparing a compound of formula 44 via halogenation of the prepared compound of formula 45 is carried out according to a conventional method in the presence of a suitable halogenating agent.

[727] Exemplary halogenating agents for the reaction include phosphorous trichloride, phosphoryl chloride, phosphorous oxybromide, phenylphosphonyl chloride and phosphorous pentachloride. Preferred is phosphoryl chloride. The reaction may be conducted at, but not limited to, 50 to 200℃ for about 0.1 to 24 hours.

[728]

[729] The next step for preparing a compound of formula 43 via arylation of the prepared compound of formula 44 with a compound of formula R_1-H (except that R_1 is -H) is carried out according to a conventional method in the presence of suitable solvent and base.

[730] Conventional solvents which have no adverse effects on the reaction may be used in this step. Preferable examples of the solvent include ether-based solvents such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, 2-butanone, diglyme,

etc.; hydrocarbon-based solvents such as benzene, pyridine, toluene, hexane, xylene, etc.; halogenated hydrocarbon-based solvents such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; alcohol-based solvents such as methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, etc.; ester-based solvents such as ethyl acetate, methyl acetate, butyl acetate, etc.; polar solvents such as acetone, *N,N* - dimethyl formamide, *N,N*-dimethyl acetamide, *N*-methylpyrrolidone, dimethyl sulfoxide, acetonitrile, etc.; and a mixed solvent thereof. The particularly preferable solvent for the reaction is *N,N*-dimethyl acetamide.

[731]

Advantageous Effects of Invention

[732] The novel heterocyclic compounds according to the present invention exhibit the same or a stronger histamine 4 receptor inhibitory activity, as compared with conventional human histamine 4 receptor (hH4R) inhibitors; show a selectivity for each of the subtype receptors of histamine and receptors, transporters and ion channels on a membrane; and have higher solubility, metabolic stability, and accordingly as a result of pharmacokinetic analysis and comparison with a compound disclosed in WO2010/030785 by using an animal model such as the SD rat, the compounds of the invention showed superior effects in pharmacokinetics profile such as AUC_{inf} and maximum blood concentration, 7-8 times as much as the comparative compound. Regarding symptoms, it is found that itch induced by histamine, Substance P and Compound 48/80, etc. is effectively suppressed, and that the heterocyclic compound according to the present invention has a superior effect, 3 times as much as a compound disclosed in WO2010/030785 for the suppression of the histamine-induced infiltration of inflammatory cells such as mast cells and eosinophils. In the oxazolone-induced atopic dermatitis model, the heterocyclic compound according to the present invention shows a very stronger anti-inflammatory effect than a compound disclosed in WO2010/030785. Especially, in the dermatophagoides farina-induced NC/Nga mouse atopic dermatitis model, it is found that the heterocyclic compound according to the present invention shows an anti-inflammatory effect, as much as a Tacrolimus which is an immunosuppressive drug, and a compound having selectivity for serotonin 3 receptor is found.

[733]

[734] Therefore, the novel heterocyclic compounds according to the present invention and pharmaceutical compositions comprising the same may be highly effective in treating or preventing inflammatory diseases, allergy, pain, nasal polyps, rhinitis, chronic sinusitis, nasal congestion, nasal itch, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis, eczema, pruritus, itchy skin, urticaria,

idiopathic chronic urticaria, scleroderma, conjunctivitis, keratoconjunctivitis, ocular inflammation, dry eye, cardiac dysfunction, arrhythmia, atherosclerosis, multiple sclerosis, inflammatory bowel disease (including colitis, Crohn's disease, ulcerative colitis), inflammatory pain, neuropathic pain, osteoarthritic pain, autoimmune thyroid disease, immune-mediated (also known as type I) diabetes, lupus, post-operative adhesions, vestibular disorders and cancer.

[735]

Mode for the Invention

[736] The present invention will be explained in further detail with reference to the following examples and experiments. However, these examples and experiments are intended only to illustrate the present invention, and the present invention is not limited to them in any way.

[737]

[738] The abbreviations used in the following examples are defined as follows.

[739]

Abbreviation	
Abb.	**Full**
ACN	Acetonitrile
AcOH	Acetic acid
$AlCl_3$	Aluminium chloride
Boc	*tert*-Butyloxycarbonyl
$(Boc)_2O$	Di-*tert*-butyl dicarbonate
BPOD	Phenylphosphonic dichloride
Br_2	Bromine
Brine	Brine is water, saturated or nearly saturated with salt (usually sodium chloride).
n-BuLi	*n*-Butyllithium
BuOH	Butanol
$CaCl_2$	Calcium chloride
Celite	Celite
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
CF_3CH_2OH	2,2,2-Trifluoroethanol
CuI	Copper iodide
$CDCl_3$	Deuterated chloroform
Cs_2CO_3	Cesium carbonate
CsF	Cesium fluoride
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
Deoxo-Fluor	Bis(2-methoxyethyl)aminosulfur trifluoride
DIPEA	*N,N*-Diisopropylethylamine
DMA	Dimethylacetamide
DMB	3', 5'-Dimethoxybenzyl
DME	Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DMSO-d_6	Fully deuterated dimethylsulfoxide
EDTA	Ethylenediaminetetraacetic acid
EtOH	Ethyl alcohol
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
Fe	Iron
HCl	Hydrochloric acid

[740]

tris-HCl	tris-Hydrochloride
n-Hex	*n*-Hexane
HI	Hydrogen iodide
HNO_3	Nitric acid
H_2SO_4	Sulfuric acid
IPA	*iso*-Propyl alcohol
K_2CO_3	Potassium carbonate
KI	Potassium iodide
KOH	Potassium hydroxide
MEK	Methyl ethyl ketone
MeI	Methyl iodide
MeOH	Methyl alcohol
$MgCl_2$	Magnesium chloride
$MgSO_4$	Magnesium sulfate
MeOH-d_4	Fully deuterated methyl alcohol
MsCl	Methanesulfonyl chloride
NADPH	Nicotinamide adenine dinucleotide phosphate
Na_2SO_4	Sodium sulfate
$Na_2S_2O_8$	Sodium persulfate
$NaHCO_3$	Sodium bicarbonate
NaH_2PO_4	Monosodium phosphate
NaOH	Sodium hydroxide
$NaBH_4$	Sodium borohydride
NaH	Sodium hydride
NaN_3	Sodium azide
NaOEt	Sodium ethoxide
NEt_3	Triethylamine
NMP	*N*-Methylpyrrolidone
NH_4Cl	Ammonium chloride
$PdCl_2(PPh_3)_2$	Bis(triphenylphosphine)palladium(II) dichloride
$Pd(OAc)_2$	Palladium(II) acetate
P(*o*-Tol)$_3$	Tri(*o*-tolyl)phosphine
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)Palladium
PMB	Para-methoxybenzyl
$POCl_3$	Phosphoryl chloride
OMs	Methanesulfonate
OTf	Triflate

[741]

OTs	Tosylate
$SnCl_2 \cdot 2H_2O$	Stannous chloride dihydrate
$SnCl_2$	Tin(II) chloride
TBAF	Tetra-*n*-butylammonium fluoride
TMB	Tri-methoxybenzyl
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TsOH	*p*-Toluenesulfonic acid
Xylene	Xylene
$Zn(CN)_2$	Zinc cyanide

[742]

[743] **Example 1**

[744] **Synthesis of 3-methyl-6-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine**

[745]

[746] (a) Synthesis of 2-chloro-3-hydrazinyl-7-methylpyrido[2,3-b]pyrazine

[747] 2,3-Dichloro-7-methylpyrido[2,3-b]pyrazine (500.0 mg, 2.33 mmol) and hydrazine monohydrate (234.0 mg, 4.66 mmol) were dissolved in EtOH (10.0 mL), stirred for 12 hours at room temperature and then distilled under reduced pressure. Et_2O was added thereto to form a solid. The formed solid was then filtered and dried under reduced pressure to obtain yellow solid compound of 2-chloro-3-hydrazinyl-7-methylpyrido[2,3-b]pyrazine.

[748]

[749] LC/MS ESI (+): 210 (M+1), 212 (M+3)

[750]

[751] (b) Synthesis of 6-chloro-3-methylpyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine

[752] The mixture of unpurified 2-chloro-3-hydrazinyl-7-methylpyrido[2,3-b]pyrazine and trimethyl orthoformate (5.0 mL) was stirred at 100℃ for one hour and then cooled to room temperature. Et_2O was added thereto to form a solid. The formed solid was then filtered and dried under reduced pressure to obtain ivory solid compound of 6-chloro-3-methylpyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine (340.0 mg, 66% in 2 steps).

[753]

[754] LC/MS ESI (+): 220 (M+1), 222 (M+3)

[755]

[756] (c) Synthesis of 3-methyl-6-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine

[757] 6-Chloro-3-methylpyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine (50.0 mg, 0.23 mmol) was dissolved in DMF (2.0 mL), and N-methyl piperazine (48.0 mg, 0.48 mmol) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for one hour and distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0 to DCM:MeOH=98:2) on amine silica. The fractions containing the product were collected and evaporated to obtain white solid compound of 3-methyl-6-(4-methyl-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine (25.0 mg, 38%).

[758]

[759] LC/MS ESI (+): 284 (M+1), 286 (M+3)

[760] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.83 (s, 1H), 8.20 (m, 1H), 7.82 (m, 1H), 4.34 (bs, 4H), 2.50 (m, 4H), 2.42 (s, 3H), 2.24 (s, 3H)

[761]

[762] **Example 2**

[763] **Synthesis of 8-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[764]

[765] (a) Synthesis of 2-chloro-7-methyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine

[766] 2,3-Dichloro-7-methylpyrido[2,3-b]pyrazine (500.0 mg, 2.30 mmol) was dissolved in DCM (8.0 mL), and *N*-methyl piperazine (468.0 mg, 2.60 mmol) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 12 hours, and it was poured into water and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0 to 99:1) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 2-chloro-7-methyl-3-(4-methylpiperazine-1-yl)pyrido[2,3-b]pyrazine.

[767]

[768] LC/MS ESI (+): 278 (M+1), 280 (M+3)

[769]

[770] (b) Synthesis of 8-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[771] Unpurified 2-chloro-7-methyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (300.0 mg, 1.08 mmol) and hydrazine monohydrate (108.0 mg, 2.16 mmol) were dissolved in EtOH (10.0 mL), stirred for 12 hours at 50℃ and then distilled under reduced pressure. The reaction mixture was poured into water and extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then evaporated under reduced pressure to obtain yellow solid compound of

2-hydrazinyl-7-methyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine. The mixture of unpurifed 2-hydrazinyl-7-methyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine and trimethyl orthoformate (2.0 mL) was stirred at 100℃ for one hour and then cooled to room temperature. Et_2O was added thereto to form a solid and the formed solid was filtered. The residue was purified by column chromatography (DCM:MeOH=99:1) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 8-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (94.0 mg, 31%)

[772]

[773] LC/MS ESI (+): 284 (M+1)

[774] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.99 (s, 1H), 8.45 (m, 2H), 4.37 (bs, 4H), 2.50 (m, 4H), 2.43 (s, 3H), 2.24 (s, 3H)

[775]

[776] **Example 3**

[777] **Synthesis of 4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[778]

[779] (a) Synthesis of 2-chloro-3-(4-methylpiperazine-1-yl)pyrido[2,3-b]pyrazine

[780] 2,3-Dichloropyrido[2,3-b]pyrazine (300.0 mg, 1.50 mmol) was dissolved in DMF (5.0 mL), and *N*-methyl piperazine (0.3 mL, 2.97 mmol) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 2 hours, and it was then poured into saturated NH_4Cl aqueous solution and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0) on amine silica. The fractions containing products were collected and evaporated to obtain pale yellow solid compound of 2-chloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (265.0 mg, 67%).

[781]

[782] LC/MS ESI (+): 264 (M+1), 266 (M+3)

[783]

[784] (b) Synthesis of 4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[785] 2-Chloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (260.0 mg, 0.99 mmol) and hydrazine monohydrate (63.0 mg, 1.97 mmol) were dissolved in EtOH (10.0 mL), stirred at room temperature for 2 hours and then distilled under reduced pressure. The reaction mixture was poured into saturated NH_4Cl aqueous solution and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2

SO_4, filtered and then evaporated under reduced pressure to obtain yellow solid compound of 2-hydrazinyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine. The mixture of unpurified 2-hydrazinyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine and trimethyl orthoformate (2.0 mL) was stirred at 80℃ for one hour and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0) on amine silica. The fractions containing the product were collected to obtain pale yellow solid compound of 4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (186.0 mg, 70%).

[786]

[787] LC/MS ESI (+): 270 (M+1)

[788] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 10.04 (s, 1H), 8.61-8.54 (m, 2H), 7.39-7.32 (m, 1H), 4.60-4.21 (m, 4H), 2.55-2.44 (m, 4H), 2.25 (s, 3H)

[789]

[790] **Example 4**

[791] **Synthesis of 8-chloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[792]

[793] (a) Synthesis of 2,3,7-trichloropyrido[2,3-b]pyrazine

[794] 5-Chloropyridin-2,3-diamine (10000.0 mg, 69.65 mmol) was added to diethyl oxalate (30.0 mL) and the reaction mixture was stirred at 100℃ for 12 hours and then cooled to room temperature. Et_2O was added thereto to form a solid. The formed solid was then filtered and dried under reduced pressure to obtain bright brown solid compound of 7-chloropyrido[2,3-b]pyrazin-2,3-diol. The mixture of unpurified 7-chloropyrido[2,3-b]pyrazin-2,3-diol and $POCl_3$ (30.0 mL) was stirred at 130℃ for 12 hours and then cooled to room temperature. The reaction mixture was poured into ice water. The formed solid was filtered and then dried under reduced pressure to obtain brown solid compound of 2,3,7-trichloropyrido[2,3-b]pyrazine (13700.0 mg, 84% in 2 steps).

[795]

[796] LC/MS ESI (+): 234 (M+1), 236 (M+3)

[797] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.23(d, 1H, J=2.6Hz), 8.86 (d, 1H, J=2.6Hz)

[798]

[799] (b) Synthesis of 2,7-dichloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine

[800] 2,3,7-Trichloropyrido[2,3-b]pyrazine (428.0 mg, 1.83 mmol) and TEA (2.5 mL, 18.30 mmol) were dissolved in DCM (10.0 mL) and *N*-methyl piperazine (0.2 mL, 2.01 mmol) diluted in DCM (5.0 mL) was added slowly at 0℃. The reaction mixture

was stirred at room temperature for 2 hours and then poured into saturated NH_4Cl aqueous solution and extrated with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 2,7-dichloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (290.0 mg, 53%).

[801]

[802] LC/MS ESI (+): 298 (M+1), 300 (M+3)

[803]

[804] (c) Synthesis of 8-chloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[805] 2,7-Dichloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (290.0 mg, 0.97 mmol) and hydrazine monohydrate (98.0 mg, 1.96 mmol) were dissolved in EtOH (10.0 mL), stirred for 2 hours at room temperature and then distilled under reduced pressure. The reaction mixture was poured into saturated NH_4Cl aqueous solution and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then evaporated under reduced pressure to obtain yellow solid compound of 7-chloro-2-hydrazinyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine. The mixture of unpurified 7-chloro-2-hydrazinyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine and trimethyl orthoformate (5.0 mL) was stirred at 80°C for one hour and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 8-chloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (215.0 mg, 73% in 2 steps).

[806]

[807] LC/MS ESI (+): 304 (M+1), 306 (M+3)

[808] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 10.01 (s, 1H), 8.85 (d, 1H, J=2.4Hz), 8.58 (d, 1H, J=2.4Hz), 4.40 (bs, 4H), 2.53 (m, 4H), 2.24 (s, 3H)

[809]

[810] **Example 5**

[811] **Synthesis of 3-chloro-6-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine**

[812]

[813] (a) Synthesis of 2,7-dichloro-3-hydrazinylpyrido[2,3-b]pyrazine

[814] 2,3,7-Trichloropyrido[2,3-b]pyrazine (150.0 mg, 0.64 mmol), TEA (129.0 mg, 1.28 mmol), hydrazine monohydrate (35.0 mg, 0.74 mmol) were dissolved in EtOH (5.0 mL), stirred at room temperature for 12 hours and then distilled under reduced pressure. Et_2O was added thereto to form a solid. The formed solid was filtered and then dried under reduced pressure to obtain yellow solid compound of 2,7-dichloro-3-hydrazinylpyrido[2,3-b]pyrazine.

[815]

[816] LC/MS ESI (+): 230 (M+1), 232 (M+3)

[817]

[818] (b) Synthesis of 3-chloro-6-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine

[819] The mixture of unpurified 2,7-dichloro-3-hydrazinylpyrido[2,3-b]pyrazine and trimethyl orthoformate (2.0 mL) was stirred at 100℃ for 2 hours and then cooled to room temperature. Et_2O was added thereto to form a solid. The formed solid was filtered to obtain yellow solid compound of 3,6-dichloropyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine. Unpurified 3,6-dichloropyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine was dissolved in DMF (2.0 mL), and then *N*-methyl piperazin (0.1 mL, 0.90 mmol) diluted in DMF (1.0 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 2 hours, and it was poured into water and extracted with EtOAc (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=99:1) on amine silica. The fractions containing product were collected and evaporated to obtain ivory solid compound of 3-chloro-6-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine (24.0 mg, 12% in 3 steps).

[820]

[821] LC/MS ESI (+): 304 (M+1), 306 (M+3)

[822] ^{1}H-NMR (300MHz, $CDCl_3$); δ: 9.46 (s, 1H), 8.22 (d, 1H, *J*=2.4Hz), 7.93 (d, 1H, *J*=2.4Hz), 4.54 (bs, 4H), 2.61 (m, 4H), 2.37 (s, 3H)

[823]

[824] **Example 6**

[825] **Synthesis of 6-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine**

[826]

[827] 2,3-Dichloropyrido[2,3-b]pyrazine (300.0 mg, 1.50 mmol) and hydrazine monohydrate (48.1 mg, 1.50 mmol) were dissolved in EtOH (7.0 mL), stirred at room temperature for 2 hours and then distilled under reduced pressure. The reaction mixture

was poured into saturated NH_4Cl aqueous solution and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then evaporated under reduced pressure to obtain 2-chloro-3-hydrazinylpyrido[2,3-b]pyrazine. The mixture of unpurified 2-chloro-3-hydrazinylpyrido[2,3-b]pyrazine and trimethyl orthoformate (2.0 mL) was stirred at 80℃ for one hour and then cooled to room temperature. Et_2O was added thereto to form a solid. The formed solid was filtered and then dried under reduced pressure to obtain 6-chloropyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine. Unpurified 6-chloropyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine was dissolved in DMF (5.0 mL), and then *N*-methyl piperazin (0.3 mL, 2.97 mmol) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 2 hours, then poured into saturated NH_4Cl aqueous solution and extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purifed by column chromatography (DCM:MeOH=100:0) on amine silica. The fractions containing the product were collected and evaporated to obtain pale yellow solid compound of 6-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine (70.0 mg, 17% in 3 steps).

[828]

[829] LC/MS ESI (+): 270 (M+1)

[830] ^{1}H-NMR (300MHz, $CDCl_3$); δ: 9.51 (s, 1H), 8.30 (dd, 1H, *J*=1.5Hz, *J*=4.6Hz), 7.94 (dd, 1H, *J*=1.5Hz, *J*=8.0Hz), 7.44 (dd, 1H, J=4.6Hz, J=8.0Hz), 4.70-4.34 (m, 4H), 2.58-2.56 (m, 4H), 2.38 (s, 3H)

[831]

[832] **Example 7**

[833] **Synthesis of 8-chloro-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[834]

[835] (a) Synthesis of *tert* -butyl 4-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate

[836] 2,3,7-Trichloropyrido[2,3-b]pyrazine (800.0 mg, 3.41 mmol) and TEA (2.4 mL, 17.05 mmol) were dissolved in DCM (20.0 mL) and then *tert*-butyl piperazin-1-carboxylate (667.0 mg, 3.58 mmol) diluted in DCM (10.0 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 12 hours and then poured into saturated NH_4Cl aqueous solution and extracted with DCM (50.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (*n*-Hex:EtOAc=90:10 to 80:20) on amine silica. The fractions containing

the product were collected and evaporated to obtain yellow solid compound of *tert* -butyl 4-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate (892.0 mg, 68%).

[837]

[838] LC/MS ESI (+): 384 (M+1), 389 (M+3)

[839]

[840] (b) Synthesis of *tert* -butyl 4-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate

[841] *tert*-Butyl 4-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate (892.0 mg, 2.32 mmol) and hydrazine monohydrate (244.0 mg, 4.87 mmol) were dissolved in EtOH (50.0 mL), stirred at room temperature for 2 hours and then distilled under reduced pressure. The reaction mixture was poured into saturated NH_4Cl aqueous solution and extracted with DCM (50.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then dried under reduced pressure to obtain yellow solid compound of *tert*-butyl 4-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate.

[842]

[843] LC/MS ESI (+): 380 (M+1), 382 (M+3)

[844]

[845] (c) Synthesis of *tert* -butyl 4-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)piperazin-1-carboxylate

[846] The mixture of unpurified *tert*-butyl 4-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate and trimethyl orthoformate (20.0 mL) was stirred at 70℃ for one hour and then cooled to room temperature. Et_2O was added thereto to form a solid. The formed solid was filtered and then dried under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0) on amine silica. The fractions containing product were collected and evaporated to obtain ivory solid compound of *tert*-butyl 4-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)piperazin-1-carboxylate (814.0 mg, 90%).

[847]

[848] LC/MS ESI (+): 390 (M+1), 392 (M+3)

[849]

[850] (d) Synthesis of 8-chloro-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[851] *tert*-Butyl 4-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)piperazin-1-carboxylate (814.0 mg, 2.09 mmol) was dissolved in DCM (20.0 mL), and TFA (5.0 mL) was

slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 2 hours and then distilled under reduced pressure. The residue was neutralized with $NaHCO_3$ aqueous solution (pH=7), and it was then extracted with DCM (50.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=90:10 to 80:20) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 8-chloro-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (503.0 mg, 83%).

[852]

[853] LC/MS ESI (+): 290 (M+1), 292 (M+3)

[854] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 10.00 (s, 1H), 8.84 (d, 1H, *J*=2.4Hz), 8.56 (d, 1H, *J*=2.4Hz), 4.40 (bs, 4H), 2.88 (m, 4H)

[855]

[856] **Example 8**

[857] **Synthesis of 1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine**

[858]

[859] (a) Synthesis of *tert* -butyl (1-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)carbamate

[860] 2,3,7-Trichloropyrido[2,3-b]pyrazine (200.0 mg, 0.85 mmol) and TEA (1.2 mL, 8.50 mmol) were dissolved in DCM (10.0 mL), and *tert*-butyl azetidin-3-ylcarbamate (162.0 mg, 0.94 mmol) diluted in DCM (5.0 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 12 hours, and it was poured into saturated NH_4Cl aqueous solution and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0 to 99:1) on silica. The fractions containing the product were collected and evaporated to obtain brown solid compound of *tert*-butyl (1-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)carbamate (224.0 mg, 71%).

[861]

[862] LC/MS ESI (+): 370 (M+1), 372 (M+3)

[863]

[864] (b) Synthesis of *tert* -butyl (1-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)carbamate

[865] *tert*-Butyl (1-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)carbamate (224.0 mg, 0.61 mmol) and hydrazine monohydrate (76.0 mg, 1.53 mmol) were dissolved in EtOH (10.0 mL), stirred at room temperature for 2 hours and then distilled under

reduced pressure. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain yellow solid compound of *tert* -butyl (1-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)carbamate (100.0 mg, 41%).

[866]

[867] LC/MS ESI (+): 366 (M+1), 368 (M+3)

[868]

[869] c) Synthesis of *tert* -butyl (1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)carbamate

[870] The mixture of *tert*-butyl (1-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)carbamate (100.0 mg, 0.27 mmol) and trimethyl orthoformate (5.0 mL) was stirred at 70℃ for one hour and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain ivory solid compound of *tert*-butyl (1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)carbamate (70.0 mg, 68%).

[871]

[872] LC/MS ESI (+): 376 (M+1), 378 (M+3)

[873]

[874] (d) Synthesis of 1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine

[875] *tert*-Butyl (1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)carbamate (70.0 mg, 0.19 mmol) was dissolved in DCM (5.0 mL), and TFA (2.0 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 2 hours and then distilled under reduced pressure. The residue was neutralized with $NaHCO_3$ aqueous solution (pH=7), and it was then extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=90:10 to 50:50) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine (6.3 mg, 12%).

[876]

[877] LC/MS ESI (+): 276 (M+1), 278 (M+3)

[878] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.95 (s, 1H), 8.80 (d, 1H, *J*=2.3Hz), 8.53 (d, 1H, *J*=2.4Hz), 4.93 (m, 1H), 4.47 (m, 1H), 4.35 (m, 1H), 3.93 (m, 2H)

[879]

[880] **Example 9**

[881] **Synthesis of (R)-1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*,*N*-dimethylpyrrolidin-3-amine**

[882]

[883] (R)-1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)pyrrolidin-3-amine (20.0 mg, 0.07 mmol) and sodium formate (20.0 mg, 0.29 mmol) were dissolved in formic acid/formamide (1.0 mL/1.0 mL), stirred at 100℃ for one hour and then distilled under reduced pressure. The reaction mixture was neutralized with $NaHCO_3$ aqueous solution (pH=7), and it was then extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=90:10 to 80:20) on silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of (R)-1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*,*N*-dimethylpyrrolidin-3-amine (13.0 mg, 59%).

[884]

[885] LC/MS ESI (+): 318 (M+1), 320 (M+3)

[886] ^{1}H-NMR (300MHz, $CDCl_3$); δ: 9.15 (s, 1H), 8.59 (d, 1H, *J*=2.2Hz), 8.01 (d, 1H, *J*=2.3Hz), 4.90 (m, 1H), 4.40-3.60 (m, 3H), 2.90 (m, 1H), 2.39 (s, 3H), 2.37 (s, 3H), 2.30 (m, 1H), 2.00 (m, 1H)

[887]

[888] **Example 10**

[889] **Synthesis of (R)-1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylpyrrolidin-3-amine**

[890] (a) Synthesis of (R)-*tert*-butyl (1-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)pyrrolidin-3-yl)(methyl)carbamate

[891] 2,3,7-Trichloropyrido[2,3-b]pyrazine (100.0 mg, 0.43 mmol) and TEA (0.6 mL, 4.30 mmol) were dissolved in DCM (10.0 mL), (R)-*tert*-butyl pyrrolidin-3-ylcarbamate (94.0 mg, 0.47 mmol) diluted in DCM (5.0 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 12 hours, and it was then poured into saturated NH_4Cl aqueous solution and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of (R)-*tert*-butyl (1-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)pyrrolidin-3-yl)(methyl)carbamate (169.0 mg, 99%).

[892]

[893] LC/MS ESI (+): 398 (M+1), 400 (M+3)

[894]

[895] (b) Synthesis of (R)- *tert* -butyl (1-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)pyrrolidin-3-yl)(methyl)carbamate

[896] (R)-*tert*-butyl (1-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)pyrrolidin-3-yl)(methyl)carbamate (169.0 mg, 0.42 mmol) and hydrazine monohydrate (53.0 mg, 1.05 mmol) were dissolved in EtOH (5.0 mL), stirred at room temperature for 2 hours and then distilled under reduced pressure to obtain yellow solid compound of (R)-*tert*-butyl (1-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)pyrrolidin-3-yl)(methyl)carbamate .

[897]

[898] LC/MS ESI (+): 394 (M+1), 396 (M+3)

[899]

[900] (c) Synthesis of (R)- *tert* -butyl (1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate

[901] The mixture of unpurified (R)-*tert*-butyl (1-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)pyrrolidin-3-yl)(methyl)carbamate and trimethyl orthoformate (5.0 mL) was stirred at 80℃ for one hour and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain ivory solid compound of (R)-*tert*-butyl (1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate.

[902]

[903] LC/MS ESI (+): 404 (M+1), 406 (M+3)

[904]

[905] (d) Synthesis of (R)-1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)- *N* -methylpyrrolidin-3-amine

[906] Unpurified (R)-*tert*-butyl (1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate was dissolved in DCM (3.0 mL), and TFA (1.0 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 2 hours and then distilled under reduced pressure. The residue was neutralized with $NaHCO_3$ aqueous solution (pH=7), and it was then extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under

reduced pressure. The residue was purified by column chromatography (DCM:MeOH=90:10 to 50:50) on silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of (R)-1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylpyrrolidin-3-amine (58.6 mg, 45% in 3 steps).

[907]

[908] LC/MS ESI (+): 304 (M+1), 306 (M+3)

[909] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.97 (s, 1H), 8.80 (d, 1H, *J*=2.4Hz), 8.53 (d, 1H, *J*=2.4Hz), 4.50-4.20 (m, 2H), 3.90-3.40 (m, 2H), 3.30 (m, 1H), 2.32 (s, 3H), 2.20-1.80 (m, 2H)

[910]

[911] **Example 11**

[912] **Synthesis of (R)-1-(3-chloropyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazin-6-yl)-*N*-methylpyrrolidin-3-amine**

[913]

[914] Ivory solid compound of (R)-1-(3-chloropyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazin-6-yl)-*N*-methylpyrrolidin-3-amine (18.0mg, 14%) was prepared as described in Example 10.

[915]

[916] LC/MS ESI (+): 304 (M+1), 306 (M+3)

[917] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.84 (s, 1H), 8.31 (d, 1H, *J*=2.2Hz), 8.04 (d, 1H, *J*=2.2Hz), 4.50-4.20 (m, 2H), 3.90-3.50 (m, 2H), 3.30 (m, 1H), 2.33 (s, 3H), 2.20-1.80 (m, 2H)

[918]

[919] **Example 12**

[920] **Synthesis of 8-bromo-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[921]

[922] (a) Synthesis of 7-bromo-2,3-dichloropyrido[2,3-b]pyrazine

[923] 5-Bromopyridin-2,3-diamine (5000.0 mg, 2.66 mmol) was added to diethyl oxalate (20.0 mL), and the mixture was stirred at 120℃ for 12 hours and then cooled to room temperature. Et_2O was added thereto to form a solid. The formed solid was then filtered and dried under reduced pressure to obtain light brown solid compound of 7-bromopyrido[2,3-b]pyrazin-2,3-diol. The mixture of unpurified 7-bromopyrido[2,3-b]pyrazin-2,3-diol and $POCl_3$ (20.0 mL) was stirred at 130℃ for 12 hours and then cooled to room temperature. The reaction mixture was poured into ice water to form a solid. The formed solid was filtered and then dried under reduced pressure to obtain brown solid compound of

7-bromo-2,3-dichloropyrido[2,3-b]pyrazine (6500.0 mg, 72% in 2 steps).

[924]

[925] LC/MS ESI (+): 278 (M+1), 280 (M+3)

[926] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.28 (d, 1H, *J*=2.4Hz), 8.99 (d, 1H, *J*=2.4Hz)

[927]

[928] (b) Synthesis of 7-bromo-2-chloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine

[929] 7-Bromo-2,3-dichloropyrido[2,3-b]pyrazine (1000.0 mg, 3.59 mmol) and TEA (5.0 mL, 35.90 mmol) were dissolved in DCM (20.0 mL), and *N*-methyl piperazine (0.2 mL, 2.01mmol) diluted in DCM (1.0 mL) was slowly added thereto at -10℃. The reaction mixture was stirred for 12 hours and then poured into saturated NH_4Cl aqueous solution and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 7-bromo-2-chloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (1000.0 mg, 81%).

[930]

[931] LC/MS ESI (+): 342 (M+1), 344 (M+3)

[932]

[933] (c) Synthesis of 8-bromo-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[934] 7-Bromo-2-chloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (413.0 mg, 0.12 mmol) and hydrazine monohydrate (150.0 mg, 0.30 mmol) were dissolved in EtOH (10.0 mL), stirred at room temperature for 4 hours and then distilled under reduced pressure. Et_2O was added thereto to form a solid. The formed solid was then filtered and dried under reduced pressure to obtain yellow solid compound of 7-bromo-2-hydrazinyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine. The mixture of unpurified 7-bromo-2-hydrazinyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine and trimethyl orthoformate (10.0 mL) was stirred at 80℃ for 2 hours and then cooled to room temperature. Et_2O was added thereto to form a solid. The formed solid was then filtered and dried under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0 to 95:5) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 8-bromo-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (368.0 mg, 29% in 3 steps).

[935]

[936] LC/MS ESI (+): 348 (M+1), 350 (M+3)

[937] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 10.01 (s, 1H), 8.95 (d, 1H, *J*=2.3Hz), 8.63 (d, 1H,

J=2.2Hz), 4.40 (bs, 4H), 2.53 (m, 4H), 2.24 (s, 3H)

[938]

[939] **Example 13**

[940] **Synthesis of 4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-carbonitrile**

[941]

[942] 8-Bromo-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (50.0 mg, 0.14 mmol), $Zn(CN)_2$ (17.0 mg, 0.14 mmol) and $Pd(PPh_3)_4$ (33.0 mg, 0.01 mmol) were dissolved in DMF (1.0 mL), and it was allowed to react in microwaver under conditions of 60W, 90℃ for 2 hours and then cooled to room temperature. The reaction mixture was then poured into water and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0 to 95:5) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-carbonitrile (6.0 mg, 13%).

[943]

[944] LC/MS ESI (+): 295 (M+1)

[945] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 10.01 (s, 1H), 9.13 (d, 1H, *J*=2.0Hz), 8.93 (d, 1H, *J*=2.0Hz), 4.88 (bs, 2H), 4.14 (bs, 2H), 2.51 (m, 4H), 2.26 (s, 3H)

[946]

[947] **Example 14**

[948] **Synthesis of 8-chloro-1-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[949]

[950] (a) Synthesis of 2,7-dichloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine

[951] 2,3,7-Trichloropyrido[2,3-b]pyrazine (200.0 mg, 0.85 mmol) and TEA (1180.0 μL, 8.53 mmol) were dissolved in DCM (8.5 mL), and *N*-methyl piperazine (220.0 μL, 0.94 mmol) diluted in DCM (0.5 mL) was slowly added thereto at -20℃. The reaction mixture was stirred at -20℃ for 12 hours, and it was then poured into saturated NH_4Cl aqueous solution and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=99:1) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 2,7-dichloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (110.0 mg, 43%).

[952]

[953] LC/MS ESI(+): 298 (M+1), 300 (M+3)

[954] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 8.94 (d, 1H, *J*=2.7 Hz), 8.51 (d, 1H, *J*=2.7 Hz), 3.61 (m, 4H), 2.52 (m, 4H), 2.25 (s, 3H).

[955]

[956] (b) Synthesis of 7-chloro-2-hydrazinyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine

[957] 2,7-Dichloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (100.0 mg, 0.36 mmol) and hydrazine monohydrate (46.0 μL, 0.84 mmol) were dissolved in EtOH (3.0 mL), stirred at room temperature for 12 hours and then evaporated under reduced pressure to obtain yellow solid compound of 7-chloro-2-hydrazinyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (50.0 mg, 57%).

[958]

[959] LC/MS ESI(+): 294 (M+1), 296 (M+3)

[960]

[961] (c) Synthesis of 8-chloro-1-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[962] The mixture of unpurified 7-chloro-2-hydrazinyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (50.0 mg, 0.17 mmol) and trimethyl orthoacetate (1.0 mL) was stirred at 80℃ for 2 hours and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=95:5) on amine silica. The fractions containing the product were collected and evaporated ivory solid compound of 8-chloro-1-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (30.0 mg, 56%).

[963]

[964] LC/MS ESI(+): 318 (M+1), 320 (M+3)

[965] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 8.56 (d, 1H, *J*=2.4 Hz), 8.42 (d, 1H, *J*=2.4 Hz), 4.36 (m, 4H), 3.02 (s, 3H), 2.49 (m, 4H), 2.25 (s, 3H)

[966]

[967] **Example 15**

[968] **Synthesis of 8-chloro-1-methyl-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[969]

[970] (a) Synthesis of *tert* -butyl

4-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate

[971] 2,3,7-Trichloropyrido[2,3-b]pyrazine (200.0 mg, 0.85 mmol) and TEA (1.2 mL, 8.53 mmol) were dissolved in DCM (8.5 mL), and *tert*-butyl piperazin-1-carboxylate (174.7 mg, 0.94 mmol) diluted in DCM (0.5 mL) was slowly added thereto at -20℃. The reaction mixture was stirred at -20℃ for 12 hours, and it was then poured into saturated NH_4Cl aqueous solution and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of *tert*-butyl 4-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate (110.0 mg, 64%).

[972]

[973] LC/MS ESI(+): 384 (M+1), 386 (M+3)

[974] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 8.96 (d, 1H, *J*=2.4 Hz), 8.54 (d, 1H, *J*=2.4 Hz), 3.61 (m, 4H), 3.54 (m, 4H), 1.43 (s, 9H)

[975]

[976] (b) Synthesis of *tert* -butyl 4-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate

[977] *tert*-Butyl 4-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate (110.0 mg, 0.29 mmol) and hydrazine monohydrate (35.0 μL, 0.72 mmol) were dissolved in EtOH (2.0 mL), stirred at room temperature for 12 hours and then evaporated under reduced pressure to obtain yellow solid compound of *tert*-butyl 4-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate (55.0 mg, 51%).

[978]

[979] LC/MS ESI(+): 380 (M+1), 382 (M+3)

[980]

[981] (c) Synthesis of *tert* -butyl 4-(8-chloro-1-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)piperazin-1-carboxylate

[982] The mixture of unpurified *tert*-butyl 4-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate (55.0 mg, 0.15 mmol) and trimethyl orthoacetate (0.7 mL) was stirred at 80℃ for 2 hours and then cooled to room temperature. Et_2O and *n*-Hex (30.0 mL) were added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain *tert*-butyl 4-(8-chloro-1-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)piperazin-1-carboxylate (35.0 mg, 60%).

[983]

[984] (d) Synthesis of 8-chloro-1-methyl-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[985] Unpurified *tert*-butyl 4-(8-chloro-1-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)piperazin-1-carboxylate (35.0 mg, 0.09 mmol) was dissolved in DCM (2.0 mL), and TFA (0.5 mL) was slowly added thereto at room temperature, and it was then stirred at room temperature for 2 hours. The reaction mixture was distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=80:20) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 8-chloro-1-methyl-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (9.0 mg, 35%).

[986]

[987] LC/MS ESI(+): 304 (M+1), 306 (M+3)

[988] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 8.55 (m, 1H), 8.42 (m, 1H), 4.34 (m, 4H), 3.04 (s, 3H), 2.87 (m, 4H)

[989]

[990] **Example 16**

[991] **Synthesis of 8-bromo-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[992]

[993] (a) Synthesis of *tert* -butyl 4-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate

[994] 7-Bromo-2,3-dichloropyrido[2,3-b]pyrazine (1000.0 mg, 2.33 mmol) and TEA (3.3 mL, 23.30 mmol) were dissolved in DCM (20.0 mL), and *tert*-butyl piperazin-1-carboxylate (478.0 mg, 2.56 mmol) diluted in DCM (10.0 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 12 hours, and it was then poured into saturated NH_4Cl aqueous solution and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purifed by column chromatography (DCM:MeOH=100:0) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of *tert*-butyl 4-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate.

[995]

[996] LC/MS ESI (+): 428 (M+1), 430 (M+3)

[997]

[998] (b) Synthesis of *tert* -butyl 4-(7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate

[999] Unpurified *tert*-butyl 4-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate and hydrazine monohydrate (292.0 mg, 5.83 mmol) were dissolved in EtOH (50.0 mL), stirred at room temperature for 12 hours and then distilled under reduced pressure. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain yellow solid compound of *tert*-butyl 4-(7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate.

[1000]

[1001] LC/MS ESI (+): 424 (M+1), 426 (M+3)

[1002]

[1003] (c) Synthesis of *tert* -butyl 4-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)piperazin-1-carboxylate

[1004] The mixture of unpurified *tert*-butyl 4-(7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate and trimethyl orthoformate (10.0 mL) was stirred at 80℃ for one hour and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain yellow solid compound of *tert* -butyl 4-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)piperazin-1-carboxylate.

[1005]

[1006] LC/MS ESI (+): 434 (M+1), 436 (M+3)

[1007]

[1008] (d) Synthesis of 8-bromo-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[1009] Unpurified *tert*-butyl 4-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)piperazin-1-carboxylate was dissolved in DCM (8.0 mL), and TFA (2.0 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 2 hours and then distilled under reduced pressure. The residue was neutralized with $NaHCO_3$ aqueous solution (pH=7) and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=99:1) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 8-bromo-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (270.0 mg, 35% in 3 steps).

[1010]

[1011] LC/MS ESI (+): 334 (M+1), 336 (M+3)

[1012] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 10.01 (s, 1H), 8.94 (d, 1H, *J*=2.3Hz), 8.63 (d, 1H,

J=2.2Hz), 4.36 (bs, 4H), 2.89 (m, 4H)

[1013]

[1014] **Example 17**

[1015] **Synthesis of 7,8-dichloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[1016]

[1017] (a) Synthesis of 5,6-dichloropyridin-2,3-diamine

[1018] 5-Chloro-3-nitropyridin-2-amine (2000.0 mg, 11.52 mmol) and $SnCl_2$ (8740.0 mg, 46.09 mmol) were added in conc. HCl (20.0 mL) and then stirred at 80-100℃ for 0.5 hour. The reaction mixture was neutralized with saturated 1N NaOH aqueous solution (pH=7), and it was then extracted with EtOAc (200.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (*n*-Hex:EtOAc=90:10) on silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 5,6-dichloropyridin-2,3-diamine (1000.0 mg, 49%).

[1019]

[1020] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 6.80 (s, 1H), 6.04 (s, 2H), 5.11 (s, 2H)

[1021]

[1022] (b) Synthesis of 2,3,6,7-tetrachloropyrido[2,3-b]pyrazine

[1023] 5,6-Dichloropyridin-2,3-diamine (1000.0 mg, 5.62 mmol) was added to diethyl oxalate (20.0 mL), and the mixture was stirred at 120℃ for 12 hours and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and dried under reduced pressure to obtain brown solid compound of 6,7-dichloropyrido[2,3-b]pyrazin-2,3(1H,4H)-dione. The mixture of unpurified 6,7-dichloropyrido[2,3-b]pyrazin-2,3(1H,4H)-dione and $POCl_3$ (20.0 mL) was stirred at 130℃ for 48 hours and then cooled to room temperature. The reaction mixture was poured into ice water to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain brown solid compound of 2,3,6,7-tetrachloropyrido[2,3-b]pyrazine (1200.0 mg, 72% in 2 steps).

[1024]

[1025] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.09 (s, 1H)

[1026]

[1027] (c) Synthesis of 2,6,7-trichloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine

[1028] 2,3,6,7-Tetrachloropyrido[2,3-b]pyrazine (190.0 mg, 0.71 mmol) and TEA (1.0 mL, 7.10 mmol) were dissolved in DCM (8.0 mL), *N*-methyl piperazine (85.0 mg, 0.85 mmol) diluted in DCM (2.0 mL) was slowly added thereto at -20℃ and stirred for 12 hours. The reaction mixture was poured into saturated NH_4Cl aqueous solution and

extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure to obtain yellow solid compound of 2,6,7-trichloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine.

[1029]

[1030] LC/MS ESI (+): 332 (M+1), 334 (M+3)

[1031]

[1032] (d) Synthesis of 7,8-dichloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[1033] Unpurified 2,6,7-trichloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine and hydrazine monohydrate (89.0 mg, 1.78 mmol) were dissolved in EtOH (10.0 mL), stirred at room temperature for 12 hours and then distilled under reduced pressure to obtain yellow solid compound of 6,7-dichloro-2-hydrazinyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine. The mixture of unpurified 6,7-dichloro-2-hydrazinyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine and trimethyl orthoformate (5.0 mL) was stirred at 80°C for one hour and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure. The residue was column chromatography (DCM:MeOH=100:0) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 7,8-dichloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (107.0 mg, 45% in 3 steps).

[1034]

[1035] LC/MS ESI (+): 338 (M+1), 340 (M+3)

[1036] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.99 (s, 1H), 9.01 (s, 1H), 4.80-3.80 (m, 4H), 2.51 (m, 4H), 2.24 (s, 3H)

[1037]

[1038] **Example 18**

[1039] **Synthesis of 1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine**

[1040]

[1041] (a) Synthesis of *tert*-butyl (1-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[1042] 2,3,7-Trichloropyrido[2,3-b]pyrazine (100.0 mg, 0.43 mmol) was dissolved in DCM (4.2 mL), *tert*-butyl azetidin-3-yl(methyl)carbamate (88.0 mg, 0.47 mmol) and TEA (0.2 mL, 1.28 mmol) were added thereto at 0°C, and it was then stirred for one hour. Solvent was removed from the reaction mixture under reduced pressure. The residue was purified by column chromatography (EtOAc:*n*-Hex=1:5) on silica. The fractions

containing the product were collected and evaporated to obtain yellow solid compound of *tert*-butyl (1-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (118.0 mg, 72%).

[1043]

[1044] LC/MS ESI(+): 384 (M+1), 386 (M+3)

[1045] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 8.83 (d, 1H, *J*=2.4 Hz), 8.40 (d, 1H, *J*=2.4 Hz), 4.86 (m, 1H), 4.62 (m, 2H), 4.48 (m, 2H), 2.90 (s, 3H), 1.41 (s, 9H)

[1046]

[1047] (b) Synthesis of *tert* -butyl (1-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[1048] *tert*-Butyl (1-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (116.0 mg, 0.30 mmol) was dissolved in EtOH (4.2 mL), and hydrazine monohydrate (24.0 μL, 0.76 mmol) was then added thereto. The reaction mixture was stirred at room temperature for one hour. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain yellow solid compound of *tert*-butyl (1-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (114.0 mg, 100%).

[1049]

[1050] LC/MS ESI(+): 380 (M+1), 382 (M+3)

[1051] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 7.77 (bs, 1H), 7.25 (bs, 1H), 7.05 (m, 3H), 4.65 (m, 2H), 4.46 (m, 1H), 4.24 (m, 2H), 2.86 (s, 3H), 1.40 (s, 9H)

[1052]

[1053] (c) Synthesis of *tert* -butyl (1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[1054] *tert*-Butyl (1-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (119.0 mg, 0.31mmol) was dissolved in trimethyl orthoformate (1.5 mL) and then stirred at 75℃ for one hour. The reaction mixture was cooled to room temperature and then dried under reduced pressure to obtain yellow solid compound of *tert*-butyl (1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (120.0 mg, 98%).

[1055]

[1056] LC/MS ESI(+): 390 (M+1), 392 (M+3)

[1057]

[1058] (d) Syntheis of 1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)- *N* -

methylazetidin-3-amine

[1059] *tert*-Butyl (1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (120.0 mg, 0.31 mmol) was dissolved in DCM (0.6 mL), and then TFA (0.4 mL) was added thereto. The reaction mixture was stirred at room temperature for one hour. Solvent was then removed from the reaction mixture under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=1:60) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (50.0 mg, 57%).

[1060]

[1061] LC/MS ESI(+): 290 (M+1), 292 (M+3)

[1062] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 9.95 (s, 1H), 8.81 (d, 1H, *J*=2.4 Hz), 8.54 (d, 1H, *J*=2.4 Hz), 4.89 (m, 1H), 4.43 (m, 2H), 3.99 (m, 1H), 3.71 (m, 1H), 2.29 (s, 3H)

[1063]

[1064] **Example 19**

[1065] **Synthesis of (S)-8-chloro-4-(3-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[1066]

[1067] (a) Synthesis of (S)-*tert*-butyl 4-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)-2-methylpiperazin-1-carboxylate

[1068] 2,3,7-Trichloropyrido[2,3-b]pyrazine (200.0 mg, 0.85 mmol) and TEA (1180.0 μL, 8.53 mmol) were dissolved in DCM (8.5 mL), and (S)-*tert*-butyl 2-methylpiperazin-1-carboxylate (187.8 mg, 0.94 mmol) diluted in DCM (0.5 mL) was slowly added thereto at -20℃. The reaction mixture was stirred at -20℃ for 12 hours, and it was poured into saturated NH_4Cl aqueous solution and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (EtOAc:*n*-Hex=30:70) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of (S)-*tert*-butyl 4-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)-2-methylpiperazin-1-carboxylate (233.0 mg, 67%).

[1069]

[1070] LC/MS ESI(+): 398 (M+1), 400 (M+3)

[1071] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 8.96 (d, 1H, *J*=2.7 Hz), 8.54 (d, 1H, *J*=2.7 Hz), 4.30 (m, 1H), 4.09 (m, 2H), 3.88 (m, 1H), 3.20 (m, 2H), 3.04 (m, 1H), 1.43 (s, 9H), 1.24 (d, 3H, *J*=6.6 Hz)

[1072]

[1073] (b) Synthesis of (S)- *tert* -butyl 4-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)-2-methylpiperazin-1-carboxylate

[1074] (S)-*tert*-butyl 4-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)-2-methylpiperazin-1-carboxylate (230.0 mg, 0.58 mmol) and hydrazine monohydrate (70.0 μL, 1.44 mmol) were dissolved in EtOH (2.0 mL). The mixture was then stirred at room temperature for 12 hours under reduced pressure to obtain yellow solid compound of (S)-*tert*-butyl 4-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)-2-methylpiperazin-1-carboxylate (220.0 mg, 97%).

[1075]

[1076] LC/MS ESI(+): 394 (M+1), 396 (M+3)

[1077]

[1078] (c) Synthesis of (S)- *tert* -butyl 4-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-2-methylpiperazin-1-carboxylate

[1079] The mixture of unpurified (S)-*tert*-butyl 4-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)-2-methylpiperazin-1-carboxylate (150.0 mg, 0.38 mmol) and trimethyl orthoformate (2.0 mL) was stirred at 80℃ for 2 hours and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain (S)-*tert*-butyl 4-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-2-methylpiperazin-1-carboxylate (150.0 mg, 81%).

[1080]

[1081] (d) Synthesis of (S)-8-chloro-4-(3-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[1082] Unpurified (S)-*tert*-butyl 4-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-2-methylpiperazin-1-carboxylate (150.0 mg, 0.37 mmol) was dissolved in DCM (1.0 mL). TFA (0.2 mL) was slowly added thereto at room temperature, and it was then stirred at room temperature for 2 hours. The reaction mixture was distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=95:5) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of (S)-8-chloro-4-(3-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (70.0 mg, 63%).

[1083]

[1084] LC/MS ESI(+): 304 (M+1), 306 (M+3)

[1085] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 9.15 (s, 1H), 8.61 (d, 1H, *J*=2.4 Hz), 8.04 (d, 1H, *J* =2.4 Hz), 6.24 (m, 1H), 5.21 (m, 1H), 3.02 (m, 5H), 1.21 (d, 3H, *J*= 6 Hz)

[1086]

[1087] **Example 20**

[1088] **Synthesis of (S)-8-chloro-4-(3,4-dimethylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[1089]

[1090] (S)-8-Chloro-4-(3-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (50.0 mg, 0.16 mmol) obtained from (d) of Example 19 and 37% formaldehyde (73.5 μL, 0.99 mmol) were dissolved in MeOH (0.5 mL). $NaBH_4$ (37.0 mg, 0.99 mmol) was slowly added thereto, and it was then stirred at room temperature for 12 hours. Brine was poured into the reaction mixture , and it was extracted with DCM (30.0 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified column chromatography (DCM:MeOH=95:5) on silica to obtain yellow solid compound of (S)-8-chloro-4-(3,4-dimethylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (70.0 mg, 48%).

[1091]

[1092] LC/MS ESI(+): 318 (M+1), 320 (M+3)

[1093] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 9.15 (s, 1H), 8.62 (d, 1H, *J*=2.4 Hz), 8.03 (d, 1H, *J* =2.1 Hz), 6.06 (m, 1H), 5.12 (m, 1H), 3.56 (m, 2H), 2.99 (m, 1H), 2.37 (m, 5H), 1.22 (d, 3H, *J*= 6.3 Hz)

[1094]

[1095] **Example 21**

[1096] **Synthesis of 8-chloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-7-carbonitrile**

[1097]

[1098] 7,8-Dichloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (10.0 mg, 0.03 mmol), $Zn(CN)_2$ (4.0 mg, 0.03 mmol) and $Pd(PPh_3)_4$ (3.0 mg, 0.003 mmol) were dissolved in DMF (1.0 mL). The mixture was allowed to react in microwaver under conditions of 60W, 100℃ for one hour and then cooled to room temperature. The reaction mixture was poured into water and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of

8-chloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-7-carbonitrile (2.0 mg, 20%).

[1099]

[1100] LC/MS ESI (+): 329 (M+1), 331 (M+3)

[1101] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 10.04 (s, 1H), 9.07 (s, 1H), 4.80 (m, 2H), 4.09 (m, 2H), 2.54 (m, 4H), 2.25 (s, 3H)

[1102]

[1103] **Example 22**

[1104] **Synthesis of 8-chloro-4-(3,4,5-trimethylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[1105]

[1106] (a) Synthesis of *tert* -butyl 3,5-dimethylpiperazin-1-carboxylate

[1107] 2,6-Dimethylpiperazine (200.0 mg, 1.75 mmol) and TEA (0.6 mL, 4.37 mmol) were dissolved in DCM (6.0 mL), and $(Boc)_2O$ (458.7 mg, 2.10 mmol) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 12 hours and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=95:5) on silica. The fractions containing the product were collected and evaporated to obtain yellow liquid compound of *tert*-butyl 3,5-dimethylpiperazin-1-carboxylate (210.0 mg, 56%).

[1108]

[1109] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 3.95 (m, 2H), 2.79 (m, 2H), 2.33 (m, 2H), 1.46 (s, 9H), 1.07 (d, 6H, *J*= 6.3 Hz)

[1110]

[1111] (b) Synthesis of *tert* -butyl 3,4,5-trimethylpiperazin-1-carboxylate

[1112] *tert*-Butyl 3,5-dimethylpiperazin-1-carboxylate (200.0 mg, 0.93 mmol) and 37% formaldehyde (440.0 μL, 5.56 mmol) were dissolved in MeOH (5.0 mL), and $NaBH_4$ (172.6 mg, 5.56 mmol) was slowly added thereto and stirred at room temperature for 12 hours. Brine was poured into the reaction mixture, and it was extracted with DCM (30.0 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified column chromatography (DCM:MeOH=95:5) on silica to obtain yellow liquid compound of *tert*-butyl 3,4,5-trimethylpiperazin-1-carboxylate (57.0 mg, 27%).

[1113]

[1114] (c) Synthesis of 1,2,6-trimethylpiperazine

[1115] *tert*-Butyl 3,4,5-trimethylpiperazin-1-carboxylate (57.0 mg, 0.25 mmol) was dissolved in DCM (1.0 mL), and TFA (0.2 mL) was slowly added thereto at room temperature. The reaction mixture was stirred at room temperature for 2 hours, then

distilled under reduced pressure and purified by column chromatography (DCM:MeOH=95:5) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow liquid compound of 1,2,6-trimethylpiperazine (32.0 mg, 100%).

[1116]

[1117] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 2.88 (m, 2H), 2.58 (m, 2H), 2.28 (s, 3H), 2.14 (m, 2H), 1.07 (d, 6H, *J*= 6 Hz)

[1118]

[1119] (d) Synthesis of 2,7-dichloro-3-(3,4,5-trimethylpiperazin-1-yl)pyrido[2,3-b]pyrazine

[1120] 2,3,7-Trichloropyrido[2,3-b]pyrazine (58.4 mg, 0.25 mmol) and TEA (347.0 μL, 2.49 mmol) were dissolved in DCM (1.0 mL), and 1,2,6-trimethylpiperazine (32.0 mg, 0.25 mmol) in DCM (0.5 mL) was slowly added thereto at -20℃. The reaction mixture was stirred at -20℃ for 12 hours, and it was then poured into saturated NH_4Cl aqueous solution and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then evaporated under reduced pressure to obtain yellow solid compound of 2,7-dichloro-3-(3,4,5-trimethylpiperazin-1-yl)pyrido[2,3-b]pyrazine (23.0 mg, 28%).

[1121]

[1122] LC/MS ESI(+): 326 (M+1), 328 (M+3)

[1123]

[1124] (e) Synthesis of 7-chloro-2-hydrazinyl-3-(3,4,5-trimethylpiperazin-1-yl)pyrido[2,3-b]pyrazine

[1125] 2,7-Dichloro-3-(3,4,5-trimethylpiperazin-1-yl)pyrido[2,3-b]pyrazine (23.0 mg, 0.07 mmol) and hydrazine monohydrate (8.0 μL, 0.18 mmol) were dissolved in EtOH (0.3 mL), and it was stirred at room temperature for 12 hours and then evaporated under reduced pressure to obtain yellow solid compound of 7-chloro-2-hydrazinyl-3-(3,4,5-trimethylpiperazin-1-yl)pyrido[2,3-b]pyrazine (23.0 mg, 100%).

[1126]

[1127] LC/MS ESI(+): 322 (M+1), 324 (M+3)

[1128]

[1129] (f) Synthesis of Synthesis of 8-chloro-4-(3,4,5-trimethylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[1130] The mixture of unpurified 7-chloro-2-hydrazinyl-3-(3,4,5-trimethylpiperazin-1-yl)pyrido[2,3-b]pyrazine (23.0 mg, 0.07 mmol) and trimethyl orthoformate (2.0 mL) was stirred at 80℃ for 2 hours and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain

8-chloro-4-(3,4,5-trimethylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (5.0 mg, 21%).

[1131]

[1132] LC/MS ESI(+): 332 (M+1), 334 (M+3)

[1133] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 9.15 (s, 1H), 8.62 (d, 1H, *J*=2.4 Hz), 8.04 (d, 1H, *J* =2.4 Hz), 6.17 (m, 1H), 5.18 (m, 1H), 3.28 (m, 1H), 2.93 (m, 1H), 2.39 (m, 2H), 2.34 (s, 3H) 1.26 (s, 6H)

[1134]

[1135] **Example 23**

[1136] **Synthesis of 8-chloro-7-ethoxy-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[1137]

[1138] 7,8-Dichloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (20.0 mg, 0.06 mmol) and NaOEt (5.0 mg, 0.07 mmol) were dissolved in EtOH (1.0 mL), and it was allowed to react in microwaver under conditions of 60W, 90°C for 2 hours and then cooled to room temperature. The reaction mixture was purified by column chromatography (DCM:MeOH=98:2) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 8-chloro-7-ethoxy-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (3.0 mg, 14%).

[1139]

[1140] LC/MS ESI (+): 348 (M+1), 350 (M+3)

[1141] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.91 (s, 1H), 8.84 (s, 1H), 4.44 (q, 2H, *J*=7.0Hz), 4.40 (m, 4H), 2.50 (m, 4H), 2.24 (s, 3H), 2.24 (t, 3H, *J*=7.0Hz)

[1142]

[1143] **Example 24**

[1144] **Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine**

[1145]

[1146] (a) Synthesis of *tert*-butyl (1-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[1147] 7-Bromo-2,3-dichloropyrido[2,3-b]pyrazine (200.0 mg, 0.72 mmol) and TEA (1.0 mL, 7.20 mmol) were dissolved in DCM (8.0 mL), and *tert*-butyl azetidin-3-yl(methyl)carbamate (147.0 mg, 0.79 mmol) diluted in DCM (2.0 mL) was slowly added thereto at 0°C. The reaction mixture was stirred at room temperature for 12 hours, and it was then poured into saturated NH_4Cl aqueous solution and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous

Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0) on amine silica. The fractions contining the product were collected and evaporated to obtain brown solid compound of *tert*-butyl (1-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate.

[1148]

[1149] LC/MS ESI (+): 428 (M+1), 430 (M+3)

[1150]

[1151] (b) Synthesis of *tert* -butyl (1-(7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[1152] Unpurified *tert*-butyl (1-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (224.0 mg, 0.61 mmol) and hydrazine monohydrate (72.0 mg, 3.78 mmol) were dissolved in EtOH (10.0 mL), stirred at room temperature for 12 hours and then distilled under reduced pressure. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain yellow solid compound of *tert*-butyl (1-(7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate.

[1153]

[1154] LC/MS ESI (+): 424 (M+1), 426 (M+3)

[1155]

[1156] (c) Synthesis of *tert* -butyl (1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[1157] The mixture of unpurified *tert*-butyl (1-(7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate and trimethyl orthoformate (10.0 mL) was stirred at 80℃ for one hour and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain ivory solid compound of *tert* -butyl (1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (137.0 mg, 45% in 3 steps).

[1158]

[1159] LC/MS ESI (+): 434 (M+1), 436 (M+3)

[1160]

[1161] (d) Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)- *N* -methylazetidin-3-amine

[1162] *tert*-Butyl

(1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (87.0 mg, 0.20 mmol) was dissolved in DCM (4.0 mL), and TFA (1.0 mL) was slowly added thereto at 0°C. The reaction mixture was stirred at room temperature for 12 hours and distilled under reduced pressure. The residue was neutralized with $NaHCO_3$ aqueous solution (pH=7), and it was then extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=98:2) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (16.0 mg, 23%).

[1163]

[1164] LC/MS ESI (+): 334 (M+1), 336 (M+3)

[1165] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.95 (s, 1H), 8.90 (d, 1H, *J*=2.1Hz), 8.59 (d, 1H, *J*=2.1Hz), 4.89 (m, 1H), 4.42 (m, 2H), 4.00 (m, 1H), 3.73 (m, 1H), 2.29 (s, 3H)

[1166]

[1167] **Example 25**

[1168] **Synthesis of 4-(3-(methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-carbonitrile**

[1169]

[1170] *tert*-Butyl (1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (50.0 mg, 0.12 mmol), $Zn(CN)_2$ (14.0 mg, 0.12 mmol) and $Pd(PPh_3)_4$ (13.0 mg, 0.01 mmol) were dissolved in DMF (1.0 mL), and it was allowed to react in microwaver under conditions of 60W, 90°C for 2 hours and then cooled to room temperature. The reaction mixture was then purified by column chromatography (DCM:MeOH=98:2) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of *tert*-butyl (1-(8-cyanopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate. *tert*-Butyl (1-(8-cyanopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate was dissolved in DCM (4.0 mL), and TFA (1.0 mL) was slowly added thereto at 0°C. The reaction mixture was stirred at room temperature for 12 hours and then distilled under reduced pressure. The residue was neutralized with $NaHCO_3$ aqueous solution (pH=7), and it was then extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography

(DCM:MeOH=98:2) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 4-(3-(methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-carbonitrile (10.0 mg, 22%).

[1171]

[1172] LC/MS ESI (+): 281 (M+1)

[1173] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.93 (s, 1H), 9.06 (d, 1H, *J*=1.9Hz), 8.88 (d, 1H, *J*=1.9Hz), 4.95 (m, 1H), 4.49 (m, 2H), 4.04 (m, 1H), 3.73 (m, 1H), 2.30 (s, 3H)

[1174]

[1175] **Example 26**

[1176] **Synthesis of 4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-carbonitrile**

[1177]

[1178] 8-Bromo-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (50.0 mg, 0.15 mmol), $Zn(CN)_2$ (18.0 mg, 0.15 mmol) and $Pd(PPh_3)_4$ (3.0 mg, 0.02 mmol) were dissolved in DMF (1.0 mL), and it was allowed to react in microwaver under conditions of 60W, 90℃ for one hour and then cooled to room temperature. The reaction mixture was purified by column chromatography (DCM:MeOH=98:2) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-carbonitrile (4.4 mg, 10%).

[1179]

[1180] LC/MS ESI (+): 281 (M+1)

[1181] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.98 (s, 1H), 9.09 (d, 1H, *J*=2.0Hz), 8.90 (d, 1H, *J*=2.1Hz), 4.80 (m, 2H), 4.05 (m, 2H), 2.90 (m, 4H)

[1182]

[1183] **Example 27**

[1184] **Synthesis of 1-(7,8-dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine**

[1185]

[1186] (a) Synthesis of *tert*-butyl methyl(1-(2,6,7-trichloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)carbamate

[1187] 2,3,6,7-Tetrachloropyrido[2,3-b]pyrazine (200.0 mg, 0.74 mmol) and TEA (1.0 mL, 7.40 mmol) were dissolved in DCM (8.0 mL), and *tert*-butyl azetidin-3-yl(methyl)carbamate (162.0 mg, 0.94 mmol) diluted in DCM (2.0 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 12 hours, poured into saturated NH_4Cl aqueous solution and extracted with DCM (30.0

mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0) on amine silica. The fractions containing the product were collected and evaporated to obtain brown solid compound of *tert*-butyl methyl(1-(2,6,7-trichloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)carbamate.

[1188]

[1189] LC/MS ESI (+): 418 (M+1), 420 (M+3)

[1190]

[1191] (b) Synthesis of *tert* -butyl (1-(6,7-dichloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[1192] Unpurified *tert*-butyl methyl(1-(2,6,7-trichloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)carbamate and hydrazine monohydrate (37.0 mg, 1.85 mmol) were dissolved in EtOH (10.0 mL), and it was then stirred at room temperature for 12 hours and then distilled under reduced pressure. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain yellow solid compound of *tert*-butyl (1-(6,7-dichloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate.

[1193]

[1194] LC/MS ESI (+): 414 (M+1), 416 (M+3)

[1195]

[1196] (c) Synthesis of *tert* -butyl (1-(7,8-dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[1197] The mixture of unpurified *tert*-butyl (1-(6,7-dichloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate and trimethyl orthoformate (20.0 mL) was stirred at 70℃ for one hour and then cooled to room temperature. Et_2O was slowly added thereto, and the formed solid was filtered and then dried under reduced pressure to obtain ivory solid compound of *tert* -butyl (1-(7,8-dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (173.0 mg, 55% in 3 steps).

[1198]

[1199] LC/MS ESI (+): 424 (M++1), 426 (M+3)

[1200]

[1201] (d) Synthesis of 1-(7,8-dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N* -methylazetidin-3-amine

[1202] *tert*-Butyl (1-(7,8-dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (123.0 mg, 0.29 mmol) was dissolved in DCM (4.0 mL), and TFA (1.0 mL) was slowly added thereto at 0°C. The reaction mixture was stirred at room temperature for 2 hours and distilled under reduced pressure. The residue was neutralized with $NaHCO_3$ aqueous solution (pH=7) and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=98:2) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 1-(7,8-dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (19.0 mg, 20%).

[1203]

[1204] LC/MS ESI (+): 324 (M+1), 326 (M+3)

[1205] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.95 (s, 1H), 8.98 (s, 1H), 4.94 (m, 1H), 4.46 (m, 2H), 4.00 (m, 1H), 3.73 (m, 1H), 2.30 (s, 3H)

[1206]

[1207] **Example 28**

[1208] **Synthesis of 8-chloro-4-(3-(methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-7-carbonitrile**

[1209]

[1210] *tert*-Butyl (1-(7,8-dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (50.0 mg, 0.15 mmol), $Zn(CN)_2$ (18.0 mg, 0.15 mmol) and $Pd(PPh_3)_4$ (18.0 mg, 0.02 mmol) were dissolved in DMF (1.0 mL), and it was allowed to react in microwaver under conditions of 60W, 90°C for one hour and then cooled to room temperature. The reaction mixture was purified by column chromatography (DCM:MeOH=98:2) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of *tert*-butyl (1-(8-chloro-7-cyanopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate. Unpurified *tert*-butyl (1-(8-chloro-7-cyanopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate was dissolved in DCM (2.0 mL), and TFA (0.5 mL) was slowly added thereto at 0°C. The reaction mixture was stirred at room temperature for 12 hours and then distilled under reduced pressure. The residue was neutralized with $NaHCO_3$ aqueous solution (pH=7), and it was extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under

reduced pressure. The residue was purified by column chromatography (DCM:MeOH=98:2) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 8-chloro-4-(3-(methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-7-carbonitrile (20.0 mg, 41%).

[1211]

[1212] LC/MS ESI (+): 315 (M+1), 317 (M+3)

[1213] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.98 (s, 1H), 9.03 (s, 1H), 4.93 (m, 1H), 4.48 (m, 2H), 4.00 (m, 1H), 3.73 (m, 1H), 2.30 (s, 3H)

[1214]

[1215] **Example 29**

[1216] **Synthesis of 8-chloro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[1217]

[1218] (a) Synthesis of 2,7-dichloro-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrido[2,3-b]pyrazine

[1219] 2,3,7-Trichloropyrido[2,3-b]pyrazine (100.0 mg, 0.43 mmol) and octahydropyrrolo[1,2-a]pyrazine (60.0 mg, 0.47 mmol) were reacted to obtain yellow solid compound of 2,7-dichloro-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrido[2,3-b]pyrazine (83.0 mg, 60%) in the same way as Example 18 (a).

[1220]

[1221] LC/MS ESI(+): 324 (M+1), 326 (M+3)

[1222] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 8.86 (d, 1H, *J*=2.7 Hz), 8.17 (d, 1H, *J*=2.4 Hz), 4.45 (m, 2H), 3.32 (m, 1H), 3.19 (m, 2H), 2.97 (m, 1H), 2.49 (m, 1H), 2.26 (m, 2H), 1.91 (m, 2H), 1.81 (m, 1H), 1.51 (m, 1H)

[1223]

[1224] (b) Synthesis of 7-chloro-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-2-hydrazinylpyrido[2,3-b]pyrazine

[1225] 2,7-Dichloro-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrido[2,3-b]pyrazine (80.0 mg, 0.25 mmol) and hydrazine monohydrate (19.0 μL, 0.62 mmol) were reacted in the same way as Example 18 (b) to obtain orange solid compound of 7-chloro-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-2-hydrazinylpyrido[2,3-b]pyrazine (50.0 mg, 63%).

[1226]

[1227] LC/MS ESI(+): 320 (M+1), 322 (M+3)

[1228] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 8.60 (d, 1H, *J*=3.0 Hz), 8.01 (d, 1H, *J*=3.0 Hz), 6.49 (bs, 1H), 4.20 (d, 2H, *J*=3.0 Hz), 3.94 (m, 2H), 3.17 (m, 3H), 2.87 (m, 1H), 2.46 (m, 1H), 2.22 (m, 2H), 1.89 (m, 2H), 1.78 (m, 1H), 1.50 (m, 1H)

[1229]

[1230] (c) Synthesis of 8-chloro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[1231] 7-Chloro-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-2-hydrazinylpyrido[2,3-b]pyrazine (45.0 mg, 0.14 mmol) and trimethyl orthoformate (1.0 mL) were reacted in the same way as Example 18 (c) at 90℃ for 5 hours to obtain orange solid compound of 8-chloro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (37.0 mg, 79%).

[1232]

[1233] LC/MS ESI(+): 330 (M+1), 332 (M+3)

[1234] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 9.16 (s, 1H), 8.61 (d, 1H, *J*=2.1 Hz), 8.04 (d, 1H, *J*=2.4 Hz), 6.39 (m, 1H), 5.50 (m, 1H), 3.55 (m, 0.5H), 3.20 (m, 3H), 2.90 (m, 0.5H), 2.42 (m, 1H), 2.20 (m, 2H), 1.88 (m, 3H), 1.52 (m, 1H)

[1235]

[1236] **Example 30**

[1237] **Synthesis of (R)-1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)pyrrolidin-3-amine**

[1238]

[1239] (a) Synthesis of (R)-*tert*-butyl (1-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)pyrrolidin-3-yl)carbamate

[1240] 2,3,7-Trichloropyrido[2,3-b]pyrazine (200.0 mg, 0.85 mmol) and TEA (1.2 mL, 8.50 mmol) were dissolved in DCM (10.0 mL), and (R)-*tert*-butyl pyrrolidin-3-ylcarbamate (175.0 mg, 0.94 mmol) diluted in DCM (5.0 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 12 hours, poured into saturated NH_4Cl aqueous solution, and it was then extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0 to 98:2) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of (R)-*tert*-butyl (1-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)pyrrolidin-3-yl)carbamate (284.0 mg, 86%).

[1241]

[1242] LC/MS ESI (+): 384 (M+1), 386 (M+3)

[1243]

[1244] (b) Synthesis of (R)- *tert* -butyl

(1-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)pyrrolidin-3-yl)carbamate

[1245] (R)-*tert*-butyl (1-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)pyrrolidin-3-yl)carbamate (284.0 mg, 0.74 mmol) and hydrazine monohydrate (92.0 mg, 1.85 mmol) were dissolved in EtOH (10.0 mL), stirred at room temperature for 2 hours and then distilled reduced pressure to obtain yellow solid compound of (R)-*tert*-butyl (1-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)pyrrolidin-3-yl)carbamate.

[1246]

[1247] LC/MS ESI (+): 380 (M+1), 382 (M+3)

[1248]

[1249] (c) Synthesis of (R)- *tert* -butyl (1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)pyrrolidin-3-yl)carbamate

[1250] The mixture of unpurified (R)-*tert*-butyl (1-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)pyrrolidin-3-yl)carbamate and trimethyl orthoformate (5.0 mL) was stirred at 70℃ for one hour and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and dried under reduced pressure to obtain ivory solid compound of (R)-*tert* -butyl (1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)pyrrolidin-3-yl)carbamate (272.0 mg, 94% in 2 steps).

[1251]

[1252] LC/MS ESI (+): 390 (M+1), 392 (M+3)

[1253]

[1254] (d) Synthesis of (R)-1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)pyrrolidin-3-amine

[1255] (R)-*tert*-butyl (1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)pyrrolidin-3-yl)carbamate (272.0 mg, 0.70 mmol) was dissolved in DCM (20.0 mL), and TFA (4.0 mL) was then slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 2 hours and distilled under reduced pressure. The residue was neutralized with $NaHCO_3$ aqueous solution (pH=7), and it was extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=90:10 to 50:50) on silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of (R)-1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)pyrrolidin-3-amine (79.0 mg, 39%).

[1256]

[1257] LC/MS ESI (+): 290 (M+1), 292 (M+3)

[1258] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.99 (s, 1H), 8.81 (d, 1H, *J*=2.4Hz), 8.53 (d, 1H, *J*=2.4Hz), 4.6-3.4 (m, 5H), 2.4-1.6 (m, 2H)

[1259]

[1260] **Example 31**

[1261] **Synthesis of 9-chloro-2-methyl-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine**

[1262]

[1263] (a) Synthesis of 3-bromo-5-chloropyridin-2-amine

[1264] 5-Chloropyridin-2-amine (5000.0 mg, 38.90 mmol) was dissolved in $CHCl_3$ (78.0 mL), and then Br_2 (2.0 mL, 38.90 mmol) was added thereto. The reaction mixture was stirred at room temperature for one hour and solvent was removed therefrom under reduced pressure. The residue was dissolved in EtOAc, and it was then washed with saturated $NaHCO_3$ aqueous solution and brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (EtOAc:n-Hex=1:9) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 3-bromo-5-chloropyridin-2-amine (7500.0 mg, 93%).

[1265]

[1266] LC/MS ESI(+): 207 (M+1), 209 (M+3)

[1267] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 7.98 (d, 1H, *J*=2.1 Hz), 7.66 (d, 1H, *J*=2.1 Hz), 4.93 (bs, 2H)

[1268]

[1269] (b) Synthesis of 2-amino-5-chloronicotinonitrile

[1270] 3-Bromo-5-chloropyridin-2-amine (2700.0 mg, 13.00 mmol) was dissolved in NMP (60.0 mL), and then $Zn(CN)_2$ (2300.0 mg, 19.50 mmol) and $Pd(PPh_3)_4$ (1500.0 mg, 1.30 mmol) were added thereto. The reaction mixture was stirred at 110℃ for 5 hours and then cooled to room temperature. Water and EtOAc were added to the reaction mixture, and it was stirred for 10 minutes and then filtered through celite. The filtrate was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (EtOAc:*n*-Hex=1:9) on silica. The fractions containing the product were collected and evaporated to obtain white solid compound of 2-amino-5-chloronicotinonitrile (1900.0 mg, 100%).

[1271]

[1272] LC/MS ESI(+): 154 (M+1), 156 (M+3)

[1273] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 8.22 (d, 1H, *J*=2.7 Hz), 8.07 (d, 1H, *J*=2.7 Hz), 7.14 (s, 2H)

[1274]

[1275] (c) Synthesis of 9-chloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-ol

[1276] 2-Amino-5-chloronicotinonitrile (300.0 mg, 1.95 mmol) was dissolved in MEK (2.0 mL), and $NaHCO_3$ (492.0 mg, 5.86 mmol) and chloroethyl formate (3.0 mL) were added thereto. The reaction mixture was refluxed and then cooled to room temperature, and it was filtered and then dried under reduced pressure to obtain atypical yellow compound of ethyl (5-chloro-3-cyanopyridin-2-yl)carbamate. Unpurified ethyl (5-chloro-3-cyanopyridin-2-yl)carbamate was dissolved in diphenylether (2.0 mL) and acetohydrazide (144.0 mg, 1.95 mmol) was added thereto. The reaction mixture was stirred at 180°C for 30 minutes and then cooled to room temperature, and then distilled under reduced pressure. The residue was purified by column chromatography (EtOAc: *n*-Hex=1:4) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 9-chloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-ol (91.0 mg, 20% in 2 steps).

[1277]

[1278] LC/MS ESI(+): 236 (M+1), 238 (M+3)

[1279] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 12.9 (s, 1H), 8.73 (d, 1H, *J*=2.4 Hz), 8.58 (d, 1H, *J*=2.4 Hz)

[1280]

[1281] (d) Synthesis of 5,9-dichloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine

[1282] 9-Chloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-ol (80.0 mg, 0.34 mmol) was dissolved $POCl_3$ (1.5 mL), and DIPEA (120.0 μL, 0.68 mmol) was added thereto. The reaction mixture was refluxed for 12 hours and then cooled to room temperature. The reaction mixture was poured into ice water, neutralized with saturated $NaHCO_3$ aqueous solution, and it was then extracted EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (EtOAc:*n*-Hex=1:5) on silica. The fractions containing the product were collected and evaporated to obtain white solid compound of 5,9-dichloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (30.0 mg, 35%).

[1283]

[1284] LC/MS ESI(+): 254 (M+1), 256 (M+3)

[1285]

[1286] (e) Synthesis of 9-chloro-2-methyl-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine

[1287] 5,9-Dichloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (28.0 mg, 0.11

mmol) was dissolved in DMF (1.1 mL), and *N*-methylpiperazin (24.0 μL, 0.22 mmol) was added thereto. The reaction mixture was stirred at room temperature for one hour and the residue was purified by column chromatography (MeOH:DCM=1:40) on amine silica. The fractions containinig the product were collected and evaporated to obtain ivory solid compound of 9-chloro-2-methyl-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (18.0 mg, 51%).

[1288]

[1289] LC/MS ESI(+): 318 (M+1), 320 (M+3)

[1290] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 8.84 (d, 1H, *J*=2.4 Hz), 8.63 (d, 1H, *J*=2.4 Hz), 4.12 (m, 4H), 2.56 (s, 3H), 2.54 (m, 4H), 2.24 (s, 3H)

[1291]

[1292] **Example 32**

[1293] **Synthesis of 9-chloro-2-methyl-5-(piperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine**

[1294]

[1295] (a) Synthesis of *tert* -butyl 4-(9-chloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-yl)piperazin-1-carboxylate

[1296] 5,9-Dichloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin (20.0 mg, 0.08 mmol) obtained from Example 31 (d) was dissolved in DMF (1.0 mL), and *tert*-butyl piperazin-1-carboxylate (29.0 mg, 0.16 mmol) was added thereto.. The reaction mixture was stirred at room temperature for one hour and purified by column chromatography (EtOAc:*n*-Hex=1:5) on silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of *tert*-butyl 4-(9-chloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-yl)piperazin-1-carboxylate (32.0 mg, 100%).

[1297]

[1298] LC/MS ESI(+): 404 (M+1), 406 (M+3)

[1299]

[1300] (b) Synthesis of 9-chloro-2-methyl-5-(piperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine

[1301] *tert*-Butyl-4-(9-chloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-yl)piperazin-1-carboxylate (30.0 mg, 0.07 mmol) was dissolved in DCM (0.6 mL), and TFA (0.4 mL) was added thereto. The reaction mixture was stirred at room temperature for one hour and purified by column chromatography (MeOH:DCM=1:40) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of

9-chloro-2-methyl-5-(piperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (22.5 mg, 100%).

[1302]

[1303] LC/MS ESI(+): 304 (M+1), 306 (M+3)

[1304] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 8.79 (d, 1H, *J*=2.7 Hz), 8.58 (d, 1H, *J*=2.7 Hz), 4.26 (m, 4H), 3.11 (m, 4H), 2.64 (s, 3H)

[1305]

[1306] **Example 33**

[1307] **Synthesis of 1-(9-chloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-yl)-*N*-methylazetidin-3-amine**

[1308]

[1309] (a) Synthesis of *tert*-butyl (1-(9-chloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-yl)azetidin-3-yl)(methyl)carbamate

[1310] 5,9-Dichloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (12.0 mg, 0.05 mmol) obtained from Example 31 (d) was dissolved in DMF (1.0 mL) and *tert*-butyl azetidin-3-yl(methyl)carbamate (17.6 mg, 0.09 mmol) was added thereto. The reaction mixture was stirred at room temperature for one hour and solvent was removed therefrom under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=1:40) on silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of *tert*-butyl (1-(9-chloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-yl)azetidin-3-yl)(methyl)carbamate (19.0 mg, 100%).

[1311]

[1312] LC/MS ESI(+): 404 (M+1), 406 (M+3)

[1313]

[1314] (b) Synthesis of 1-(9-chloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-yl)-*N*-methylazetidin-3-amine

[1315] *tert*-Butyl (1-(9-chloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-yl)azetidin-3-yl)(methyl)carbamate (18.0 mg, 0.04 mmol) was dissolved in DCM (0.6 mL), and TFA (0.4 mL) was added thereto. The reaction mixture was stirred at room temperature for one hour and was purified by column chromatography (MeOH:DCM=1:40) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 1-(9-chloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-yl)-*N*-methylazetid

in-3-amine (7.0 mg, 55%).

[1316]

[1317] LC/MS ESI(+): 304 (M+1), 306 (M+3)

[1318] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 8.73 (d, 1H, J=2.7 Hz), 8.51 (d, 1H, J=2.7 Hz), 4.84 (m, 2H), 4.38 (m, 2H), 3.80 (m, 1H), 2.60 (s, 3H), 2.49 (s, 3H)

[1319]

[1320] **Example 34**

[1321] **Synthesis of 9-chloro-2-cyclopropyl-*N*,*N*-diethylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amine**

[1322]

[1323] (a) Synthesis of 9-chloro-2-cyclopropylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-ol

[1324] Ethyl (5-chloro-3-cyanopyridin-2-yl)carbamate was synthesized from 2-amino-5-chloronicotinonitrile (500.0 mg, 3.26 mmol) in the same way as Example 31 (c), and allowed to react with cyclopropanecarbohydrazide (326.0 mg, 3.26 mmol) to obtain brown solid compound of 9-chloro-2-cyclopropylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-ol (37.0 mg, 4% in 2 steps).

[1325]

[1326] LC/MS ESI(+): 262 (M+1), 264 (M+3)

[1327] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 12.86 (bs, 1H), 8.71 (d, 1H, *J*=2.7 Hz), 8.53 (d, 1H, *J*=2.7 Hz), 2.23 (m, 1H), 1.09 (m, 2H), 0.99 (m, 2H)

[1328]

[1329] (b) Synthesis of 9-chloro-2-cyclopropyl-*N*,*N*-diethylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amine

[1330] 9-Chloro-2-cyclopropylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-ol (35.0 mg, 0.13 mmol) was dissolved in $POCl_3$ (1.5 mL), and TEA (37.0 μL, 0.27 mmol) was added thereto. The reaction mixture was refluxed for 12 hours and then cooled to room temperature. The reaction mixture was poured into ice water and neutralized with saturated $NaHCO_3$ aqueous solution, and it was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (EtOAc: *n*-Hex=1:4) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 9-chloro-2-cyclopropyl-N,N-diethylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amine (32.0 mg, 74%).

[1331]

[1332] LC/MS ESI(+): 317 (M+1), 319 (M+3)

[1333] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 8.71 (d, 1H, *J*=2.7 Hz), 8.51 (d, 1H, *J*=2.7 Hz), 4.04 (q, 4H, *J*=6.9 Hz), 2.23 (m, 1H), 1.39 (t, 6H, *J*=6.9 Hz), 1.13 (m, 4H)

[1334]

[1335] **Example 35**

[1336] **Synthesis of 9-chloro-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine**

[1337]

[1338] (a) Synthesis of 9-chloropyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5(6H)-one

[1339] 2-Amino-5-chloronicotinonitrile (500.0 mg, 3.26 mmol) was dissolved in MEK (3.5 mL), and $NaHCO_3$ (820.4 mg, 9.77 mmol) and chloroethyl formate (5.0 mL) were added thereto. The reaction mixture was refluxed for 24 hours and then cooled to room temperature and filtered and then dried under reduced pressure to obtain atypical yellow compound of ethyl (5-chloro-3-cyanopyridin-2-yl)carbamate. Unpurified ethyl (5-chloro-3-cyanopyridin-2-yl)carbamate was dissolved in diphenylether (3.5 mL) and formhydrazide (195.5 mg, 3.26 mmol) was then added thereto. The reaction mixture was stirred at 180°C for one hour and then cooled to room temperature, and purified by column chromatography (EtOAc:*n*-Hex=1:1) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 9-chloropyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5(6H)-one (63.0 mg, 9%).

[1340]

[1341] LC/MS ESI(+): 221 (M+1), 223 (M+3)

[1342] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 12.95 (s, 1H), 8.74 (d, 1H, *J*=2.1 Hz), 8.63 (d, 1H, *J*=2.4 Hz), 8.59 (s, 1H).

[1343]

[1344] (b) Synthesis of 5,9-dichloropyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine

[1345] 9-Chloropyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5(6H)-one (63.0 mg, 0.29 mmol) was dissolved in $POCl_3$ (2.0 mL), and DIPEA (150.0 μL, 0.86 mmol) was added. The reaction mixture was refluxed for 12 hours and then cooled to room temperature. The reaction mixture was poured into ice water and neutralized with saturated $NaHCO_3$ aqueous solution and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (EtOAc:*n*-Hex=1:1) on silica. The fractions containing the product were collected and evaporated to obtain white solid compound of 5,9-dichloropyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (50.4 mg, 72%).

[1346]

[1347] LC/MS ESI(+): 240 (M+1), 241 (M+3)

[1348]

[1349] (c) Synthesis of 9-chloro-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine

[1350] 5,9-Dichloropyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (15.0 mg, 0.06 mmol) was dissolved in DMF (0.5 mL), *N*-methylpiperazine (10.3 μL, 0.09 mmol) and TEA (25.0 μL, 0.19 mmol) were added thereto. The reaction mixture was stirred at room temperature for one hour and then purified by column chromatography (MeOH:DCM=1:19) on silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 9-chloro-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (6.0 mg, 33%).

[1351]

[1352] LC/MS ESI(+): 304 (M+1), 306 (M+3)

[1353] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 8.82 (d, 1H, *J*=3.0 Hz), 8.63 (d, 1H, *J*=2.7 Hz), 8.37 (s, 1H), 4.33 (m, 4H), 2.65 (m, 4H), 2.38 (s, 3H).

[1354]

[1355] **Example 36**

[1356] **Synthesis of 1-(9-chloropyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-yl)-N-methylazetidin-3-amine**

[1357]

[1358] 5,9-Dichloropyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (15.0 mg, 0.06 mmol) obtained from Example 35 (b) was dissolved in DMF (0.5 mL), and *tert*-butylazetidin-3-yl(methyl)carbamate (17.3 mg, 0.09 mmol) and TEA (25.0 μL, 0.19 mmol) were added thereto. The reaction mixture was stirred at room temperature for one hour and distilled under reduced pressure and then dissolved in DCM (1.0 mL) without purification, and TFA (0.2 mL) was then added thereto. The reaction mixture stirred at room temperature for one hour and purified by column chromatography (MeOH:DCM=1:19) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 1-(9-chloropyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-yl)-*N*-methylazetidin-3-amine (2.6 mg, 15%).

[1359]

[1360] LC/MS ESI(+): 290 (M+1), 292 (M+3)

[1361] ^{1}H-NMR (300 MHz, $CDCl_3$+MeOH-d_4); δ: 8.70 (d, 1H, *J*=2.7 Hz), 8.53 (d, 1H, *J*=2.7 Hz), 8.28 (d, 1H, *J*=2.7 Hz), 4.84 (m, 2H), 4.45 (m, 2H), 3.82 (m, 1H), 2.46 (s, 3H).

[1362]

[1363] **Example 37**

[1364] **Synthesis of 9-chloro-5-(piperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine**

[1365]

[1366] 5,9-Dichloropyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (15.0 mg, 0.06 mmol) obtained from Example 35 (b) was dissolved in DMF (0.5 mL), and *tert*-butyl piperazin-1-carboxylate (16.7 mg, 0.09 mmol) and TEA (25.0 μL, 0.19 mmol) were then added thereto. The reaction mixture was stirred at room temperature for one hour and concentrated under reduced pressure, and it was then dissolved in DCM (1.0 mL) without purification and TFA (0.2 mL) was added thereto. The reaction mixture was stirred at room temperature for one hour, and purified by column chromatography (MeOH:DCM=1:19) on amine silica. The fractions containing the product were collected and evaporated to obtain white solid compound of 9-chloro-5-(piperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (1.7 mg, 10%).

[1367]

[1368] LC/MS ESI(+): 290 (M+1), 292 (M+3)

[1369] ^{1}H-NMR (300 MHz, $CDCl_3$+MeOH-d_4); δ: 8.82 (d, 1H, *J*=2.4 Hz), 8.68 (d, 1H, *J* =2.7 Hz), 8.38 (s, 1H), 4.51 (m, 4H), 3.39 (m, 4H).

[1370]

[1371] **Example 38**

[1372] **Synthesis of 9-chloro-2-cyclopropyl-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine**

[1373]

[1374] (a) Synthesis of 5,9-dichloro-2-cyclopropylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine

[1375] 9-Chloro-2-cyclopropylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-ol (125.0 mg, 0.48 mmol) was allowed to react with $POCl_3$ (2.5 mL) and DIPEA (0.2 mL, 0.96 mmol) in the same way as Example 31 (d) to obtain ivory solid compound of 5,9-dichloro-2-cyclopropylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (90.0 mg, 67%).

[1376]

[1377] LC/MS ESI(+): 280 (M+1), 282 (M+3)

[1378] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 9.01 (d, 1H, *J*=2.7 Hz), 8.76 (d, 1H, *J*=2.7 Hz), 2.34 (m, 1H), 1.22 (m, 4H)

[1379]

[1380] (b) Synthesis of 9-chloro-2-cyclopropyl-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]p

yrimidine

[1381] 5,9-Dichloro-2-cyclopropylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (25.0 mg, 0.09 mmol) and *N*-methylpiperazine (20.0 μL, 0.18 mmol) were allowed to react in the same way as Example 31 (e) to obtain ivory solid compound of 9-chloro-2-cyclopropyl-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (22.0 mg, 72%).

[1382]

[1383] LC/MS ESI(+): 344 (M+1), 346 (M+3)

[1384] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 8.77 (d, 1H, *J*=2.7 Hz), 8.56 (d, 1H, *J*=2.7 Hz), 4.31 (t, 4H, *J*=5.1 Hz), 2.64 (t, 4H, *J*=5.1 Hz), 2.38 (s, 3H), 2.25 (m, 1H), 1.15 (m, 4H)

[1385]

[1386] **Example 39**

[1387] **Synthesis of 9-chloro-2-cyclopropyl-5-(piperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine**

[1388]

[1389] 5,9-Dichloro-2-cyclopropylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (30.0 mg, 0.11 mmol) obtained from the way as Example 38 (a) was dissolved in DCM (1.0 mL) and *tert*-butyl piperazin-1-carboxylate (40.0 mg, 0.21 mmol) was added thereto. The reaction mixture was stirred for one hour and TFA (0.8 mL) was then added, and it reacted for another one hour. The reaction mixture was purified by column chromatography (MeOH:DCM=1:40) on amine silica. The fractions containing the product were collected and evaporated. Et_2O and *n*-Hex were added thereto and the resulting solid was filtered to obtain ivory solid compound of 9-chloro-2-cyclopropyl-5-(piperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (31.0 mg, 89%).

[1390]

[1391] LC/MS ESI(+): 330 (M+1), 332 (M+3)

[1392] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 8.77 (d, 1H, *J*=2.7 Hz), 8.56 (d, 1H, *J*=2.7 Hz), 4.25 (t, 4H, *J*=5.1 Hz), 3.10 (t, 4H, *J*=5.1 Hz), 2.25 (m, 1H), 1.15 (m, 4H)

[1393]

[1394] **Example 40**

[1395] **Synthesis of 9-chloro-2-(methoxymethyl)-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine**

[1396]

[1397] (a) Synthesis of 9-chloro-2-(methoxymethyl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-ol

[1398] 2-Amino-5-chloronicotinonitrile (500.0 mg, 3.26 mmol) was dissolved in MEK (4.0 mL) and K_2CO_3 (1350.0 mg, 9.78 mmol), $MgSO_4$ (250.0 mg, 1.25 mmol) and chloroethylformate (6.0 mL) were added thereto. The reaction mixture was refluxed for 24 hours, then cooled to room temperature, filtered and then dried under reduced pressure to obtain atypical yellow compound of ethyl (5-chloro-3-cyanopyridin-2-yl)carbamate. Unpurified ethyl (5-chloro-3-cyanopyridin-2-yl)carbamate was dissolved in diphenylether (2.0 mL) and 2-methoxyacetohydrazide (271.0 mg, 2.61 mmol) was added. The reaction mixture was stirred at 150°C for 3 hours and then cooled to room temperature, and then purified by column chromatography (EtOAc:*n*-Hex=1:4) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 9-chloro-2-(methoxymethyl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-ol (150.0 mg, 17% in 2 steps).

[1399]

[1400] LC/MS ESI(+): 266 (M+1), 268 (M+3)

[1401] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 12.99 (s, 1H), 8.74 (d, 1H, *J*=2.4 Hz), 8.64 (d, 1H, *J*=2.7 Hz), 4.63 (s, 2H), 3.38 (s, 3H)

[1402]

[1403] (b) Synthesis of 5,9-dichloro-2-(methoxymethyl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine

[1404] 9-Chloro-2-(methoxymethyl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-ol (146.0 mg, 0.51 mmol) was allowed to react with $POCl_3$ (1.5 mL) and DIPEA (0.2 mL, 1.03 mmol) in the same way as Example 31 (d) to obtain ivory solid compound of 5,9-dichloro-2-(methoxymethyl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (89.0 mg, 61%).

[1405]

[1406] LC/MS ESI(+): 284 (M+1), 286 (M+3)

[1407] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 9.06 (d, 1H, *J*=2.4 Hz), 8.87 (d, 1H, *J*=2.7 Hz), 4.85 (s, 2H), 3.59 (s, 3H)

[1408]

[1409] (c) Synthesis of 9-chloro-2-(methoxymethyl)-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine

[1410] 5,9-Dichloro-2-(methoxymethyl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (25.0 mg, 0.09 mmol) and *N*-methylpiperazine (20.0 μL, 0.18 mmol) were allowed to react in DCM (1.0 mL) in the same way as Example 31 (e) to obtain ivory solid compound of 9-chloro-2-(methoxymethyl)-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,

5-c]pyrimidine (18.0 mg, 58%).

[1411]

[1412] LC/MS ESI(+): 348 (M+1), 350 (M+3)

[1413] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 8.81 (d, 1H, *J*=2.7 Hz), 8.67 (d, 1H, *J*=2.7 Hz), 4.76 (s, 2H), 4.33 (t, 4H, *J*=4.8 Hz), 3.57 (s, 3H), 2.64 (t, 4H, *J*=4.8 Hz), 2.38 (s, 3H)

[1414]

[1415] **Example 41**

[1416] **Synthesis of 9-chloro-2-ethyl-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine**

[1417]

[1418] (a) Synthesis of 9-chloro-2-ethylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-ol

[1419] Ethyl (5-chloro-3-cyanopyridin-2-yl)carbamate was synthesized from 2-Amino-5-chloronicotinonitrile (500.0 mg, 3.26 mmol) in the same way as Example 31 (c), and allowed to react with ethylcarbohydrazide (150.0 mg, 1.79 mmol) to obtain yellow solid compound of 9-chloro-2-ethylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-ol (95.0 mg, 12% in 2 steps)

[1420]

[1421] LC/MS ESI(+): 250 (M+1), 252 (M+3)

[1422] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 12.90 (s, 1H), 8.72 (d, 1H, *J*=2.7 Hz), 8.59 (d, 1H, *J*=2.7 Hz), 2.86 (q, 2H, *J*=7.5 Hz), 1.35 (t, 3H, *J*=7.5 Hz)

[1423]

[1424] (b) Synthesis of 5,9-dichloro-2-ethylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine

[1425] 9-Chloro-2-ethylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-ol (92.0 mg, 0.37 mmol) was dissolved in $POCl_3$ (1.5 mL) and DIPEA (130.0 μL, 0.74 mmol) was added thereto. The reaction mixture was refluxed for 12 hours and then cooled to room temperature. Triethylbenzyl ammonium chloride (92.0 mg, 0.42 mmol) was added to the reaction mixture, stirred at 130℃ for 2 hours and then cooled to room temperature. The reaction mixture was poured into ice water, neutralized with saturated $NaHCO_3$ aqueous solution and then extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled with reduced pressure. The residue was purified by column chromatography (DCM) on silica. The fractons containing the product were collected and evaporated to obtain pale yellow solid compound of 5,9-dichloro-2-ethylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (21.0 mg, 21%).

[1426]

[1427] LC/MS ESI(+): 268 (M+1), 270 (M+3)

[1428] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 9.12 (d, 1H, *J*=2.7 Hz), 8.96 (d, 1H, *J*=2.7 Hz), 2.99 (q, 2H, *J*=7.5 Hz), 1.35 (t, 3H, *J*=7.5 Hz)

[1429]

[1430] (c) Synthesis of 9-chloro-2-ethyl-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine

[1431] 5,9-Dichloro-2-ethylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (10.0 mg, 0.04 mmol) and *N*-methylpiperazine (8.3 μL, 0.08 mmol) in DCM were reacted in the same way as Example 31 (e) to obtain white solid compound of 9-chloro-2-ethyl-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (5.2 mg, 42%).

[1432]

[1433] LC/MS ESI(+): 332 (M+1), 334 (M+3)

[1434] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 8.84 (d, 1H, *J*=2.7 Hz), 8.64 (d, 1H, *J*=2.7 Hz), 4.13 (m, 4H), 2.91 (q, 2H, *J*=7.5 Hz), 2.53 (m, 4H), 2.24 (s, 3H), 1.36 (t, 3H, *J*=7.5 Hz)

[1435]

[1436] **Example 42**

[1437] **Synthesis of 9-chloro-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine**

[1438]

[1439] (a) Synthesis of 6-chloropyrido[2,3-d]pyrimidin-2,4(1H,3H)-dione

[1440] The mixture of 2-amino-5-chloronicotineamide (169.0 mg, 0.98 mmol) and diphosgene (646.0 mg, 3.14 mmol) dissolved in 1,4-dioxane (10.0 mL) was stirred at 120℃ for 12 hours and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain ivory solid compound of 6-chloropyrido[2,3-d]pyrimidin-2,4(1H,3H)-dione (163.0 mg, 84%).

[1441]

[1442] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 11.59 (s, 2H), 8.60 (d, 1H, *J*=2.8Hz), 8.19 (d, 1H, *J*=2.6Hz)

[1443]

[1444] (b) Synthesis of 2,4,6-trichloropyrido[2,3-d]pyrimidine

[1445] The mixture of 6-chloropyrido[2,3-d]pyrimidin-2,4(1H,3H)-dione (163.0 mg, 0.82 mmol) and BPOD (2.0 mL) was stirred at 180℃ for 6 hours and then cooled to room temperature. The reaction mixture was poured into water, and it was neutralized with saturated $NaHCO_3$ aqueous solution (pH=7) and then extracted with EtOAc (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure to obtain white solid compound of

2,4,6-trichloropyrido[2,3-d]pyrimidine (169.0 mg, 88%).

[1446]

[1447] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 8.97 (d, 1H, *J*=2.8Hz), 8.49 (d, 1H, *J*=2.8Hz)

[1448]

[1449] (c) Synthesis of 2,6-dichloropyrido[2,3-d]pyrimidin-4-ol

[1450] 2,4,6-Trichloropyrido[2,3-d]pyrimidine (90.0 mg, 0.38 mmol) was dissolved in 1N NaOH/BuOH (0.8 mL/0.8 mL), stirred at room temperature for 2 hours, then distilled under reduced pressure, neutralized with 1N HCl aqueous solution (pH=7) and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then reduced pressure to obtain ivory solid compound of 2,6-dichloropyrido[2,3-d]pyrimidin-4-ol (63.0 mg, 76%).

[1451]

[1452] LC/MS ESI (+): 216 (M+1), 218 (M+3)

[1453]

[1454] (d) Synthesis of Synthesis of 6-chloro-2-(4-methylpiperazin-1-yl)pyrido[2,3-d]pyrimidin-4(3H)-one

[1455] The mixture of 2,6-dichloropyrido[2,3-d]pyrimidin-4-ol (63.0 mg, 0.29 mmol) and *N*-methyl piperazine (0.5 mL) dissolved in EtOH (5.0 mL) was stirred at 80℃ for one hour, then cooled to room temperature and distilled in reduced pressure. The reaction mixture was poured into water, and it was extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled reduced pressure to obtain ivory solid compound of 6-chloro-2-(4-methylpiperazin-1-yl)pyrido[2,3-d]pyrimidin-4(3H)-one (63.0 mg, 77%).

[1456]

[1457] LC/MS ESI (+): 280 (M+1), 282 (M+3)

[1458]

[1459] (e) Synthesis of 4,6-dichloro-2-(4-methylpiperazin-1-yl)pyrido[2,3-d]pyrimidine

[1460] The mixture of 6-chloro-2-(4-methylpiperazin-1-yl)pyrido[2,3-d]pyrimidin-4(3H)-one (63.0 mg, 0.23 mmol) and $POCl_3$ (1.0 mL) was stirred at 90℃ for 12 hours, and then distilled under reduced pressure to obtain brown solid compound of 4,6-dichloro-2-(4-methylpiperazin-1-yl)pyrido[2,3-d]pyrimidine.

[1461]

[1462] LC/MS ESI (+): 298 (M+1), 300 (M+3)

[1463]

[1464] (f) Synthesis of 6-chloro-4-hydrazinyl-2-(4-methylpiperazin-1-yl)pyrido[2,3-d]pyrimidine

[1465] Unpurified 4,6-dichloro-2-(4-methylpiperazin-1-yl)pyrido[2,3-d]pyrimidine, TEA (233.0 mg, 2.30 mmol) and hydrazine monohydrate (115.0 mg, 2.30 mmol) were dissolved in EtOH (10.0 mL). The mixture was stirred at -20℃ for one hour and then distilled under reduced pressure to obtain yellow solid compound of 6-chloro-4-hydrazinyl-2-(4-methylpiperazin-1-yl)pyrido[2,3-d]pyrimidine.

[1466]

[1467] LC/MS ESI (+): 294 (M+1), 296 (M+3)

[1468]

[1469] (g) Synthesis of 9-chloro-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine

[1470] The mixture of unpurified 6-chloro-4-hydrazinyl-2-(4-methylpiperazin-1-yl)pyrido[2,3-d]pyrimidine and trimethyl orthoformate (2.0 mL) was stirred at 100℃ for 2 hours and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered to obtain purple solid compound of 9-chloro-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (0.1 mg, 0.1%).

[1471]

[1472] LC/MS ESI (+): 304 (M+1), 306 (M+3)

[1473] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.54 (s, 1H), 8.82 (s, 1H), 8.76 (s, 1H), 3.66 (bs, 4H), 2.55 (m, 4H), 2.26 (s, 3H)

[1474]

[1475] **Example 43**

[1476] **Synthesis of 8-chloro-2-methyl-4-(4-methylpiperazin-1-yl)-2H-pyrazolo[3,4-c][1,8]naphthylidine**

[1477]

[1478] (a) Synthesis of ethyl 2-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-oxoacetate

[1479] 5-Chloro-1H-pyrrolo[2,3-b]pyridine (500.0 mg, 3.28 mmol) and $AlCl_3$ (2180.0 mg, 16.38 mmol) were dissolved in DCM (10.0 mL), and ethyl 2-chloro-2-oxoacetate (44.0 μL, 3.93 mmol) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 12 hours. EtOH and ice were added to the reaction mixture at 0℃ and then extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure to obtain yellow solid of compound of ethyl 2-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-oxoacetate (200.0 mg, 23%).

[1480]

[1481] LC/MS ESI(+): 253 (M+1), 255 (M+3)

[1482] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 10.39 (s, 1H), 8.72 (d, 1H, *J*=2.4 Hz), 8.68 (d, 1H, *J* =3 Hz), 8.39 (d, 1H, *J*=2.4 Hz), 4.44 (q, 2H, *J*=7.2 Hz), 1.45 (t, 3H, *J*=6.9 Hz)

[1483]

[1484] (b) Synthesis of 8-chloro-2-methyl-2H-pyrazolo[3,4-c][1,8]naphthylidine-4(5H)-one

[1485] Ethyl 2-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-oxoacetate (200.0 mg, 0.79 mmol), methylhydrazine sulfate (228.0 mg, 1.58 mmol) and acetic acid (68.0 μL, 11.87 mmol) were dissolved in EtOH (2.0 mL), and it was allowed to react in microwaver under conditions of 100W, 120℃ for 30 minutes, and then cooled to room temperature. NH_4Cl aqueous solution was then added thereto and extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, then distilled under reduced pressure and purified by column chromatography (MeOH:DCM=5:95) on silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 8-chloro-2-methyl-2H-pyrazolo[3,4-c][1,8]naphthylidine-4(5H)-one (30.0 mg, 16%).

[1486]

[1487] LC/MS ESI(+): 235 (M+1), 237 (M+3)

[1488] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 11.88 (s, 1H), 8.71 (s, 1H), 8.52 (d, 1H, *J*=2.7 Hz), 8.38 (d, 1H, *J*=2.4 Hz), 4.14 (s, 3H)

[1489]

[1490] (c) Synthesis of 4,8-dichloro-2-methyl-2H-pyrazolo[3,4-c][1,8]naphthylidine

[1491] 8-Chloro-2-methyl-2H-pyrazolo[3,4-c][1,8]naphthylidine-4(5H)-one (30.0 mg, 0.13 mmol) was dissolved in $POCl_3$ (1.5 mL) and DIPEA (66.0 μL, 0.38 mmol) was then added thereto. The reaction mixture was refluxed for 12 hours and then cooled to room temperature. The reaction mixture was poured into ice water, neutralized with saturated $NaHCO_3$ aqueous solution (pH=7) and then extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then concentrated under reduced pressure to obtain solid compound of 4,8-dichloro-2-methyl-2H-pyrazolo[3,4-c][1,8]naphthylidine (30.0 mg, 90%).

[1492]

[1493] LC/MS ESI(+): 253 (M+1), 255 (M+3)

[1494]

[1495] (d) Synthesis of 8-chloro-2-methyl-4-(4-methylpiperazin-1-yl)-2H-pyrazolo[3,4-c][1,8]naphthylidine

[1496] 4,8-Dichloro-2-methyl-2H-pyrazolo[3,4-c][1,8]naphthylidine (10.0 mg, 0.04 mmol) was dissolved in DMF (0.3 mL), and *N*-methylpiperazine (23.3 μL, 0.21 mmol) and TEA (58.0 μL, 0.42 mmol) were added thereto. The reaction mixture was stirred at room temperature for one hour and purified by column chromatography (MeOH:DCM=1:9) on silica. The fractions containing the product were collected and

evaporated to obtain ivory solid compound of 8-chloro-2-methyl-4-(4-methylpiperazin-1-yl)-2H-pyrazolo[3,4-c][1,8]naphthylidine (3.7 mg, 30%).

[1497]

[1498] LC/MS ESI(+): 317 (M+1), 319 (M+3)

[1499] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 8.55 (s, 1H), 8.11 (s, 1H), 7.99 (d, 1H, *J*=2.4 Hz), 4.46 (m, 4H), 4.22 (s, 3H), 2.60 (m, 4H), 2.36 (s, 3H)

[1500]

[1501] **Example 44**

[1502] **Synthesis of 1-(8-chloro-2-methyl-2H-pyrazolo[3,4-c][1,8]naphthylidine-4-yl)-*N*-methylazetidin-3-amine**

[1503]

[1504] 4,8-Dichloro-2-methyl-2H-pyrazolo[3,4-c][1,8]naphthylidine (10.0 mg, 0.04 mmol) was dissolved in DMF (0.3 mL), and *tert*-butyl azetidin-3-yl(methyl)carbamate (39.1 mg, 0.21 mmol) and TEA (58.0 μL, 0.42 mmol) were added thereto. The reaction mixture was stirred at room temperature for one hour, concentrated under reduced pressure, dissolved in DCM (1.0 mL) without purification and then TFA (0.2 mL) was added thereto. The reaction mixture was stirred at room temperature for one hour and purified by column chromatography (MeOH:DCM=5:95) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 1-(8-chloro-2-methyl-2H-pyrazolo[3,4-c][1,8]naphthylidine-4-yl)-*N*-methylazetidin-3-amine (3.2 mg, 25%).

[1505]

[1506] LC/MS ESI(+): 303 (M+1), 305 (M+3)

[1507] ^{1}H-NMR (300 MHz, $CDCl_3$+MeOH-d_4); δ: 8.47 (s, 1H), 8.27 (s, 1H), 8.13 (d, 1H, *J*=2.4 Hz), 4.89 (m, 2H), 4.71 (m, 2H), 4.23 (s, 3H), 3.99 (m, 1H), 2.76 (s, 3H).

[1508]

[1509] **Example 45**

[1510] **Synthesis of 8-chloro-2-methyl-4-(piperazin-1-yl)-2H-pyrazolo[3,4-c][1,8]naphthylidine**

[1511]

[1512] 4,8-Dichloro-2-methyl-2H-pyrazolo[3,4-c][1,8]naphthylidine (10.0 mg, 0.04 mmol) was dissolved in DMF (0.3 mL), and *tert*-butyl piperazin-1-carboxylate (39.1 mg, 0.21 mmol) and TEA (58.0 μL, 0.42 mmol) were added thereto. The reaction mixture was stirred at room temperature for one hour, concentrated under reduced pressure, dissolved in DCM (1.0 mL) without purification and then TFA (0.2 mL) was added thereto. The reaction mixture was stirred at room temperature for one hour and purified by column chromatography (MeOH:DCM=5:95) on amine silica. The fractions

containing the product were collected and evaporated to obtain ivory solid compound of 8-chloro-2-methyl-4-(piperazin-1-yl)-2H-pyrazolo[3,4-c][1,8]naphthylidine (2.0 mg, 16%).

[1513]

[1514] LC/MS ESI(+): 303 (M+1), 305 (M+3)

[1515] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 8.50 (d, 1H, *J*=2.7 Hz), 8.16 (s, 1H), 8.04 (d, 1H, *J* =2.7 Hz), 4.52 (m, 4H), 4.20 (s, 3H), 3.17 (m, 4H).

[1516]

[1517] **Example 46**

[1518] **Synthesis of 8-chloro-4-(4-methylpiperazin-1-yl)imidazo[1,2-a]pyrido[2,3-e]pyrazine**

[1519]

[1520] (a) Synthesis of 2,7-dichloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine

[1521] 2,3,7-Trichloropyrido[2,3-b]pyrazine (500.0 mg, 2.13 mmol) and TEA (3.1 mL, 21.30 mmol) were dissolved in DCM (15.0 mL), and *N*-methyl piperazine (0.3 mL, 2.34 mmol) diluted in DCM (5.0 mL) was slowly added thereto at 0°C. The reaction mixture was stirred at room temperature for 12 hours, poured into saturated NH_4Cl aqueous solution and then extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=20:1) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 2,7-dichloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (331.0 mg, 52%).

[1522]

[1523] LC/MS ESI (+): 298 (M+1), 300 (M+3)

[1524]

[1525] (b) Synthesis of 7-chloro-*N*-(2,2-diethoxyethyl)-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazin-2-amine

[1526] The mixture of 2,7-dichloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (100.0 mg, 0.34 mmol) and 2,2-diethoxyethylamine (2.0 mL) was stirred at room temperature for 2 hours. The reaction mixture was poured into water and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure to obtain yellow solid compound of 7-chloro-*N*-(2,2-diethoxyethyl)-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazin-2-amine.

[1527]

[1528] LC/MS ESI (+): 395 (M+1), 397 (M+3)

[1529]

[1530] (c) Synthesis of

8-chloro-4-(4-methylpiperazin-1-yl)imidazo[1,2-a]pyrido[2,3-e]pyrazine

[1531] The mixture of unpurified 7-chloro-*N* -(2,2-diethoxyethyl)-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazin-2-amine and TsOH (128.0 mg, 0.68 mmol) dissolved in IPA (5.0 mL) was stirred at 100℃ for 2 hours, then cooled to room temperature and distilled under reduced pressure. The reaction mixture was poured into and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried under anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=20:1 to 90:10) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 8-chloro-4-(4-methylpiperazin-1-yl)imidazo[1,2-a]pyrido[2,3-e]pyrazine (56.0 mg, 55% in 2 steps).

[1532]

[1533] LC/MS ESI (+): 303 (M+1), 305 (M+3)

[1534] ^{1}H-NMR (300MHz,DMSO-d_6); δ: 8.81 (d, 1H, *J*=2.4Hz), 8.74 (d, 1H, *J*=1.2Hz), 8.53 (d, 1H, *J*=2.4Hz), 7.72 (d, 1H, *J*=1.4Hz), 4.42 (bs, 4H), 2.49 (m, 4H), 2.23 (s, 3H)

[1535]

[1536] **Example 47**

[1537] **Synthesis of 8-chloro-4-(piperazin-1-yl)imidazo[1,2-a]pyrido[2,3-e]pyrazine**

[1538]

[1539] (a) Synthesis of *tert* -butyl 4-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate

[1540] 2,3,7-Trichloropyrido[2,3-b]pyrazine (400.0 mg, 1.71 mmol) and TEA (2.4 mL, 17.10 mmol) were dissolved in DCM (8.0 mL) and *tert*-butyl piperazin-1-carboxylate (350.0 mg, 1.88 mmol) diluted in DCM (2.0 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 2 hours, poured into saturated NH_4Cl aqueous solution and then extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=19:1) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of *tert*-butyl 4-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate.

[1541]

[1542] LC/MS ESI (+): 384 (M+1), 386 (M+3)

[1543]

[1544] (b) Synthesis of *tert* -butyl 4-(7-chloro-2-((2,2-diethoxyethyl)amino)pyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate

[1545] The mixture of unpurified *tert*-butyl 4-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate and 2,2-diethoxyethylamine (2.0 mL) was stirred at room temperature for 12 hours, poured into water and then extracted with EtOAc (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure to obtain yellow solid compound of *tert*-butyl 4-(7-chloro-2-((2,2-diethoxyethyl)amino)pyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate.

[1546]

[1547] LC/MS ESI (+): 481 (M+1), 483 (M+3)

[1548]

[1549] (c) Synthesis of 8-chloro-4-(piperazin-1-yl)imidazo[1,2-a]pyrido[2,3-e]pyrazine

[1550] The mixture of unpurified *tert*-butyl 4-(7-chloro-2-((2,2-diethoxyethyl)amino)pyrido[2,3-b]pyrazin-3-yl)piperazin-1-carboxylate and TsOH (662.0 mg, 3.48 mmol) dissolved in IPA (10.0 mL) was stirred at 100℃ for one hour, then cooled to room temperature and distilled under reduced pressure. The reaction mixture was poured into water, neutralized with $NaHCO_3$ aqueous solution (pH=7) and then extracted with DCM (50.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=20:1 to 90:10) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 8-chloro-4-(piperazin-1-yl)imidazo[1,2-a]pyrido[2,3-e]pyrazine (155.0 mg, 31% in 2 steps).

[1551]

[1552] LC/MS ESI (+): 289 (M+1), 291 (M+3)

[1553] ^{1}H-NMR (300MHz,DMSO-d_6); δ: 8.79 (d, 1H, *J*=2.5Hz), 8.74 (m, 1H), 8.52 (d, 1H, *J*=2.4Hz), 7.72 (m, 1H), 4.35 (bs, 4H), 2.84 (m, 4H)

[1554]

[1555] **Example 48**

[1556] **Synthesis of 1-(8-iodopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine**

[1557]

[1558] (a) Synthesis of *tert*-butyl (1-(8-iodopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[1559]

[1560] *tert*-Butyl

(1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (50.0 mg, 0.11 mmol), *N,N'*-dimethylethane-1,2-diamine (1.0 mg, 0.01 mmol), CuI (1.1 mg, 5.50 μmol) and KI (38.0 mg, 0.22 mmol) were added to 1-butanol (1.0 mL), stirred at 100°C for 18 hours, distilled under reduced pressure and then purified by column chromatography (DCM:MeOH=98:2 to 95:5) on silica. The fractions containing the product were collected and evaporated to obtain white solid compound of *tert*-butyl (1-(8-iodopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (25.0 mg, 45%).

[1561]

[1562] LC/MS ESI (+): 482 (M+1)

[1563]

[1564] (b) Synthesis of 1-(8-iodopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine

[1565]

[1566] *tert*-Butyl (1-(8-iodopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (25.0 mg, 0.05 mmol) was dissolved in DCM (3.0 mL), and TFA (0.5 mL) was slowly added thereto at 0°C. The reaction mixture was stirred at room temperature for one hour and distilled under reduced pressure. The residue was neutralized with $NaHCO_3$ aqueous solution (pH=7) and extracted with DCM/MeOH (9/1, 30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, distilled under reduced pressure and then purified by column chromatography (DCM:MeOH=96:4) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 1-(8-iodopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (15.0 mg, 75%).

[1567]

[1568] LC/MS ESI (+): 382 (M+1)

[1569] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.96 (s, 1H), 8.97 (d, 1H, *J*=2.1Hz), 8.68 (d, 1H, *J*=2.1Hz), 4.89 (m, 1H), 4.42 (m, 2H), 4.00 (m, 1H), 3.70 (m, 1H), 2.29 (s, 3H)

[1570]

[1571] **Example 49**

[1572] **Synthesis of 8-iodo-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[1573]

[1574] (a) Synthesis of 5-iodopyridin-2,3-diamine

[1575] 5-Iodo-3-nitropyridin-2-amine (2000.0 mg, 7.55mmol), Fe (4800.0 mg, 85.90 mmol)

and conc. HCl (0.1 mL) were added to a mixture of EtOH (7.0 mL) and water (2.0 mL), and the suspension was stirred at 100℃ for 30. The reaction mixture was cooled to room temperature, filtered through celite and then distilled under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=1:40) on silica. The fractions containing the product were collected and evaporated to obtain brown solid compound of 5-iodopyridin-2,3-diamine (1710.0 mg, 97%).

[1576]

[1577] LC/MS ESI(+): 236 (M+1)

[1578] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 7.37 (d, 1H, J=2.1Hz), 6.91 (d, 1H, J=2.1Hz), 5.59 (s, 2H), 4.91 (s, 2H)

[1579]

[1580] (b) Synthesis of 2,3-dichloro-7-iodopyrido[2,3-b]pyrazine

[1581] The mixture of 5-iodopyridin-2,3-diamine (1400.0 mg, 5.96 mmol) and diethyl oxalate (10.0 mL) was stirred at 100℃ for 12 hours and then cooled to room temperature. Et_2O was added to the reaction mixture to form a solid, and the formed solid was then filtered and dried under reduced pressure to obtain brown solid compound of 7-iodopyrido[2,3-b]pyrazin-2,3-diol. The mixture of unpurified 7-iodopyrido[2,3-b]pyrazin-2,3-diol and $POCl_3$ (15.0 mL) was stirred at 150℃ for 12 hours and then cooled to room temperature. The reaction mixture was poured into ice water, and the formed solid was filtered and then dried under reduced pressure to obtain brown solid compound of 2,3-dichloro-7-iodopyrido[2,3-b]pyrazine (1080.0 mg, 56%).

[1582]

[1583] LC/MS ESI(+): 326 (M+1), 328 (M+3)

[1584]

[1585] (c) Synthesis of 2-chloro-7-iodo-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine

[1586] 2,3-Dichloro-7-iodopyrido[2,3-b]pyrazine (50.0 mg, 0.15 mmol) and TEA (213.0 μL, 1.53 mmol) were dissolved in DCM (2.0 mL) and *N*-methylpiperazine (16.0 μL, 0.15 mmol) was slowly added thereto at 0℃. The reaction mixture was stirred at 0℃ for one hour, concentrated, and then purified by column chromatography (MeOH:DCM=5:95) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 2-chloro-7-iodo-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (40.0 mg, 67%).

[1587]

[1588] LC/MS ESI (+): 390 (M+1), 392 (M+3)

[1589]

[1590] (d) Synthesis of 2-hydrazinyl-7-iodo-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine

[1591] 2-Chloro-7-iodo-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (40.0 mg, 0.10 mmol) and hydrazine monohydrate (7.5 μL, 0.15 mmol) were dissolved in EtOH (1.0 mL), stirred at room temperature for 3 hours to form a solid. The formed solid was filtered to obtain yellow solid compound of 2-hydrazinyl-7-iodo-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (39.4 mg, 100%).

[1592]

[1593] LC/MS ESI(+): 386 (M+1)

[1594]

[1595] (e) Synthesis of 8-iodo-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[1596] The mixture of 2-hydrazinyl-7-iodo-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (39.4 mg, 0.10 mmol) and trimethyl orthoformate (2.0 mL) was stirred at 80℃ for 3 hours and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and dried under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=5:95) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 8-iodo-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (13.5 mg, 34%).

[1597]

[1598] LC/MS ESI(+): 396 (M+1)

[1599] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 10.00 (s, 1H), 9.00 (d, 1H, *J*=2.1Hz), 8.71 (d, 1H, *J*=2.1Hz), 4.57-4.17 (m, 4H), 2.52 (m, 4H), 2.24 (s, 3H)

[1600]

[1601] **Example 50**

[1602] **Synthesis of *N* -methyl-1-(8-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine**

[1603]

[1604] (a) Synthesis of 5-methylpyridin-2,3-diamine

[1605] 5-Methyl-3-nitropyridin-2-amine (50000.0 mg, 0.33 mol) was dissolved in MeOH/EtOAc (1000.0 mL), and 10% of Pd/C (5000.0 mg) was added thereto. The flask was substituted with hydrogen. The reaction mixture was reacted at room temperature for 8 hours, then filtered through celite and evaporated under reduced pressure to obtain brown solid compound of 5-methylpyridin-2,3-diamine (98000.0 mg, 82%).

[1606]

[1607] ^{1}H-NMR (300MHz, $CDCl_3$); δ: 7.48 (s, 1H), 6.74 (s, 1H), 4.06 (bs, 2H), 3.27 (bs, 2H), 2.16 (s, 3H)

[1608]

[1609] (b) Synthesis of 7-methylpyrido[2,3-b]pyrazin-2,3-diol

[1610] 5-Methylpyridin-2,3-diamine (98000.0 mg, 0.80 mol) and oxalic acid (76900.0 mg, 0.85 mol) were added to 3N HCl (784.0 mL). The mixture was stirred at 120℃ for 24 hours and then cooled to room temperature. The formed solid was filtered and dried under reduced pressure to obtain brown solid compound of 7-methylpyrido[2,3-b]pyrazin-2,3-diol (140000.0 mg, 100%).

[1611]

[1612] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 12.26 (bs, 1H), 11.97(bs, 1H), 7.90 (s, 1H), 7.25 (s, 1H), 2.25 (s, 3H)

[1613]

[1614] (c) Synthesis of 2,3-dichloro-7-methylpyrido[2,3-b]pyrazine

[1615] The mixture of 7-methylpyrido[2,3-b]pyrazin-2,3-diol (140000.0 mg, 0.79 mol) and $POCl_3$ (900.0 mL) was stirred at 130℃ for 24 hours and then cooled to room temperature. The reaction mixture was poured into ice water to form a solid. The formed solid was filtered, dried under reduced pressure and then purified by column chromatography (DCM) on silica. The fractions containing the product were collected and evaporated to obtain brown solid compound of 2,3-dichloro-7-methylpyrido[2,3-b]pyrazine (55000.0 mg, 33%).

[1616]

[1617] (d) Synthesis of *tert* -butyl (1-(2-chloro-7-methylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[1618] 2,3-Dichloro-7-methylpyrido[2,3-b]pyrazine (750.0 mg, 3.47 mmol) and *tert*-butyl azetidin-3-yl(methyl)carbamate hydrochloride (850.0 mg, 3.82 mmol) were allowed to react in the same way as Example 2 (c) to obtain pale yellow solid compound of *tert* -butyl (1-(2-chloro-7-methylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (720.0 mg, 57%).

[1619]

[1620] LC/MS ESI(+): 364 (M+1)

[1621] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 8.74 (d, 1H, *J*=2.1 Hz), 7.91 (d, 1H, *J*=2.1 Hz), 5.05 (m, 1H), 4.71 (m, 2H), 4.53 (m, 2H), 2.99 (s, 3H), 2.51 (s, 3H), 1.50 (s, 9H)

[1622]

[1623] (e) Synthesis of *tert* -butyl methyl(1-(8-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)carbamate

[1624] *tert*-Butyl (1-(2-chloro-7-methylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (320.0 mg, 0.88 mmol) and hydrazine monohydrate (0.1 mL, 3.50 mmol) were

dissolved in EtOH (8.0 mL) and stirred at 40℃ for 12 hours. Et_2O was added thereto to form a solid, and the formed solid was filtered and dried under reduced pressure to obtain dark brown compound of *tert*-butyl (1-(2-hydrazinyl-7-methylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate. Unpurified compound of *tert*-butyl (1-(2-hydrazinyl-7-methylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate and trimethyl orthoformate (4.0 mL) were reacted to obtain brown solid compound of *tert*-butyl methyl(1-(8-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)carbamate (92.0 mg, 29% in 2 steps).

[1625]

[1626] LC/MS ESI(+): 370 (M+1)

[1627] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 9.14 (s, 1H), 8.52 (d, 1H, *J*=2.1 Hz), 7.84 (d, 1H, *J*=2.1 Hz), 4.60 (m, 5H), 2.99 (s, 3H), 2.46(s, 3H), 1.47 (s, 9H)

[1628]

[1629] (f) Synthesis of *N* -methyl-1-(8-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine

[1630] *tert*-Butyl methyl(1-(8-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)carbamate (90.0 mg, 0.24 mmol) was dissolved in a mixture of DCM (2.0 mL) and TFA (3.0 mL). The reaction mixture was stirred at 0℃ for one hour and then purified by column chromatography (DCM:MeOH=50:1) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of *N* -methyl-1-(8-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine (39.0 mg, 59%).

[1631]

[1632] LC/MS ESI(+): 270 (M+1)

[1633] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 9.13 (s, 1H), 8.51 (d, 1H, *J*=2.1 Hz), 7.83 (d, 1H, *J*=2.1 Hz), 5.09 (m, 1H), 4.75-4.55 (m, 2H), 4.20 (m, 1H), 3.89 (m, 1H), 2.50 (s, 6H)

[1634]

[1635] **Example 51**

[1636] **Synthesis of 1-(8-(difluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N* -methylazetidin-3-amine**

[1637]

[1638] (a) Synthesis of *tert* -butyl (1-(8-formylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[1639] 2.5M of *n*-BuLi in hexane solution was slowly added to a suspension of *tert*-butyl (1-(8-iodopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (270.0 mg, 0.56 mmol) and THF (5.6 mL) at -78℃. The reaction mixture was stirred at -78℃ for 10 minutes, and DMF (0.5 mL) and THF (2.0 mL) was then added thereto. The reaction mixture was stirred for one hour and NH_4Cl aqueous solution was added thereto, and it was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=1:60) on silica. The fractions containing the product were collected and evaporated to obtain pale white solid compound of *tert*-butyl (1-(8-formylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (18.0 mg, 8%).

[1640]

[1641] LC/MS ESI(+): 384 (M+1)

[1642] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 10.14 (s, 1H), 10.10 (s, 1H), 9.04 (d, 1H, *J*=2.1 Hz), 8.97 (d, 1H, *J*=2.1 Hz), 5.09-5.00 (m, 2H), 4.89 (m, 1H), 4.60 (m, 1H), 4.46 (m, 1H), 2.94 (s, 3H), 1.42 (s, 9H)

[1643]

[1644] (b) Synthesis of *tert* -butyl (1-(8-(difluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[1645] Suspension of *tert*-butyl (1-(8-formylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (11.0 mg, 0.03 mmol) and Deoxo-Fluor (0.8 mL) was allowed to react in microwaver under conditions of 50W, 70℃ for 1.5 hours and then cooled to room temperature. The reaction mixture was poured into ice water and NH_4Cl aqueous solution was added thereto, and it was extracted with MeOH:DCM=1:20 solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=1:60) on silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of *tert*-butyl (1-(8-(difluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (5.0 mg, 45%).

[1646]

[1647] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 9.23 (s, 1H), 8.76 (s, 1H), 8.19 (s, 1H), 7.04-6.66 (m, 1H), 5.18 (m, 1H), 4.99 (m, 1H), 4.74 (m, 1H), 4.56 (m, 1H), 4.35-4.25 (m, 1H), 3.01 (s, 3H), 1.49 (s, 9H)

[1648]

[1649] (c) Synthesis of 1-(8-(difluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine

[1650] TFA (0.4 mL) was added to the mixture of *tert*-butyl (1-(8-(difluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (5.0 mg, 0.01 mmol) and DCM (0.6 mL), and it was then stirred at room temperature for one hour. The reaction mixture was purified by column chromatography (MeOH:DCM=1:40) on amine silica. The fractions containing the product were collected and evaporated. Et_2O was added to the residue to form a solid. The formed solid was filtered and dried under reduced pressure to obtain ivory solid compound of 1-(8-(difluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (1.5 mg, 41%).

[1651]

[1652] LC/MS ESI(+): 306 (M+1)

[1653] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 10.07 (s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 7.42-7.05 (m, 1H), 4.93 (m, 1H), 4.52-4.40 (m, 2H), 4.01 (m, 1H), 3.72 (m, 1H), 2.30 (s, 3H)

[1654]

[1655] **Example 52**

[1656] **Synthesis of *N*-methyl-1-(8-(trifluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine**

[1657]

[1658] (a) Synthesis of 3-nitro-5-(trifluoromethyl)pyridin-2-amine

[1659] 5-(trifluoromethyl)pyridin-2-amine (1700.0 mg, 10.49 mmol) was dissolved in conc. H_2SO_4 (10.0 mL), and then conc. HNO_3 (1.7 mL, 26.22 mmol) was slowly added thereto. The reaction mixture was stirred at 80°C for 48 hours, then added to ice water, alkalized with 1N NaOH aqueous solution (pH=9) and then extracted with EtOAc (200.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (*n*-Hex:EtOAc=50:50) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 3-nitro-5-(trifluoromethyl)pyridin-2-amine (538.0 mg, 25%).

[1660]

[1661] LC/MS ESI (+): 208 (M+1)

[1662] ^{1}H-NMR (300MHz, $CDCl_3$); δ: 8.67 (d, 1H, *J*=1.7Hz), 8.59 (d, 1H, *J*=1.7Hz), 7.92 (bs, 1H), 6.10 (bs, 1H)

[1663]

[1664] (b) Synthesis of 5-(trifluoromethyl)pyridin-2,3-diamine

[1665] 3-Nitro-5-(trifluoromethyl)pyridin-2-amine (538.0 mg, 2.60 mmol) and $SnCl_2$ $2H_2O$ (2340.0 mg, 10.39 mmol) were added to DMF (5.0 mL), and it was stirred at 60℃ for 12 hours. The reaction mixture was poured into saturated $NaHCO_3$ aqueous solution and neutralized (pH=7), and it was then extracted with EtOAc (200.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then evaporated under reduced pressure to obtain brown solid compound of 5-(trifluoromethyl)pyridin-2,3-diamine.

[1666]

[1667] LC/MS ESI (+): 178 (M+1)

[1668]

[1669] (c) Synthesis of 2,3-dichloro-7-(trifluoromethyl)pyrido[2,3-b]pyrazine

[1670] Unpurified 5-(trifluoromethyl)pyridin-2,3-diamine was added to diethyl oxalate (10.0 mL). The mixture was stirred at 120℃ for 12 hours and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered under reduced pressure to obtain brown solid compound of 7-(trifluoromethyl)pyrido[2,3-b]pyrazin-2,3-diol. The mixture of unpurified 7-(trifluoromethyl)pyrido[2,3-b]pyrazin-2,3-diol and $POCl_3$ (10.0 mL) was stirred at 130℃ for 12 hours and then cooled to room temperature. The reaction mixture was poured into ice water to form a solid. The formed solid was filtered and then dried under reduced pressure to obtain brown solid compound of 2,3-dichloro-7-(trifluoromethyl)pyrido[2,3-b]pyrazine (370.0 mg, 53% in 3 steps).

[1671]

[1672] LC/MS ESI (+): 268 (M+1), 270 (M+3), 272(M+5)

[1673]

[1674] (d) Synthesis of *tert* -butyl (1-(2-chloro-7-(trifluoromethyl)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[1675] 2,3-Dichloro-7-(trifluoromethyl)pyrido[2,3-b]pyrazine (100.0 mg, 0.37 mmol) and TEA (0.26 mL, 1.85 mmol) were dissolved in DCM (10.0 mL), and *tert*-butyl azetidin-3-yl(methyl)carbamate hydrochloride (83.0 mg, 0.37 mmol) diluted in DCM (5.0 mL) and TEA (0.26 mL, 1.85 mmol) were slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for one hour. The reaction mixture was poured into saturated NH_4Cl aqueous solution and extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0) on amine silica. The fractions containing the product were collected and evaporated to obtain brown solid compound of *tert*-butyl

(1-(2-chloro-7-(trifluoromethyl)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate.

[1676]

[1677] LC/MS ESI (+): 418 (M+1)

[1678]

[1679] (e) Synthesis of *tert* -butyl (1-(2-hydrazinyl-7-(trifluoromethyl)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[1680] Unpurified *tert*-butyl (1-(2-chloro-7-(trifluoromethyl)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate and hydrazine monohydrate (47.0 mg, 0.93 mmol) were dissolved in EtOH (5.0 mL), stirred at room temperature for 12 hours and then distilled under reduced pressure. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain yellow solid compound of *tert*-butyl (1-(2-hydrazinyl-7-(trifluoromethyl)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate.

[1681]

[1682] LC/MS ESI (+): 414 (M+1)

[1683]

[1684] (f) Synthesis of *tert* -butyl methyl(1-(8-(trifluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)carbamate

[1685] The mixture of unpurified *tert*-butyl (1-(2-hydrazinyl-7-(trifluoromethyl)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate and trimethyl orthoformate (10.0 mL) was stirred at 80℃ for one hour and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain ivory solid compound of *tert*-butyl methyl(1-(8-(trifluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)carbamate.

[1686]

[1687] LC/MS ESI (+): 424 (M+1)

[1688]

[1689] (g) Synthesis of *N* -methyl-1-(8-(trifluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine

[1690] Unpurified *tert*-butyl methyl(1-(8-(trifluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3

-yl)carbamate was dissolved in DCM (4.0 mL) and then TFA (0.5 mL) was slowly added thereto at 0°C. The reaction mixture was stirred at room temperature for one hour. The reaction mixture was distilled under reduced pressure. The residue was neutralized with $NaHCO_3$ aqueous solution (pH=7) and then extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=98:2) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of *N*-methyl-1-(8-(trifluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine (26.7 mg, 20% in 4 steps).

[1691]

[1692] LC/MS ESI (+): 324 (M+1)

[1693] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 10.1 (s, 1H), 9.01 (bs, 1H), 8.83 (bs, 1H), 4.95 (m, 1H), 4.48 (m, 2H), 4.03 (m, 1H), 3.74 (m, 1H), 2.30 (s, 3H)

[1694]

[1695] **Example 53**

[1696] **Synthesis of 4-(4-methylpiperazin-1-yl)-8-(trifluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[1697]

[1698] (a) Synthesis of 2-chloro-3-(4-methylpiperazin-1-yl)-7-(trifluoromethyl)pyrido[2,3-b]pyrazine

[1699] 2,3-Dichloro-7-(trifluoromethyl)pyrido[2,3-b]pyrazine (50.0 mg, 0.19 mmol) and TEA (0.3 mL, 1.90 mmol) were dissolved in DCM (5.0 mL), and *N*-methylpiperazine (21.0 μL, 0.19 mmol) diluted in DCM (5.0 mL) was slowly added thereto at 0°C. The reaction mixture was stirred at room temperature for 2 hours, and it was poured into saturated NH_4Cl aqueous solution and then extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 2-chloro-3-(4-methylpiperazin-1-yl)-7-(trifluoromethyl)pyrido[2,3-b]pyrazine (53.0 mg, 85%).

[1700]

[1701] LC/MS ESI (+): 332 (M+1), 334 (M+3)

[1702]

[1703] (b) Synthesis of 4-(4-methylpiperazin-1-yl)-8-(trifluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazi

ne

[1704] 2-Chloro-3-(4-methylpiperazin-1-yl)-7-(trifluoromethyl)pyrido[2,3-b]pyrazine (53.0 mg, 0.16 mmol) and hydrazine monohydrate (0.1 mL, 2.04 mmol) were dissolved in EtOH (2.0 mL), stirred at room temperature for one hour and then distilled under reduced pressure. The reaction mixture was poured into saturated NH_4Cl aqueous solution and then extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then dried under reduced pressure to obtain yellow solid compound of 2-hydrazinyl-3-(4-methylpiperazin-1-yl)-7-(trifluoromethyl)pyrido[2,3-b]pyrazine. The mixture of unpurified 2-hydrazinyl-3-(4-methylpiperazin-1-yl)-7-(trifluoromethyl)pyrido[2,3-b]pyrazine and trimethyl orthoformate (2.0 mL) was stirred at 80℃ for one hour and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 4-(4-methylpiperazin-1-yl)-8-(trifluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (14.3 mg, 23% in 3 steps).

[1705]

[1706] LC/MS ESI (+): 338 (M+1)

[1707] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 10.13 (s, 1H), 9.05 (d, 1H, *J*=2.1Hz), 8.87 (d, 1H, *J*=2.1Hz), 5.00~4.00 (m, 4H), 2.53 (m, 4H), 2.26 (s, 3H)

[1708]

[1709] **Example 54**

[1710] **Synthesis of 1-(8-ethynylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine**

[1711]

[1712] (a) Synthesis of *tert*-butyl methyl(1-(8-((trimethylsilyl)ethynyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)carbamate

[1713] *tert*-Butyl (1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (50.0 mg, 0.12 mmol), TMS-acetylene (81.0 μL, 0.58 mmol), $PdCl_2(PPh_3)_2$ (8.1 mg, 0.01 mmol), CuI (4.4 mg, 0.02 mmol) and TEA (0.5 mL) were added to DMF (0.5 mL), and the mixture was allowed to react in microwaver under conditions of 50W, 70℃ for 1.5 hous, then cooled to room temperature. DCM and water were added to the reaction mixture to form a solid, and the fomed solid was filtered to obtain gray solid. The gray solid obtained was stirred in solution of MeOH:DCM=1:9 and then filtered.

The filtrate was distilled under reduced pressure to obtain gray solid compound of *tert* -butyl methyl(1-(8-((trimethylsilyl)ethynyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)carbamate (50.0 mg, 96%).

[1714]

[1715] LC/MS ESI(+): 452 (M+1)

[1716] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 10.00 (s, 1H), 8.75 (d, 1H, *J*=2.1 Hz), 8.57 (d, 1H, *J*=2.1 Hz), 5.25-4.85 (m, 2H), 4.82 (m, 1H), 4.51 (m, 1H), 4.41 (m, 1H), 2.93 (s, 3H), 1.42 (s, 9H), 0.27 (s, 9H)

[1717]

[1718] (b) Synthesis of 1-(8-ethynylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N* -methylazetidin-3-amine

[1719] *tert*-Butyl methyl(1-(8-((trimethylsilyl)ethynyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)carbamate (50.0 mg, 0.11 mmol) was dissolved in 4N HCl dioxane solution (1.0 mL). The reaction mixture was stirred at room temperature for one hour to form a solid, and the formed solid was filtered. The resulting solid was dissolved in THF (1.0 mL), and TBAF (0.2 mL, 0.22 mmol) was added thereto. The reaction mixture was stirred at room temperature for one hour and MeOH was added thereto to form a solid. The formed solid was filtered and then dried under reduced pressure to obtain ivory solid compound of 1-(8-ethynylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N* -methylazetidin-3-amine (6.0 mg, 19%).

[1720]

[1721] LC/MS ESI(+): 280 (M+1)

[1722] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 9.99 (s, 1H), 8.76 (d, 1H, *J*=1.8 Hz), 8.60 (d, 1H, *J*=1.8 Hz), 4.94 (m, 1H), 4.60-4.40 (m, 3H), 4.10 (m, 1H), 3.81 (m, 1H), 3.16 (m, 1H), 2.36 (s, 3H)

[1723]

[1724] **Example 55**

[1725] **Synthesis of *N* -methyl-1-(8-vinylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine**

[1726]

[1727] (a) Synthesis of *tert* -butyl methyl(1-(8-vinylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)carbamate

[1728] *tert*-Butyl (1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (150.0 mg, 0.35 mmol), tributylvinyltin (1.0 mL, 3.45 mmol), $Pd(OAc)_2$ (15.0

mg, 0.07 mmol), CuI (39.4 mg, 0.21 mmol), P(*o*-Tol)$_3$ (42.0 mg, 0.14 mmol) and TEA (240.0 μL, 1.73 mmol) were added to CH_3CN (2.5 mL). The mixture was allowed to react in microwaver under conditions of 100W, 100℃ for 3 hours and then cooled to room temperature. The reaction mixture was purified by column chromatography (MeOH:DCM=1:60) on silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of *tert*-butyl methyl(1-(8-vinylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)carbamate (15.0 mg, 11%).

[1729]

[1730] LC/MS ESI(+): 382 (M+1)

[1731] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 10.00 (s, 1H), 8.78 (s, 1H), 8.62 (bs, 1H), 6.86 (m, 1H), 6.06 (m, 1H), 5.45 (m, 1H), 5.20-4.65 (m, 3H), 4.65-4.20 (m, 2H), 2.93 (s, 3H), 1.42 (s, 9H)

[1732]

[1733] (b) Synthesis of *N* -methyl-1-(8-vinylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine

[1734] *tert*-Butyl methyl(1-(8-vinylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)carbamate (15.0 mg, 0.02 mmol) was dissolved in DCM (0.6 mL), and TFA (0.4 mL) was then added thereto. The reaction mixture was stirred at room temperature for one hour and then purified by column chromatography (MeOH:DCM=1:40) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of *N* -methyl-1-(8-vinylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine (1.5 mg, 29%).

[1735]

[1736] LC/MS ESI(+): 282 (M+1)

[1737] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 9.99 (s, 1H), 8.76 (s, 1H), 8.60 (s, 1H), 6.86 (m, 1H), 6.06 (m, 1H), 5.45 (m, 1H), 4.90 (m, 1H), 4.55-4.25 (m, 2H), 3.99 (m, 1H), 3.71 (m, 1H), 2.29 (s, 3H)

[1738]

[1739] **Example 56**

[1740] **Synthesis of 1-(8-ethylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N* -methylazetidin-3-amine**

[1741]

[1742] *tert*-Butyl methyl(1-(8-vinylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)carbamate (12.0 mg, 0.03 mmol) was dissolved in MeOH (1.0 mL), and 10% of Pd/C (4.8 mg)

was added thereto. The flask was substituted with hydrogen and then allowed to react for 12 hours. The reaction mixture was filtered through celite and then distilled under reduced pressure. The residue was dissolved in DCM (0.6 mL), and TFA (0.4 mL) was added thereto. The reaction mixture was stirred for one hour and then purified by column chromatography (MeOH:DCM=1:40) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 1-(8-ethylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (3.5 mg, 39%).

[1743]

[1744] LC/MS ESI(+): 284 (M+1)

[1745] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 9.15 (s, 1H), 8.52 (d, 1H, *J*=2.1 Hz), 7.82 (d, 1H, *J* =2.1 Hz), 5.09 (m, 1H), 4.78-4.50 (m, 2H), 4.22 (m, 1H), 3.85 (m, 1H), 2.80 (q, 2H, *J* =7.5 Hz), 2.49 (s, 3H), 1.35 (t, 3H, *J*=7.5 Hz)

[1746]

[1747] **Example 57**

[1748] **Synthesis of 4-(3-(methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-ol**

[1749]

[1750] 1-(8-Methoxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (38.0 mg, 0.13 mmol) was dissolved in DCM (3.0 mL) and then cooled to -78℃. 1M of tribromoborane (3.0 mL) dissolved in DCM at concentration of 1M was added thereto. The temperature was gradually raised to 40℃. The reaction mixture was stirred for 12 hours, and then cooled to -78℃, and MeOH (3.0 mL) was added thereto. The reaction mixture temperature was allowed to increase to room temperature. Then, the the reaction mixture was concentrated and purified by column chromatography (DCM:MeOH=95:5 to 90:10) on amine silica. The fractions containing the product were collected and evaporated to obtain white solid compound of 4-(3-(methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-ol (18.0 mg, 50%).

[1751]

[1752] LC/MS ESI (+): 272 (M+1)

[1753] ^{1}H-NMR (300MHz, MeOH-d_4); δ: 9.73 (s, 1H), 8.20 (m, 1H), 7.90 (m, 1H), 4.81 (m, 2H), 4.45 (m, 2H), 4.01 (m, 1H), 2.59 (s, 3H)

[1754]

[1755] **Example 58**

[1756] **Synthesis of 1-(8-methoxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine**

[1757]

[1758] (a) Synthesis of *tert* -butyl (1-(8-methoxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[1759] The mixture containing MeOH (4.5 mL) and NaH (450.0 mg) was stirred at room temperature for 30 minutes and then added to a solution of *tert*-butyl (1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (300.0 mg, 0.69 mmol) and CuI (262.8 mg, 1.38 mmol) dissolved in DMF (4.5 mL). The reaction mixture was allowed to react in microwaver under conditions of 60W, 90°C for 30 minutes, cooled to room temperature, then concentrated and purified by column chromatography (MeOH:DCM=5:95) on silica. The fractions containing the product were collected and evaporated to obtain white solid compound of *tert*-butyl (1-(8-methoxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (49.0 mg, 55%).

[1760]

[1761] LC/MS ESI(+): 386 (M+1)

[1762]

[1763] (b) Synthesis of 1-(8-methoxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)- *N* -methylazetidin-3-amine

[1764] *tert*-Butyl (1-(8-methoxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (49.0 mg, 0.13 mmol) was dissolved in DCM (0.6 mL), and TFA (0.4 mL) was slowly added thereto at 0°C. The reaction mixture was stirred at room temperature for one hour, then concentrated and purified by column chromatography (MeOH:DCM=5:95) on amine silica. The fractions containing the product were collected and evaporated to obtain white solid compound of 1-(8-methoxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (25.0 mg, 33%).

[1765]

[1766] LC/MS ESI (+): 286 (M+1)

[1767] ^{1}H-NMR (300MHz, MeOH-d_4); δ: 9.82 (s, 1H), 8.30 (d, 1H, *J*=2.7Hz), 8.15 (d, 1H, *J*=2.7Hz), 4.76-4.19 (m, 4H), 4.00 (s, 3H), 3.83 (m, 1H), 2.43 (s, 3H)

[1768]

[1769] **Example 59**

[1770] **Synthesis of 1-(8-(difluoromethoxy)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)- *N* -methylazetidin-3-amine**

[1771]

[1772] (a) Synthesis of *tert* -butyl

(1-(8-(benzyloxy)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[1773] *tert*-Butyl (1-(8-(benzyloxy)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (200.0 mg, 0.60 mmol), 1,10-phenanthroline (21.6 mg, 0.12 mmol), cesium carbonate (391.0 mg, 1.20 mmol) and CuI (114.3 mg, 0.60 mmol) were dissolved in benzyl alcohol (4.0 mL). The mixture was allowed to react in microwaver under conditions of 100W, 100℃ for 2 hours and then cooled to room temperature, and 36.0 mL of water was added thereto. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (MeOH:DCM=5:95) on silica. The fractions containing the product were collected and evaporated to obtain white solid compound of *tert*-butyl (1-(8-(benzyloxy)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (120.0 mg, 43%).

[1774]

[1775] LC/MS ESI (+): 462 (M+1)

[1776]

[1777] (b) Synthesis of *tert* -butyl (1-(8-hydroxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[1778] *tert*-Butyl (1-(8-(benzyloxy)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (120.0 mg, 0.32 mmol) and 10% of Pd/C (30.0 mg) were dissolved in MeOH (10.0 mL). The flask was substituted with hydrogen and then stirred at room temperature for 3 days. The reaction mixture was filtered through celite, distilled under reduced pressure and then purified by column chromatography (MeOH:DCM=5:95). The fractions containing the product were collected and evaporated to obtain white solid compound of *tert*-butyl (1-(8-hydroxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (40.0 mg, 34%).

[1779]

[1780] LC/MS ESI (+): 372 (M+1)

[1781]

[1782] (c) Synthesis of 1-(8-(difluoromethoxy)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)- *N* -methylazetidin-3-amine

[1783] *tert*-Butyl (1-(8-hydroxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)car

bamate (20.0 mg, 0.05 mmol) was dissolved in CH_3CN (0.7 mL), and KOH (60.0 mg, 1.08 mmol) dissolved in water (0.7 mL) was added thereto, and diethyl (bromodifluoromethyl)phosphonate (60.0 μL, 0.32 mmol) was then added thereto. The mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure and dissolved in DCM (1.0 mL) without further purification, and then TFA (0.2 mL) was added thereto. The reaction mixture was stirred at room temperature for one hour and purified by column chromatography (MeOH:DCM=5:95) on amine silica. The fractions containing the product were collected and evaporated to obtain white solid compound of 1-(8-(difluoromethoxy)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (10.0 mg, 17%).

[1784]

[1785] LC/MS ESI (+): 322 (M+1)

[1786] ^{1}H-NMR (300MHz, MeOH-d_4); δ: 9.79 (s, 1H), 8.41 (m, 2H), 7.24-6.75 (m, 1H), 5.03 (m, 1H), 4.57 (m, 2H), 4.15 (m, 1H), 3.82 (m, 1H), 2.43 (s, 3H)

[1787]

[1788] **Example 60**

[1789] **Synthesis of 8-chloro-7-methoxy-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[1790]

[1791] 7,8-Dichloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (10.0 mg, 0.03 mmol) and NaH (4.0 mg: in 60% oil, 0.12 mmol) were dissolved in MeOH (1.0 mL). The mixture was allowed to react in microwaver under conditions of 60W, 90℃ for one hour. The reaction mixture was distilled under reduced pressure and then purified by column chromatography (DCM:MeOH=99:1) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 8-chloro-7-methoxy-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (3.7 mg, 37%).

[1792]

[1793] LC/MS ESI (+): 334 (M+1), 336 (M+3)

[1794] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.91 (s, 1H), 8.85 (s, 1H), 4.41 (m, 4H), 4.01 (m, 3H), 2.50 (m, 4H), 2.26 (s, 3H)

[1795]

[1796] **Example 61**

[1797] **Synthesis of 8-chloro-7-methoxy-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[1798]

[1799] *tert*-Butyl 4-(7,8-dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)piperazin-1-carboxylate (20.0 mg, 0.05 mmol) obtained from 2,3,6,7-tetrachloropyrido[2,3-b]pyrazine in the same way as (c) to (e) of Example 2 and NaH (9.0 mg: in 60% oil, 0.25 mmol) were dissolved in MeOH (1.0 mL). The mixture was stirred in microwaver under conditions of 60W, 90℃ for one hour and then distilled under reduced pressure. The reaction mixture was purified by column chromatography (DCM:MeOH=100:0) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of *tert*-butyl 4-(8-chloro-7-methoxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)piperazin-1-carb oxylate. *tert*-Butyl 4-(8-chloro-7-methoxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)piperazin-1-carb oxylate was dissolved in DCM (2.0 mL), and then TFA (0.5 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 2 hours and then distilled under reduced pressure. The residue was neutralized with TEA (pH=7) and then purified by column chromatography (DCM:MeOH=99:1) on amine silica. The fractions containing the produt were collected and evaporated to obtain ivory solid compound of 8-chloro-7-methoxy-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (9.0 mg, 60% in 2 steps).

[1800]

[1801] LC/MS ESI (+): 320 (M+1), 322 (M+3)

[1802] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.98 (s, 1H), 8.92 (s, 1H), 4.40 (m, 4H), 4.08 (s, 3H), 2.94 (m, 4H)

[1803]

[1804] **Example 62**

[1805] **Synthesis of 7,8-dichloro-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[1806]

[1807] *tert*-Butyl 4-(7,8-dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)piperazin-1-carboxylate (20.0 mg, 0.05 mmol) was dissolved in DCM (2.0 mL), and TFA (0.5 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 2 hours and distilled under reduced pressure. The residue was neutralized with TEA (pH=7) and purified by column chromatography (DCM:MeOH=99:1) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of

7,8-dichloro-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (14.0 mg, 92%).

[1808]

[1809] LC/MS ESI (+): 324 (M+1), 326 (M+3)

[1810] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 10.01 (s, 1H), 9.08 (s, 1H), 5.00-4.00 (m, 4H), 2.95 (m, 4H)

[1811]

[1812] **Example 63**

[1813] **Synthesis of 8-chloro-7-ethoxy-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[1814]

[1815] *tert*-Butyl 4-(7,8-dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)piperazin-1-carboxylate (20.0 mg, 0.05 mmol) and NaOEt (16.0 mg, 0.25 mmol) were dissolved in EtOH (1.0 mL). The mixture was allowed to react in microwaver under conditions of 60W, 90℃ for one hour, cooled to room temperature, distilled under reduced pressure and then purified by column chromatography (DCM:MeOH=99:1) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of *tert*-butyl 4-(8-chloro-7-ethoxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)piperazin-1-carbo xylate. *tert*-Butyl 4-(8-chloro-7-ethoxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)piperazin-1-carbo xylate was dissolved in DCM (2.0 mL), and TFA (0.5 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 2 hours and distilled under reduced pressure. The residue was neutralized with TEA (pH=7) and then purified by column chromatography (DCM:MeOH=99:1) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 8-chloro-7-ethoxy-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (4.0 mg, 25% in 2 stpes).

[1816]

[1817] LC/MS ESI (+): 334 (M+1), 336 (M+3)

[1818] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.98 (m, 1H), 8.91 (m, 1H), 4.53 (q, 2H, J =7.1Hz), 4.40 (m, 4H), 2.95 (m, 4H), 1.46 (t, 3H, J=7.1Hz)

[1819]

[1820] **Example 64**

[1821] **Synthesis of 8-chloro-4-(4-methylpiperazin-1-yl)-7-(2,2,2-trifluoroethoxy)pyrido[2,3-e][1,2,4]tr**

iazolo[4,3-a]pyrazine

[1822]

[1823] 7,8-Dichloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin (10.0 mg, 0.03 mmol) and NaH (12.0 mg: in 60% oil, 0.30 mmol) were dissolved in CF_3CH_2OH (1.0 mL). The mixture was then stirred in microwaver under conditions of 60W, 120℃ for one hour, distilled under reduced pressure and then purified by column chromatography (DCM:MeOH=99:1) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 8-chloro-4-(4-methylpiperazin-1-yl)-7-(2,2,2-trifluoroethoxy)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (3.51 mg, 29%).

[1824]

[1825] LC/MS ESI (+): 402 (M+1), 404 (M+3)

[1826] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.93 (m, 1H), 8.93 (m, 1H), 5.14 (q, 2H, *J* =8.9Hz), 4.43 (m, 4H), 2.50 (m, 4H), 2.25 (s, 3H)

[1827]

[1828] **Example 65**

[1829] **Synthesis of 1-(8-bromo-9-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N* -methylazetidin-3-amine**

[1830]

[1831] (a) Synthesis of 5-bromo-4-methylpyridin-2,3-diamine

[1832] 5-Bromo-4-methyl-3-nitropyridin-2-amine (700.0 mg, 3.02 mmol), Fe (1680.0 mg, 30.20 mmol) and conc. HCl (50.0 μL) were added to EtOH (2.8 mL) and water (0.7 mL). The suspension was stirred at 100℃ for 30 minutes. The reaction mixture was cooled to room temperature, filtered through celite and then distilled under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=1:40) on silica. The fractions containing the product were collected and evaporated to obtain brown solid compound of 5-bromo-4-methylpyridin-2,3-diamine (550.0 mg, 90%).

[1833]

[1834] LC/MS ESI(+): 202 (M+1), 204 (M+3)

[1835] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 7.37 (s, 1H), 5.49 (s, 2H), 4.74 (s, 2H), 2.12 (s, 3H)

[1836]

[1837] (b) Synthesis of 7-bromo-8-methylpyrido[2,3-b]pyrazin-2,3-diol

[1838] The mixture of 5-bromo-4-methylpyridin-2,3-diamine (550.0 mg, 2.72 mmol) and diethyloxalate (10.0 mL) was stirred at 100℃ for 12 hours and then cooled to room temperature. Et_2O was added to the reaction mixture to form a solid, and the formed solid was filtered and dried under reduced pressure to obtain brown solid compound of

7-bromo-8-methylpyrido[2,3-b]pyrazin-2,3-diol (595.0 mg, 85%).

[1839]

[1840] LC/MS ESI(+): 256 (M+1), 258 (M+3)

[1841] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 12.40 (s, 1H), 11.57 (s, 1H), 8.19 (s, 1H), 2.45 (s, 3H)

[1842]

[1843] (c) Synthesis of 7-bromo-2,3-dichloro-8-methylpyrido[2,3-b]pyrazine

[1844] The mixture of 7-bromo-8-methylpyrido[2,3-b]pyrazin-2,3-diol (560.0 mg, 2.19 mmol) and $POCl_3$ (5.0 mL) was stirred at 100℃ for 12 hours and then cooled to room temperature. The reaction mixture was poured into ice water to form a solid. The formed solid was filtered and dried under reduced pressure. The resulting solid was dissolved in DCM and purified by column chromatography (EtOAc:*n*-Hex=1:9) on silica. The fractions containing the product were collected and evaporated to obtain red solid compound of 7-bromo-2,3-dichloro-8-methylpyrido[2,3-b]pyrazine (365.0 mg, 54%).

[1845]

[1846] LC/MS ESI(+): 292 (M+1), 294 (M+3), 296 (M+5)

[1847] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 9.25 (s, 1H), 2.78 (s, 3H)

[1848]

[1849] (d) Synthesis of *tert* -butyl (1-(7-bromo-2-chloro-8-methylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[1850] TEA (72.0 μL, 0.51 mmol) was added to the mixture of 7-bromo-2,3-dichloro-8-methylpyrido[2,3-b]pyrazine (50.0 mg, 0.17 mmol), *tert*-butyl azetidin-3-yl(methyl)carbamate hydrochloride (40.0 mg, 0.18 mmol) and DCM (1.7 mL) at 0℃ and stirred for one hour. The reaction mixture was purified by column chromatography (EtOAc:*n*-Hex=1:5) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of *tert*-butyl (1-(7-bromo-2-chloro-8-methylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (58.0 mg, 76%).

[1851]

[1852] LC/MS ESI(+): 442 (M+1), 444 (M+3)

[1853] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 8.85 (s, 1H), 4.86 (m, 1H), 4.65-4.55 (m, 2H), 4.49-4.40 (m, 2H), 2.90 (s, 3H), 2.66 (s, 3H), 1.41 (s, 9H)

[1854]

[1855] (e) Synthesis of *tert* -butyl (1-(8-bromo-9-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[1856] Hydrazine monohydrate (20.0 μL, 0.63 mmol) was added to a suspension of *tert*-butyl (1-(7-bromo-2-chloro-8-methylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (56.0 mg, 0.13 mmol) and EtOH (1.0 mL). The reaction mixture was stirred at room temperature for one hour and then distilled under reduced pressure. Et_2O was added to the residue to form a solid. The formed solid was filtered and dried under reduced pressure to obtain brown solid compound of *tert*-butyl (1-(7-bromo-2-hydrazinyl-8-methylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate. Unpurified *tert*-butyl (1-(7-bromo-2-hydrazinyl-8-methylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate was dissolved in trimethyl orthoformate (2.0 mL), and it was stirred at 85℃ for 3 hours. The reaction mixture was cooled to room temperature and then distilled under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=1:40) on silica. The fractions containing the product were collected and evaporated to obtain pale brown solid compound of *tert*-butyl (1-(8-bromo-9-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (25.0 mg, 45%).

[1857]

[1858] LC/MS ESI(+): 448 (M+1), 450 (M+3)

[1859]

[1860] (f) Synthesis of 1-(8-bromo-9-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine

[1861] TFA (0.4 mL) was added to mixture of *tert*-butyl (1-(8-bromo-9-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (25.0 mg, 0.06 mmol) and DCM (0.6 mL), and it was stirred at room temperature for one hour. The reaction mixture was purified by column chromatography (MeOH:DCM=1:40) on amine silica. The fractions containing the product were collected and evaporated. Et_2O was added to the residue and form a solid, and the formed solid was filtered and dried under reduced pressure to obtain ivory solid compound of 1-(8-bromo-9-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (13.0 mg, 68%).

[1862]

[1863] LC/MS ESI(+): 348 (M+1), 350 (M+3)

[1864] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 9.82 (s, 1H), 8.63 (s, 1H), 4.90 (m, 1H), 4.45-4.35 (m, 2H), 3.99 (m, 1H), 3.71 (m, 1H), 2.90 (s, 3H), 2.30 (s, 3H)

[1865]

[1866] **Example 66**

[1867] **Synthesis of**

8-bromo-9-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[1868]

[1869] (a) Synthesis of 7-bromo-2-chloro-8-methyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine

[1870] TEA (72.0 μL, 0.51 mmol) was added to mixture of 7-bromo-2,3-dichloro-8-methylpyrido[2,3-b]pyrazine (50.0 mg, 0.17 mmol), *N*-methylpiperazine (20.0 μL, 0.18 mmol) and DCM (1.7 mL) at 0℃, and it was stirred for one hour. The reaction mixture was purified by column chromatography (EtOAc:*n*-Hex=1:5) on amine silica. The fractions containing the produt were collected and evaporated to obtain yellow solid compound of 7-bromo-2-chloro-8-methyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (50.0 mg, 82%).

[1871]

[1872] LC/MS ESI(+): 356 (M+1), 358 (M+3), 360 (M+5)

[1873] ^{1}H-NMR (300 MHz, DMSO-d_6); δ = 8.96 (s, 1H), 3.64-3.58 (m, 4H), 2.69 (s, 3H), 2.55-2.50 (m, 4H), 2.25 (s, 3H)

[1874]

[1875] (b) Synthesis of 8-bromo-9-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[1876] Hydrazine monohydrate (22.0 μL, 0.70 mmol) was added to suspension of 7-bromo-2-chloro-8-methyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (50.0 mg, 0.14 mmol) and EtOH (1.0 mL). The reaction mixture was stirred at room temperature for one hour and then distilled under reduced pressure. Et_2O was added to the residue to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain yellow solid compound of 7-bromo-2-hydrazinyl-8-methyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine. Unpurified 7-bromo-2-hydrazinyl-8-methyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine was dissolved in trimethyl orthoformate (2.0 mL) and then stirred at 85℃ for 3 hours. The reaction mixture was then cooled to room temperature and distilled under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=1:40) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 8-bromo-9-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (24.0 mg, 47%).

[1877]

[1878] LC/MS ESI(+): 362 (M+1), 364 (M+3)

[1879] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 9.85 (s, 1H), 8.66 (s, 1H), 4.60-4.30 (m, 4H), 2.92 (s, 3H), 2.54-2.50 (m, 4H), 2.25 (s, 3H)

[1880]

[1881] **Example 67**

[1882] **Synthesis of 1-(8,9-dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N* -methylazetidin-3-amine**

[1883]

[1884] (a) Synthesis of *N* -(4-chloropyridin-2-yl)pivalamide

[1885] 4-Chloropyridin-2-amine (1500.0 mg, 11.70 mmol) was dissolved in pyridine (6.0 mL), and pivaloyl chloride (2.2 mL, 17.50 mmol) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 12 hours, poured into water and extracted with EtOAc (100.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (*n*-Hex:EtOAc=90:10 to 80:20) on silica. The fractions containing the product were collected and evaporated to obtain white solid compound of *N*-(4-chloropyridin-2-yl)pivalamide (2460.0 mg, 99%).

[1886]

[1887] LC/MS ESI (+): 213 (M+1), 215 (M+3)

[1888] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 10.12 (s, 1H), 8.32 (d, 1H, *J*=5.3Hz), 8.16 (s, 1H), 7.25 (d, 1H, *J*=5.3Hz), 1.23 (s, 9H)

[1889]

[1890] (b) Synthesis of *N* -(4,5-dichloropyridin-2-yl)pivalamide

[1891] *N*-(4-Chloropyridin-2-yl)pivalamide (2160.0 mg, 10.16 mmol) and *N* -chlorosuccinimide (6781.0 mg, 50.78 mmol) were dissolved in anhydrous CH_3CN (100.0 mL). The mixture was stirred at 70℃ for 2 hours and then cooled to room temperature. The reaction mixture was poured into water and extracted with EtOAc (100.0 mL). The organic layer was washed with 1N NaOH and brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (*n*-Hex:EtOAc=90:10) on silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of *N* -(4,5-dichloropyridin-2-yl)pivalamide (1990.0 mg, 79%).

[1892]

[1893] LC/MS ESI (+): 247 (M+1), 249 (M+3), 251 (M+5)

[1894] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 10.29 (s, 1H), 8.54 (s, 1H), 8.34 (s, 1H), 1.23 (s, 9H)

[1895]

[1896] (c) Synthesis of 4,5-dichloro-3-nitropyridin-2-amine

[1897] *N*-(4,5-Dichloropyridin-2-yl)pivalamide (1990.0 mg, 8.05 mmol) was slowly added to and dissolved in conc. H_2SO_4 (11.0 mL) at 10℃, and then conc. HNO_3/conc. H_2SO_4 (332.0 μL/415.0 μL) was slowly added thereto. The reaction mixture was stirred at room temperature for 2.5 hours, poured into ice water, alkalized with 1N NaOH aqueous solution (pH=9) and then extracted with EtOAc (200.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (*n*-Hex:EtOAc=90:10 to 80:20) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 4,5-dichloro-3-nitropyridin-2-amine (548.0 mg, 32%).

[1898]

[1899] LC/MS ESI (+): 208 (M+1), 210 (M+3), 212 (M+5)

[1900]

[1901] (d) Synthesis of 4,5-dichloropyridin-2,3-diamine

[1902] 4,5-Dichloro-3-nitropyridin-2-amine (548.0 mg, 2.63 mmol), Zn powder (1274.0 mg, 19.50 mmol) and anhydrous $CaCl_2$ (1578.0 mg, 14.20 mmol) were added to 95% of EtOH (20.0 mL), and the mixture was stirred at 100℃ for one hour. The reaction mixture was filtered through celite, and evaporated under reduced pressure to obtain brown solid compound of 4,5-dichloropyridin-2,3-diamine.

[1903]

[1904] LC/MS ESI (+): 178 (M+1), 180 (M+3), 182 (M+5)

[1905]

[1906] (e) Synthesis of 2,3,7,8-tetrachloropyrido[2,3-b]pyrazine

[1907] Unpurified 4,5-dichloropyridin-2,3-diamine was added to diethyl oxalate (10.0 mL). The mixture was stirred at 120℃ for 12 hours and then cooled to room temperature. Et_2O was filtered thereto to form a solid, and the formed solid was filtered and dried under reduced pressure to obtain light brown solid compound of 7,8-dichloropyrido[2,3-b]pyrazin-2,3(1H,4H)-dione. The mixture of unpurified 7,8-dichloropyrido[2,3-b]pyrazin-2,3(1H,4H)-dione and $POCl_3$ (10.0 mL) was stirred at 130℃ for 48 hours and then cooled to room temperature. The reaction mixture was poured into ice water to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain brown solid compound of 2,3,7,8-tetrachloropyrido[2,3-b]pyrazine (290.0 mg, 41% in 3 steps).

[1908]

[1909] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.35 (s, 1H)

[1910]

[1911] (f) Synthesis of *tert*-butyl methyl(1-(2,7,8-trichloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)carbamate

[1912] 2,3,7,8-Tetrachloropyrido[2,3-b]pyrazine (100.0 mg, 0.37 mmol) and TEA (0.3 mL, 1.85 mmol) were dissolved in DCM (8.0 mL), and *tert*-butyl azetidin-3-yl(methyl)carbamate hydrochloride (83.0 mg, 0.37 mmol) diluted in DCM (2.0 mL) and TEA (0.3 mL, 1.85 mmol) were slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for one hour and poured into saturated NH_4Cl aqueous solution, and it was then extracted with DCM (30.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and distilled under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=100:0) on amine silica. The fractions containing the product were collected and evaporated to obtain brown solid compound of *tert*-butyl methyl(1-(2,7,8-trichloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)carbamate.

[1913]

[1914] LC/MS ESI (+): 418 (M+1), 420 (M+3)

[1915]

[1916] (g) Synthesis of *tert* -butyl (1-(7,8-dichloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[1917] Unpurified *tert*-butyl methyl(1-(2,7,8-trichloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)carbamate and hydrazine monohydrate (46.0 mg, 0.93 mmol) were dissolved in EtOH (3.0 mL). The mixture was stirred at room temperature for 20 minutes and distilled under reduced pressure to obtain *tert*-butyl (1-(7,8-dichloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate.

[1918]

[1919] LC/MS ESI (+): 414 (M+1), 416 (M+3)

[1920]

[1921] (h) Synthesis of *tert* -butyl (1-(8,9-dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[1922] The mixture of unpurified *tert*-butyl (1-(7,8-dichloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate and trimethyl orthoformate (2.0 mL) was stirred at 80℃ for one hour and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain *tert*-butyl (1-(8,9-dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate.

[1923]

[1924] LC/MS ESI (+): 424 (M+1), 426 (M+3)

[1925]

[1926] (i) Synthesis of 1-(8,9-dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)- *N* -methylazetidin-3-amine

[1927] Unpurified *tert*-butyl (1-(8,9-dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate was dissolved in DCM (2.0 mL), and TFA (0.5 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for one hour and distilled under reduced pressure. The residue was neutralized with TEA and purified by column chromatography (DCM:MeOH=98:2) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 1-(8,9-dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N* -methylazetidin-3-amine (3.5 mg, 3% in 4 steps).

[1928]

[1929] LC/MS ESI (+): 324 (M+1), 326 (M+3)

[1930] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 10.30 (s, 1H), 8.68 (s, 1H), 4.94 (m, 1H), 4.46 (m, 2H), 4.03 (m, 1H), 3.73 (m, 1H), 2.30 (s, 3H)

[1931]

[1932] **Example 68**

[1933] **Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)- *N* -methylazetidin-3-amine hydrochloride**

[1934]

[1935] The mixture of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N* -methylazetidin-3-amine (200.0 mg, 0.60 mmol) and 4N HCl dioxane solution (10.0 mL) was stirred at room temperature for 12 hours. The formed solid was filtered and then dried to obtain white solid compound of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine hydrochloride (200.0 mg, 90%).

[1936]

[1937] LC/MS ESI (+): 334 (M+1), 336(M+3)

[1938] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 10.0 (s, 1H), 9.69 (bs, 2H), 9.00 (d, 1H, *J* =2.2Hz), 8.66 (d, 1H, *J*=2.2Hz), 5.20~4.80 (m, 2H), 4.70~4.40 (m, 2H), 4.20 (m, 1H), 2.64(m, 3H)

[1939]

[1940] **Example 69**

[1941] **Synthesis of 1-(8-bromopyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)- *N* -methylazetidin-3-amine hydrochloride**

[1942]

[1943] Suspension of 1-(8-bromopyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (190.0 mg, 0.57 mmol) and 4N HCl dioxane solution (5.0 mL) was stirred at room temperature for 8 hours. Et_2O was added thereto to form a solid, and the formed solid was filtered and dried under reduced pressure to obtain yellow solid compound of 1-(8-bromopyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine hydrochloride (210.0 mg, 99%).

[1944]

[1945] LC/MS ESI(+): 335 (M+1), 337 (M+3)

[1946] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 9.77 (bs, 2H), 9.00 (d, 1H, *J*=2.4 Hz), 8.88 (d, 1H, *J*=2.4 Hz), 5.10-4.90 (m, 2H), 4.75-4.45 (m, 2H), 4.31 (m, 1H), 2.66 (s, 3H)

[1947]

[1948] **Example 70**

[1949] **Synthesis of 8-chloro-4-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1*H*)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[1950]

[1951] (a) Synthesis of 2,7-dichloro-3-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1*H*)-yl)pyrido[2,3-b]pyrazine

[1952] 2,3,7-Trichloropyrido[2,3-b]pyrazine (100.0 mg, 0.43 mmol) and TEA (0.6 mL, 4.26 mmol) were dissolved in DCM (3.0 mL), and 2-methyloctahydropyrrolo[3,4-c]pyrrole (59.1 mg, 0.47 mmol) dilutied in DCM (1.0 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 12 hours, then concentrated and purified by column chromatography (MeOH:DCM=5:95) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 2,7-dichloro-3-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1*H*)-yl)pyrido[2,3-b]pyrazine (72.0 mg, 52%).

[1953]

[1954] LC/MS ESI (+): 324 (M+1), 326 (M+3)

[1955]

[1956] (b) Synthesis of 7-chloro-2-hydrazinyl-3-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1*H*)-yl)pyrido[2,3-b]pyrazine

[1957] 2,7-Dichloro-3-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1*H*)-yl)pyrido[2,3-b]pyrazine (72.0 mg, 0.22 mmol) and hydrazine monohydrate (32.0 μL, 0.67 mmol) were dissolved in EtOH (3.0 mL). The mixture was stirred at room temperature for 12 hours and a solid was formed. The formed solid was filtered to obtain yellow solid compound of 7-chloro-2-hydrazinyl-3-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1*H*)-yl)pyrido[2,3-b]pyrazine (71.0 mg, 100%).

[1958]

[1959] LC/MS ESI(+): 320 (M+1), 322 (M+3)

[1960]

[1961] (c) Synthesis of 8-chloro-4-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1 *H*)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[1962] The mixture of 7-chloro-2-hydrazinyl-3-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-yl)pyrido[2,3-b]pyrazine (71.0 mg, 0.22 mmol) and trimethyl orthoformate (3.0 mL) was stirred at 80℃ for 3 hours and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and dried under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=5:95) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 8-chloro-4-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1*H*)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (20.0 mg, 27%).

[1963]

[1964] LC/MS ESI(+): 330 (M+1), 332 (M+3)

[1965] ^{1}H-NMR (300MHz, $CDCl_3$); δ: 9.14 (s, 1H), 8.58 (d, 1H, *J*=2.4Hz), 8.01 (d, 1H, *J*=2.4Hz), 4.70-4.58 (m, 2H), 4.23-4.02 (m, 2H), 3.14-3.03 (m, 2H), 2.71-2.65 (m, 4H), 2.34 (s, 3H)

[1966]

[1967] **Example 71**

[1968] **Synthesis of 8-bromo-4-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1 *H*)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[1969]

[1970] (a) Synthesis of 7-bromo-2-chloro-3-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1 *H*)-yl)pyrido[2,3-b]pyrazine

[1971] 7-Bromo-2,3-dichloropyrido[2,3-b]pyrazine (100.0 mg, 0.36 mmol) and TEA (0.5 mL, 3.58 mmol) were dissolved in DCM (3.0 mL), and 2-methyloctahydropyrrolo[3,4-c]pyrrole (49.6 mg, 0.39 mmol) diluted in DCM (1.0 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 12 hours, then concentrated and purified by column chromatography (MeOH:DCM=5:95) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 7-bromo-2-chloro-3-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1*H*)-yl)pyrido[2,3-b]pyrazine (63.0 mg, 48%).

[1972]

[1973] LC/MS ESI (+): 368 (M+1), 370 (M+3)

[1974]

[1975] (b) Synthesis of

7-bromo-2-hydrazinyl-3-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1 *H*)-yl)pyrido[2,3-b]pyrazine

[1976] 7-Bromo-2-chloro-3-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1*H*)-yl)pyrido[2,3-b]pyrazine (63.0 mg, 0.17 mmol) and hydrazine monohydrate (25.0 μL, 0.51 mmol) were dissolved in EtOH (3.0 mL). The mixture was stirred at room temperature for 12 hours to form a solid. The fomed solid was filtered to obtain yellow solid compound of 7-bromo-2-hydrazinyl-3-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1*H*)-yl)pyrido[2,3-b]pyrazine (62.0 mg, 100%).

[1977]

[1978] LC/MS ESI(+): 364 (M+1), 366 (M+3)

[1979]

[1980] (c) Synthesis of 8-bromo-4-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1 *H*)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[1981] The mixture of 7-bromo-2-hydrazinyl-3-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1*H*)-yl)pyrido[2,3-b]pyrazine (62.0 mg, 0.17 mmol) and trimethyl orthoformate (3.0 mL) was stirred at 90℃ for 6 hours and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and dried under reduced pressure. The residue was purified by column chromatography (EtOAc:*n*-Hex:MeOH=4:4:1) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 8-bromo-4-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1*H*)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (11.0 mg, 16%).

[1982]

[1983] LC/MS ESI(+): 374 (M+1), 376 (M+3)

[1984] ^{1}H-NMR (300MHz, $CDCl_3$); δ: 9.17 (s, 1H), 8.64 (d, 1H, *J*=2.1Hz), 8.14 (d, 1H, *J*=2.1Hz), 4.73-4.55 (m, 2H), 4.22-3.98 (m, 2H), 3.12-3.02 (m, 2H), 2.63 (m, 4H), 2.32 (s, 3H)

[1985]

[1986] **Example 72**

[1987] **Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-3-methylazetidin-3-amine**

[1988]

[1989] (a) Synthesis of *tert* -butyl (1-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)-3-methylazetidin-3-yl)carbamate

[1990] *tert*-Butyl (3-methylazetidin-3-yl)carbamate hydrochloride (43.0 mg, 0.23 mmol) and TEA (0.8 mL, 0.54 mmol) were added to the mixture of

7-bromo-2,3-dichloropyrido[2,3-b]pyrazine (50.0 mg, 0.18 mmol) and DCM (1.8 mL) at 0℃ and then stirred for one hour. The reaction mixture was concentrated under reduced pressure to obtain yellow solid compound of *tert*-butyl (1-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)-3-methylazetidin-3-yl)carbamate.

[1991]

[1992] LC/MS ESI(+): 428 (M+1), 430 (M+3)

[1993]

[1994] (b) Synthesis of *tert* -butyl (1-(7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)-3-methylazetidin-3-yl)carbamate

[1995] Hydrazine monohydrate (28.0 μL, 0.90 mmol) was added to the suspension of un-purified *tert*-butyl (1-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)-3-methylazetidin-3-yl)carbamate and EtOH (1.0 mL). The reaction mixture was stirred at room temperature for one hour and concentrated under reduced pressure to obtain yellow solid compound of *tert*-butyl (1-(7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)-3-methylazetidin-3-yl)carbamate.

[1996]

[1997] LC/MS ESI(+): 424 (M+1), 426 (M+3)

[1998]

[1999] (c) Synthesis of *tert* -butyl (1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-3-methylazetidin-3-yl)carbamate

[2000] Suspension of unpurified *tert*-butyl (1-(7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)-3-methylazetidin-3-yl)carbamate and trimethyl orthoformate (3.0 mL) was stirred at 90℃ for 3 hours and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered, and pressure was reduced to obtain pale brown solid compound of *tert*-butyl (1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-3-methylazetidin-3-yl)carbamate (25.0 mg, 32% in 3 steps).

[2001]

[2002] LC/MS ESI(+): 434 (M+1), 436 (M+3)

[2003]

[2004] (d) Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-3-methylazetidin-3-amine

[2005] *tert*-Butyl (1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-3-methylazetidin-3-yl)carbamate (25.0 mg, 0.06 mmol) was dissolved in DCM (0.6 mL), and TFA (0.4 mL) was added thereto. The reaction mixture was stirred at room temperature for one hour and then purified by column chromatography (MeOH:DCM=1:40) on amine silica. The

fractions containing the product were collected and evaporated to obtain brown solid compound of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-3-methylazetidin-3-amine (9.0 mg, 47%).

[2006]

[2007] LC/MS ESI(+): 334 (M+1), 336 (M+3)

[2008] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 9.95 (s, 1H), 8.90 (d, 1H, *J*=2.4 Hz), 8.59 (d, 1H, *J*=2.4 Hz), 4.58 (m, 1H), 4.47 (m, 1H), 4.15-3.95 (m, 2H), 2.40 (bs, 2H), 1.43 (s, 3H)

[2009]

[2010] **Example 73**

[2011] **Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*,3-dimethylazetidin-3-amine**

[2012]

[2013] (a) Synthesis of benzyl 3-((*tert*-butoxycarbonyl)amino)-3-methylazetidin-1-carboxylate

[2014] *tert*-Butyl (3-methylazetidin-3-yl)carbamate hydrochloride (400.0 mg, 1.80 mmol) was dissolved in DCM (9.0 mL), and benzyl chloroformate (0.8 mL, 5.39 mmol) and TEA (1.3 mL, 9.00 mmol) were added thereto at 0℃. The reaction mixture was allowed to react at room temperature for 12 hours and then purified by column chromatography (EtOAc:*n*-Hex=1:4) on silica. The fractions containing the product were collected and evaporated to obtain white solid compound of benzyl 3-((*tert*-butoxycarbonyl)amino)-3-methylazetidin-1-carboxylate (680.0 mg, 99%).

[2015]

[2016] LC/MS ESI(+): 321 (M+1)

[2017] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 7.38-7.30 (m, 5H), 5.10 (s, 2H), 4.76 (bs, 1H), 4.20-4.10 (m, 2H), 3.90-3.75 (m, 2H), 1.53 (s, 3H), 1.44 (m, 9H)

[2018]

[2019] (b) Synthesis of benzyl 3-((*tert*-butoxycarbonyl)(methyl)amino)-3-methylazetidin-1-carboxylate

[2020] Benzyl 3-((*tert*-butoxycarbonyl)amino)-3-methylazetidin-1-carboxylate (676.0 mg, 2.11 mmol) was dissolved in THF (21.0 mL), and NaH (110.0 mg, 2.74 mmol) was added thereto. The reaction mixture was stirred for 10 minutes, and MeI (0.2 mL, 3.17 mmol) was then added thereto, and stirred at room temperature for 12 hours and then allowed to react at 50℃ for 12 hours. The reaction mixture was cooled to room temperature and purified by column chromatography (EtOAc:*n*-Hex=1:7) on silica. The fractions containing the product were collected and evaporated to obtain sticky colorless liquid compound of benzyl 3-((*tert*-butoxycarbonyl)(methyl)amino)-3-methylazetidin-1-carboxylate (180.0 mg, 26%).

[2021]

[2022] LC/MS ESI(+): 335 (M+1)

[2023] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 7.40-7.30 (m, 5H), 5.11 (s, 2H), 4.12-4.05 (m, 2H), 3.75-3.60 (m, 2H), 2.69 (s, 3H), 1.48 (s, 3H), 1.45 (m, 9H)

[2024]

[2025] (c) Sytnthesis of *tert* -butyl methyl(3-methylazetidin-3-yl)carbamate

[2026] Benzyl 3-((*tert*-butoxycarbonyl)(methyl)amino)-3-methylazetidin-1-carboxylate (180.0 mg, 0.54 mmol) was dissolved in MeOH (2.0 mL), and 10% of Pd/C (18.0 mg) was added thereto. The flask was substituted with hydrogen and stirred for 12 hours. The reaction mixture was filtered through celite and distilled under reduced pressure to obtain sticky colorless liquid compound of *tert*-butyl methyl(3-methylazetidin-3-yl)carbamate (50.0 mg, 46%).

[2027]

[2028] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 3.85-3.75 (m, 2H), 3.23-3.15 (m, 2H), 2.64 (s, 3H), 1.52 (s, 3H), 1.44 (m, 9H)

[2029]

[2030] (d) Synthesis of *tert* -butyl (1-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)-3-methylazetidin-3-yl)(methyl)carbamate

[2031] TEA (90.0 μL, 0.65 mmol) was added at 0℃ to a mixture of *tert*-butyl methyl(3-methylazetidin-3-yl)carbamate (47.0 mg, 0.24 mmol), 7-bromo-2,3-dichloropyrido[2,3-b]pyrazine (60.0 mg, 0.22 mmol) and DCM (2.2 mL), and it was stirred for one hour. The reaction mixture was purified by column chromatography (EtOAc:*n*-Hex=1:5) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of *tert*-butyl (1-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)-3-methylazetidin-3-yl)(methyl)carbamate (10.0 mg, 11%).

[2032]

[2033] LC/MS ESI(+): 442 (M+1), 444 (M+3)

[2034]

[2035] (e) Synthesis of *tert* -butyl (1-(7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)-3-methylazetidin-3-yl)(methyl)carbamate

[2036] *tert*-Butyl (1-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)-3-methylazetidin-3-yl)(methyl)carbamate (10.0 mg, 0.02mmol) was dissolved in EtOH (1.0 mL), and hydrazine monohydrate (3.5 μL, 0.11 mmol) was added thereto. The reaction mixture was stirred at room temperature for one hour and concentrated under reduced pressure to obtain

yellow solid compound of *tert*-butyl (1-(7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)-3-methylazetidin-3-yl)(methyl)carbamate.

[2037]

[2038] LC/MS ESI(+): 438 (M+1), 440 (M+3)

[2039]

[2040] (f) Synthesis of *tert* -butyl (1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-3-methylazetidin-3-yl)(methyl)carbamate

[2041] Unpurified *tert*-butyl (1-(7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)-3-methylazetidin-3-yl)(methyl)carbamate was dissolved in trimethyl orthoformate (1.0 mL), and it was stirred at 80°C for one hour. The reaction mixture was then cooled to room temperature and distilled under reduced pressure to obtain atypical yellow compound of *tert*-butyl (1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-3-methylazetidin-3-yl)(methyl)carbamate.

[2042]

[2043] LC/MS ESI(+): 448 (M+1), 450 (M+3)

[2044]

[2045] (g) Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)- *N* ,3-dimethylazetidin-3-amine

[2046] Unpurified *tert*-butyl (1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-3-methylazetidin-3-yl)(methyl)carbamate was dissolved in 4N HCl dioxane solution, and the reaction mixture was stirred at room temperature for one hour and distilled under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=1:60) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N* ,3-dimethylazetidin-3-amine (3.0 mg, 38% in 3 steps).

[2047]

[2048] LC/MS ESI(+): 348 (M+1), 350 (M+3)

[2049] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 9.95 (s, 1H), 8.90 (d, 1H, *J*=2.4 Hz), 8.59 (d, 1H, *J*=2.4 Hz), 4.60-4.40 (m, 2H), 4.18-3.96 (m, 2H), 2.27 (s, 3H), 1.41 (s, 3H)

[2050]

[2051] **Example 74**

[2052] **Synthesis of 8-bromo-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1 *H*)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[2053]

[2054] (a) Synthesis of 7-bromo-2-chloro-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1 *H*)-yl)pyrido[2,3-b]pyrazine

[2055] 7-Bromo-2,3-dichloropyrido[2,3-b]pyrazine (206.0 mg, 0.74 mmol) and octahydropyrrolo[1,2-a]pyrazine (102.0 mg, 0.81 mmol) were allowed to react in the same way as Example 24 (a) to obtain yellow solid compound of 7-bromo-2-chloro-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl)pyrido[2,3-b]pyrazine (180.0 mg, 66%).

[2056]

[2057] LC/MS ESI(+): 370 (M+1), 372 (M+3)

[2058] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 8.93 (d, 1H, *J*=2.4 Hz), 8.32 (d, 1H, *J*=2.4 Hz), 4.46 (m, 2H), 3.15 (m, 3H), 2.92 (m, 1H), 2.48 (m, 1H), 2.22 (m, 2H), 1.89 (m, 3H), 1.57 (m, 1H)

[2059]

[2060] (b) Synthesis of 8-bromo-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1 *H*)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[2061] 7-Bromo-2-chloro-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl)pyrido[2,3-b]pyrazine (100.0 mg, 0.36 mmol) and hydrazine monohydrate (0.028 mL, 0.90 mmol) were dissolved in EtOH (8.0 mL), and the mixture was stirred at 40℃ for 12 hours. Et_2 O/EtOH was added thereto to form a solid, and the formed solid was filtered and dried under reduced pressure to obtain yellow compound of 7-bromo-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl)-2-hydrazinylpyrido[2,3-b]pyrazine. The mixture of unpurified 7-bromo-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl)-2-hydrazinylpyrido[2,3-b]pyrazine (60.0 mg, 0.17 mmol) and trimethyl orthoformate (1.0 mL) was stirred at 80℃ for 1.5 hours and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and dried under reduced pressure to obtain brown solid compound of 8-bromo-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (35.0 mg, 26% in 2 steps).

[2062]

[2063] LC/MS ESI(+): 374 (M+1), 376 (M+3)

[2064] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 9.16 (s, 1H), 8.70 (d, 1H, *J*=2.1 Hz), 8.17 (d, 1H, *J* =2.1 Hz), 6.40 (m, 1H), 5.52 (m, 1H), 3.57 (m, 1H), 3.20 (m, 2H), 2.92 (m, 1H), 2.44 (m, 1H), 2.20 (m, 2H), 1.79 (m, 3H), 1.55 (m, 1H)

[2065]

[2066] **Example 75**

[2067] **Synthesis of 4-(hexahydropyrrolo[1,2-a]pyrazin-2(1 *H*)-yl)-8-iodopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[2068]

[2069] (a) Synthesis of 2-chloro-3-(hexahydropyrrolo[1,2-a]pyrazin-2(*1H*)-yl)-7-iodopyrido[2,3-b]pyrazine

[2070] 2,3-Dichloro-7-iodopyrido[2,3-b]pyrazine (50.0 mg, 0.15 mmol) and TEA (213.0 μL, 1.53 mmol) were dissolved in DCM (2.0 mL), and octahydropyrrolo[1,2-a]pyrazine (19.0 mg, 0.15 mmol) was added thereto at 0℃. The reaction mixture was stirred at 0℃ for one hour, then concentrated and purified by column chromatography (MeOH:DCM=3:97) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 2-chloro-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl)-7-iodopyrido[2,3-b]pyrazine (38.0 mg, 58%).

[2071]

[2072] LC/MS ESI (+): 416 (M+1), 418 (M+3)

[2073]

[2074] (b) Synthesis of 3-(hexahydropyrrolo[1,2-a]pyrazin-2(1 *H*)-yl)-2-hydrazinyl-7-iodopyrido[2,3-b]pyrazine

[2075] 2-Chloro-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl)-7-iodopyrido[2,3-b]pyrazine (38.0 mg, 0.09 mmol) and hydrazine monohydrate (6.7 μL, 0.14 mmol) were dissolved in EtOH (1.0 mL). The mixture was stirred at room temperature for 3 hours to form a solid, and the formed solid was filtered to obtain yellow solid compound of 3-(hexahydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl)-2-hydrazinyl-7-iodopyrido[2,3-b]pyrazin e (37.5 mg, 100%).

[2076]

[2077] LC/MS ESI(+): 412 (M+1)

[2078]

[2079] (c) Synthesis of 4-(hexahydropyrrolo[1,2-a]pyrazin-2(1 *H*)-yl)-8-iodopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[2080] The mixture of 3-(hexahydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl)-2-hydrazinyl-7-iodopyrido[2,3-b]pyrazine (39.4 mg, 0.10 mmol) and trimethyl orthoformate (2.0 mL) was stirred at 80℃ for 3 hours and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and dried under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=5:95) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 4-(hexahydropyrrolo[1,2-a]pyrazin-2(1 *H*)-yl)-8-iodopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (9.0 mg, 26%).

[2081]

[2082] LC/MS ESI(+): 422 (M+1)

[2083] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 10.01 (s, 1H), 9.01 (d, 1H, *J*=2.1Hz), 8.71 (d, 1H, *J*=2.1Hz), 6.18-5.25 (m, 1H), 3.42-3.35 (m, 1H), 3.28-3.24 (m, 1H), 3.20-3.15 (m,

1H), 3.08-2.87 (m, 2H), 2.25 (m, 1H), 2.15-2.03 (m, 2H), 1.88 (m, 1H), 1.81-1.68 (m, 2H), 1.45 (m. 1H)

[2084]

[2085] **Example 76**

[2086] **Synthesis of 8-chloro-4-(4-cyclopropylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[2087]

[2088] (a) Synthesis of 2,7-dichloro-3-(4-cyclopropylpiperazin-1-yl) pyrido[2,3-b]pyrazine

[2089] 2,3,7-Trichloropyrido[2,3-b]pyrazine (70.0 mg, 0.30 mmol) and 1-cyclopropylpiperazine (59.7 mg, 0.30 mmol) were allowed to react in the same way as Example 2 (c) to obtain yellow solid compound of 2,7-dichloro-3-(4-cyclopropylpiperazin-1-yl) pyrido[2,3-b]pyrazine (59.5 mg, 61%).

[2090]

[2091] LC/MS ESI(+): 324 (M+1), 326 (M+3)

[2092] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 8.93 (d, 1H, *J*=2.7 Hz), 8.50 (d, 1H, *J*=2.7 Hz), 3.59 (m, 4H), 2.74 (m, 4H), 1.71 (m, 1H), 0.45 (m, 2H), 0.39 (m, 2H)

[2093]

[2094] (b) Synthesis of 7-chloro-3-(4-cyclopropylpiperazin-1-yl)-2-hydrazinylpyrido[2,3-b]pyrazine

[2095] 2,7-Dichloro-3-(4-cyclopropylpiperazin-1-yl) pyrido[2,3-b]pyrazine (56.7 mg, 0.17 mmol) and hydrazine monohydrate (14.0 μL, 0.43 mmol) were allowed to react in the same way as Example 2 (d) to obtain orange solid compound of 7-chloro-3-(4-cyclopropylpiperazin-1-yl)-2-hydrazinylpyrido[2,3-b]pyrazine (50.0 mg, 100%).

[2096]

[2097] LC/MS ESI(+): 320 (M+1), 322 (M+3)

[2098]

[2099] (c) Synthesis of 8-chloro-4-(4-cyclopropylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[2100] 7-Chloro-3-(4-cyclopropylpiperazin-1-yl)-2-hydrazinylpyrido[2,3-b]pyrazine (64.0 mg, 0.14 mmol) and trimethyl orthoformate (2.0 mL) were allowed to react at 85℃ for 2 hours in the same way as Example 2 (e) to obtain ivory solid compound of 8-chloro-4-(4-cyclopropylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (40.6 mg, 62%).

[2101]

[2102] LC/MS ESI(+): 330 (M+1), 332 (M+3)

[2103] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 10.01 (s, 1H), 8.85 (d, 1H, *J*=2.7 Hz), 8.57 (d, 1H, *J*

=2.7 Hz), 4.80-3.93 (m, 4H), 2.73 (m, 4H), 1.68 (m, 1H), 0.46 (m, 2H), 0.40 (m, 2H)

[2104]

[2105] **Example 77**

[2106] **Synthesis of 4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[2107]

[2108] (a) Synthesis of (1S,4S)- *tert* -butyl 5-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-carboxylate

[2109] At 0℃, TEA (0.2 mL, 1.28 mmol) was added to a mixture of 2,3,7-trichloropyrido[2,3-b]pyrazine (100.0 mg, 0.43 mmol), (1S,4S)-*tert*-butyl 2,5-diazabicyclo[2.2.1]heptan-2-carboxylate (89.0 mg, 0.45 mmol) in DCM (4.3 mL), and then stirred for 3 hours. The reaction mixture was purified by column chromatography (EtOAc:*n*-Hex=1:5) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of (1S,4S)-*tert*-butyl 5-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-carboxylate (120.0 mg, 71%).

[2110]

[2111] LC/MS ESI(+): 396 (M+1), 398 (M+3)

[2112] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 8.79 (d, 1H, *J*=2.7 Hz), 8.11 (d, 1H, *J*=2.7 Hz), 5.30 (m, 1H), 4.78-4.55 (m, 1H), 4.20 (m, 1H), 3.95-3.63 (m, 2H), 3.53 (m, 1H), 1.99 (m, 2H), 1.56 (m, 9H)

[2113]

[2114] (b) Synthesis of (1S,4S)- *tert* -butyl 5-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-2,5-diazabicyclo[2.2.1]heptan-2-carboxylate

[2115] Hydrazine monohydrate (48.0 μL, 1.51 mmol) was added to suspension of (1S,4S)-*tert*-butyl 5-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)-2,5-diazabicyclo[2.2.1]heptan-2-carboxylate (120.0 mg, 0.30 mmol) and EtOH (1.5 mL). The reaction mixture was stirred at room temperature for one hour. Et_2O was then added thereto to form a solid, and the formed solid was filtered and dried under reduced pressure. Trimethyl orthoformate (3.0 mL) was added to the formed solid. The mixture was stirred at 85℃ for one hour and then cooled to room temperature. Et_2O was added thereto to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain yellow solid compound of (1S,4S)-*tert*-butyl 5-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-2,5-diazabicyclo[2.2.1]heptan-2-carboxylate (91.0 mg, 83%).

[2116]

[2117] LC/MS ESI(+): 402 (M+1), 404 (M+3)

[2118] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 9.98 (m, 1H), 8.83 (m, 1H), 8.56 (m, 1H), 6.27 (s, 0.7H), 5.27 (s, 0.3H), 4.57 (m, 1H), 4.24 (m, 0.7H), 3.80 (m, 1H), 3.50 (m, 1H), 3.40 (m, 1.3H), 2.20-1.98 (m, 2H), 1.38-1.49 (m, 9H)

[2119]

[2120] (c) Synthesis of 4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[2121] TFA (0.8 mL) was added to the mixture of (1S,4S)-*tert*-butyl 5-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-2,5-diazabicyclo[2.2.1]heptan-2-carboxylate (90.0 mg, 0.22 mmol) and DCM (1.2 mL), and it was then stirred at room temperature for one hour. The reaction mixture was purified by column chromatography (MeOH:DCM=1:60) on amine silica. The fractions containing the product were collected and evaporated. Et_2O was added to the residue to form a solid, and the formed solid was filtered and dried under reduced pressure to obtain ivory solid compound of 4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (58.0 mg, 85%).

[2122]

[2123] LC/MS ESI(+): 302 (M+1), 304 (M+3)

[2124] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 9.96 (m, 1H), 8.79 (m, 1H), 8.52 (s, 1H), 6.19 (s, 0.7H), 5.17 (s, 0.3H), 4.16 (s, 0.7H), 3.78 (s, 1H), 3.70 (m, 1.3H), 3.12-2.80 (m, 2H), 1.95-1.70 (m, 2H)

[2125]

[2126] **Example 78**

[2127] **Synthesis of 8-chloro-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[2128]

[2129] 37% of formaldehyde (28.0 μL, 0.38 mmol) and $NaBH_4$ (14.0 mg, 0.38 mmol) were added to suspension of 4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (38.0 mg, 0.13 mmol) and MeOH (1.3 mL). The reaction mixture was stirred at room temperature for one hour and then distilled under reduced pressure. EtOAc and water were added to the residue, and it was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography

(MeOH:DCM=1:60) on amine silica. The fractions containing the product were collected and evaporated, and then DCM/Et_2O was added thereto to form a solid. The formed solid was filtered and then dried under reduced pressure to obtain ivory solid compound of 8-chloro-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (20.0 mg, 50%).

[2130]

[2131] LC/MS ESI(+): 316 (M+1), 318 (M+3)

[2132] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 9.96 (m, 1H), 8.79 (m, 1H), 8.53 (m, 1H), 6.13 (s, 0.7H), 5.13 (s, 0.3H), 4.40 (m, 0.3H), 4.04 (m, 0.3H), 3.88 (m, 0.7H), 3.60 (m, 1.7H), 2.97 (m, 1H), 2.64 (m, 1H), 2.36 (s, 3H), 2.08-1.80 (m, 2H)

[2133]

[2134] **Example 79**

[2135] **Synthesis of 8-chloro-4-(1,4-diazepan-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[2136]

[2137] (a) Synthesis of *tert* -butyl 4-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)-1,4-diazepan-1-carboxylate

[2138] 2,3,7-Trichloropyrido[2,3-b]pyrazine (70.0 mg, 0.30 mmol) was dissolved in DCM (3.0 mL), and then *tert*-butyl 1,4-diazepan-1-carboxylate (60.0 μL, 0.30 mmol) and TEA (135.0 μL, 0.90 mmol) were added thereto at 0℃. The reaction mixture was stirred at room temperature for 2 hours and then diluted with DCM. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered and then concentrated under reduced pressure. The residue was purified by column chromatography (*n*-Hex:EtOAc=3:1) on amine silica. The fractions containing the product were collected and concentrated to obtain yellow liquid compound of *tert*-butyl 4-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)-1,4-diazepan-1-carboxylate (85.0 mg, 71%).

[2139]

[2140] LC/MS ESI(+): 398(M+1), 400(M+3)

[2141] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 8.82(d, 1H, *J*=2.67Hz), 8.12(d, 1H, *J*=2.67Hz), 4.15-3.92(m, 4H), 3.78-3.70(m, 2H), 3.57-3.38(m, 2H), 2.18-2.06(m, 2H), 1.41(s, 9H)

[2142]

[2143] (b) Synthesis of *tert* -butyl 4-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)-1,4-diazepan-1-carboxylate

[2144] Hydrazine monohydrate (6.5 μL, 0.60 mmol) was added to the mixture of *tert*-butyl 4-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)-1,4-diazepan-1-carboxylate (82.0 mg, 0.20 mmol) and EtOH (2.0 mL), and then stirred at room temperature for 3 hours. The reaction mixture was diluted in Et_2O, and it was then stirred at room temperature for

one hour. The formed solid was filtered and dried under reduced pressure to obtain yellow solid compound of *tert*-butyl 4-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)-1,4-diazepan-1-carboxylate.

[2145]

[2146] LC/MS ESI(+): 394(M+1), 396(M+3)

[2147]

[2148] (c) Synthesis of 8-chloro-4-(1,4-diazepan-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[2149] The mixture of unpurified *tert*-butyl 4-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)-1,4-diazepan-1-carboxylate and trimethyl orthoformate (1.1 mL) was stirred at 80°C for 2 hours and then cooled to room temperature. The reaction mixture was concentrated under reduced pressure. Unpurified *tert*-butyl 4-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-1,4-diazepan-1-carboxylate was dissolved in DCM (1.0 mL), and TFA (0.5 mL) was slowly added thereto at room temperature, and it was then stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=10:1) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 8-chloro-4-(1,4-diazepan-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (28.0 mg, 35% in 3 steps).

[2150]

[2151] LC/MS ESI(+): 304(M+1), 306(M+3)

[2152] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 9.14(s, 1H), 8.60(d, 1H, *J*=2.3 Hz), 8.01(d, 1H, *J*=2.3 Hz), 4.84-4.72(m, 2H), 4.28-4.17(m, 2H), 3.21(t, 2H, *J*=5.7 Hz), 2.94(t, 2H, *J*=5.7 Hz), 2.12-2.02(m, 2H)

[2153]

[2154] **Example 80**

[2155] **Synthesis of 8-chloro-4-(4-methyl-1,4-diazepan-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[2156]

[2157] (a) Synthesis of 2,7-dichloro-3-(4-methyl-1,4-diazepan-1-yl)pyrido[2,3-b]pyrazine

[2158] 2,3,7-Trichloropyrido[2,3-b]pyrazine (50.0 mg, 0.21 mmol) was dissolved in DCM (2.0 mL), and 1-methyl-1,4-diazepane (26.1 μL, 0.21 mmol) and TEA (94.7 μL, 0.63 mmol) were then added thereto at 0°C. The reaction mixture was stirred at room temperature for 2 hours and then diluted in DCM. The organic layer was washed with water and brine, dried anhydrous $MgSO_4$, filtered and then concentrated under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=10:1) on

amine silica. The fractions containing the product were collected and concentrated to obtain brown solid compound of 2,7-dichloro-3-(4-methyl-1,4-diazepan-1-yl)pyrido[2,3-b]pyrazine (42.0 mg, 64%).

[2159]

[2160] LC/MS ESI(+): 312(M+1), 314(M+3)

[2161] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 8.80(d, 1H, J=2.6 Hz), 8.11(d, 1H, J=2.6 Hz), 4.09-4.03(m, 2H), 4.01-3.95(m, 2H), 3.02-2.93(m, 2H), 2.78-2.69(m, 2H), 2.46(s, 3H), 2.25-2.13(m, 2H)

[2162]

[2163] (b) Synthesis of 7-chloro-2-hydrazinyl-3-(4-methyl-1,4-diazepan-1-yl)pyrido[2,3-b]pyrazine

[2164] Hydrazine monohydrate (3.9 μL, 0.36 mmol) was added to the mixture of 2,7-dichloro-3-(4-methyl-1,4-diazepan-1-yl)pyrido[2,3-b]pyrazine (38.5 mg, 0.12 mmol) and EtOH (1.2 mL), and it was then stirred at room temperature for 2 hours. The reaction mixture was diluted in Et_2O, and it was then stirred at room temperature for one hour. The formed solid was filtered and dried under reduced pressure to obtain unpurified yellow solid compound of 7-chloro-2-hydrazinyl-3-(4-methyl-1,4-diazepan-1-yl)pyrido[2,3-b]pyrazine.

[2165]

[2166] LC/MS ESI(+): 308(M+1), 310(M+3)

[2167]

[2168] (c) Synthesis of 8-chloro-4-(4-methyl-1,4-diazepan-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[2169] The mixture of unpurified 7-chloro-2-hydrazinyl-3-(4-methyl-1,4-diazepan-1-yl)pyrido[2,3-b]pyrazine and trimethyl orthoformate (0.7 mL) was stirred at 80℃ for 2 hours and then cooled to room temperature. The reaction mixture was concentrated under reduced pressure and then purified by column chromatography (DCM:MeOH=20:1) on amine silica. The fractions containing the product were collected and concentrated to obtain yellow solid compound of 8-chloro-4-(4-methyl-1,4-diazepan-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (16.0 mg, 42% in 2 steps).

[2170]

[2171] LC/MS ESI(+): 318(M+1), 320(M+3)

[2172] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 9.14(s, 1H), 8.59(d, 1H, *J*=2.3 Hz), 8.01(d, 1H, *J*=2.3 Hz), 4.87-4.74(m, 2H), 4.18-4.14(m, 2H), 2.92-2.86(m, 2H), 2.67-2.60(m, 2H), 2.39(s, 3H), 2.21-2.09(m, 2H)

[2173]

[2174] **Example 81**

[2175] **Synthesis of (R)-1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylpyrrolidin-3-amine**

[2176]

[2177] (a) Synthesis of (R)-*tert*-butyl (1-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)pyrrolidin-3-yl)(methyl)carbamate

[2178] 7-Bromo-2,3-dichloropyrido[2,3-b]pyrazine (70.0 mg, 0.25 mmol) and TEA (175.0 μL, 1.26 mmol) were dissolved in DCM (1.0 mL), and (R)-*tert*-butyl methyl(pyrrolidin-3-yl)carbamate (55.2 mg, 0.28 mmol) dissolved in DCM (0.5 mL) was added thereto at 0℃. The reaction mixture was stirred at 0℃ for 12 hours and then concentrated to obtain (R)-*tert*-butyl (1-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)pyrrolidin-3-yl)(methyl)carbamate (111.1 mg, 100%).

[2179]

[2180] LC/MS ESI (+): 442 (M+1), 444 (M+3)

[2181]

[2182] (b) Synthesis of (R)-*tert*-butyl (1-(7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)pyrrolidin-3-yl)(methyl)carbamate

[2183] (R)-*tert*-Butyl (1-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)pyrrolidin-3-yl)(methyl)carbamate (111.1 mg, 0.25 mmol) and hydrazine monohydrate (25.0 μL, 0.50 mmol) were dissolved in EtOH (1.5 mL). The mixture was stirred at room temperature for 3 hours to form a solid, and the formed solid was filtered to obtain yellow solid compound of (R)-*tert*-butyl (1-(7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)pyrrolidin-3-yl)(methyl)carbamate (110.0 mg, 100%).

[2184]

[2185] LC/MS ESI(+):438 (M+1), 440 (M+3)

[2186]

[2187] (c) Synthesis of (R)-*tert*-butyl (1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate

[2188] The mixture of (R)-*tert*-butyl (1-(7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)pyrrolidin-3-yl)(methyl)carbamate (110.0 mg, 0.25 mmol) and trimethyl orthoformate (1.0 mL) was stirred at 80℃ for 2 hours and then cooled to room temperature. The reaction mixture was concentrated and then firstly purified by column chromatography (MeOH:DCM=5:95) on silica, and secondly purified by column chromatography (EtOAc:*n*-Hex=50:50) on amine silica.

The fractions containing the product were collected and evaporated to obtain yellow solid compound of (R)-*tert*-butyl (1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (40.0 mg, 36%).

[2189]

[2190] LC/MS ESI(+): 448 (M+1), 450 (M+3)

[2191]

[2192] (d) Synthesis of (R)-1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylpyrrolidin-3-amine

[2193] (R)-*tert*-butyl (1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)pyrrolidin-3-yl)(methyl)carbamate (40.0 mg, 0.09 mmol) was dissolved in DCM (1.0 mL), and TFA (0.4 mL) was added thereto. The reaction mixture was stirred at room temperature for one hour and then purified by column chromatography (MeOH:DCM=5:95) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of (R)-1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylpyrrolidin-3-amine (20.7 mg, 67%).

[2194]

[2195] LC/MS ESI(+): 348 (M+1), 350 (M+3)

[2196] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.98 (s, 1H), 8.89 (d, 1H, *J*=2.1Hz), 8.57 (d, 1H, *J*=2.1Hz), 4.36-4.20 (m, 2H), 3.81-3.61 (m, 2H), 3.30 (m, 1H), 2.32 (s, 3H), 2.11-1.86 (m, 3H)

[2197]

[2198] **Example 82**

[2199] **Synthesis of 8-chloro-4-(hexahydro-1*H*-pyrrolo[3,4-b]pyridin-6(2*H*)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[2200]

[2201] (a) Synthesis of *tert*-butyl 6-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)octahydro-1*H*-pyrrolo[3,4-b]pyridin-1-carboxylate

[2202] 2,3,7-Trichloropyrido[2,3-b]pyrazine (150.0 mg, 0.64 mmol) was dissolved in DCM (6.0 mL). *tert*-Butyl octahydro-1H-pyrrolo[3,4-b]pyridin-1-carboxylate (151.0 mg, 0.67 mmol) and TEA (288.0 μL, 1.92 mmol) were then added to the mixture at 0°C. The reaction mixture was stirred at room temperature for 2 hours and then diluted in DCM. The organic layer was washed water and brine, dried over anhydrous $MgSO_4$, filtered and then concentrated under reduced pressure. The residue was purified by column chromatography (*n*-Hex:EtOAc=3:1) on amine silica. The fractions containing the product were collected and concentrated to obtain ivory solid compound of *tert*-butyl

6-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)octahydro-1H-pyrrolo[3,4-b]pyridin-1-carboxylate (173.0 mg, 61%).

[2203]

[2204] LC/MS ESI(+): 424(M+1), 426(M+3)

[2205] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 8.81(d, 1H, *J*=2.7 Hz), 8.38(d, 1H, *J*=2.7 Hz), 4.69(m, 1H), 4.00-3.80(m, 4H), 3.70(m, 1H), 2.85(m, 1H), 2.26(m, 1H), 1.77-1.61(m, 2H), 1.42(s, 9H), 1.38-1.26(m, 2H)

[2206]

[2207] (b) Synthesis of *tert* -butyl 6-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)octahydro-1 *H* -pyrrolo[3,4-b]pyridin-1-carboxylate

[2208] Hydrazine monohydrate (37.7 μL, 1.20 mmol) was added to the mixture of *tert*-butyl 6-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)octahydro-1*H*-pyrrolo[3,4-b]pyridin-1-carboxylate (170.0 mg, 0.40 mmol) and EtOH (4.0 mL), and it was then stirred at room temperature for 3 hours. The reaction mixture was diluted in Et_2O and stirred at room temperature for one hour to form a solid. The formed solid was filtered and then dried under reduced pressure to obtain yellow solid compound of *tert*-butyl 6-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)octahydro-1*H*-pyrrolo[3,4-b]pyridin-1-carboxylate.

[2209]

[2210] LC/MS ESI(+): 420(M+1), 422(M+3)

[2211]

[2212] (c) Synthesis of *tert* -butyl 6-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)octahydro-1 *H* -pyrrolo[3,4-b]pyridin-1-carboxylate

[2213] The mixture of unpurified *tert*-butyl 6-(7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)octahydro-1*H*-pyrrolo[3,4-b]pyridin-1-carboxylate and trimethyl orthoformate (4.0 mL) was stirred at 80℃ for 2 hours and then cooled to room temperature. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (*n*-Hex:EtOAc=3:1) on amine silica. The fractions containing the product were collected and concentrated to obtain yellow solid compound of *tert*-butyl 6-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)octahydro-1*H*-pyrrolo[3,4-b]pyridin-1-carboxylate (79.0 mg, 46% in 2 steps).

[2214]

[2215] LC/MS ESI(+): 430(M+1), 432(M+3)

[2216] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 9.16(s, 1H), 8.59(d, 1H, *J*=2.3 Hz), 8.03(d, 1H, *J*=2.3 Hz), 4.91(m, 1H), 4.75(m, 1H), 4.35-4.00(m, 3H), 3.94-3.71(m, 1H), 2.81(m,

1H), 2.37(m, 1H), 1.91-1.68(m, 2H), 1.62-1.31(m, 11H)

[2217]

[2218] (d) Synthesis of 8-chloro-4-(hexahydro-1 *H* -pyrrolo[3,4-b]pyridin-6(2 *H*)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[2219] *tert*-Butyl 6-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)octahydro-1*H* -pyrrolo[3,4-b]pyridin-1-carboxylate (76.0 mg, 0.17 mmol) was dissolved in DCM (2.0 mL), and TFA (126.0 μL, 1.70 mmol) was slowly added thereto at room temperature. The mixture was stirred at room temperature for 8 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=10:1) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 8-chloro-4-(hexahydro-1*H*-pyrrolo[3,4-b]pyridin-6(2*H*)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (51.0 mg, 91%).

[2220]

[2221] LC/MS ESI(+): 330(M+1), 332(M+3)

[2222] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 9.95(s, 1H), 8.77(d, 1H, *J*=2.7 Hz), 8.50(d, 1H, *J*=2.7 Hz), 4.53-4.41(m, 1H), 4.27-4.10(m, 1H), 3.84-3.64(m, 2H), 3.42-3.31(m, 1H), 2.89-2.79(m, 1H), 2.58-2.51(m, 1H), 2.44-2.26(m, 2H), 1.84-1.35(m, 4H)

[2223]

[2224] **Example 83**

[2225] **Synthesis of 8-chloro-4-(1-methylhexahydro-1 *H* -pyrrolo[3,4-b]pyridin-6(2 *H*)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[2226]

[2227] 8-Chloro-4-(hexahydro-1*H*-pyrrolo[3,4-b]pyridin-6(2*H*)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (35.0 mg, 0.10 mmol) was dissolved in MeOH (0.7 mL), and 37% of formaldehyde (40.5 mg, 0.50 mmol) dissolved in MeOH (0.3 mL) was added thereto at 0℃, and $NaBH_4$ (18.9 mg, 0.50 mmol) was then added thereto. The mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted in EtOAc. The organic layer was then washed with water and brine, dried over anhydrous $MgSO_4$, filtered and then concentrated under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=20:1) on amine silica. The fractions containing the product were collected and concentrated to obtain brown solid compound of 8-chloro-4-(1-methylhexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (7.4 mg, 22%).

[2228]

[2229] LC/MS ESI(+): 344(M+1), 346(M+3)

[2230] ^{1}H-NMR (300 MHz, $CDCl_3$); δ: 9.15(s, 1H), 8.58(d, 1H, *J*=2.3 Hz), 8.02(d, 1H, *J*=2.3 Hz), 5.06(m, 0.4H), 4.69-4.60(m, 0.6H), 4.51-4.39(m, 1H), 4.19(m, 0.4H),

4.03(m, 1H), 3.80(m, 0.6H), 2.89-2.75(m, 2H), 2.67-2.47(m, 1H), 2.34(s, 3H), 2.18(m, 1H), 1.95-1.55(m, 4H)

[2231]

[2232] **Example 84**

[2233] **Synthesis of 1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*,*N*-dimethylazetidin-3-amine**

[2234]

[2235] $NaBH_4$ (29.0 mg, 0.77 mmol) was added to suspension of 1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (74.0 mg, 0.26 mmol), 37% of formaldehyde (29.0 μL, 0.38 mmol) and MeOH (2.5 mL). The reaction mixture was stirred at room temperature for 5 hours, and EtOAc and water were added thereto, and it was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=1:100) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*,*N*-dimethylazetidin-3-amine (12.0 mg, 16%).

[2236]

[2237] LC/MS ESI(+): 304 (M+1), 306 (M+3)

[2238] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 9.95 (s, 1H), 8.81 (d, 1H, *J*=2.4 Hz), 8.54 (d, 1H, *J*=2.4 Hz), 4.81 (m, 1H), 4.53 (m, 1H), 4.34. (m, 1H), 4.11 (m, 1H), 3.35 (m, 1H), 2.18 (s, 6H)

[2239]

[2240] **Example 85**

[2241] **Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*,*N*-dimethylazetidin-3-amine**

[2242]

[2243] $NaBH_4$ (11.0 mg, 0.29 mmol) was added to suspension of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (32.0 mg, 0.10 mmol), 37% of formaldehyde (11.0 μL, 0.14 mmol) and MeOH (1.0 mL). The reaction mixture was stirred at room temperature for 5 hours, and EtOAc and water were then added thereto, and it was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=1:100) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*,*N*-dimethylazetidin-3-am

ine (3.0 mg, 9%).

[2244]

[2245] LC/MS ESI(+): 348 (M+1), 350 (M+3)

[2246] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 9.95 (s, 1H), 8.90 (d, 1H, *J*=2.4 Hz), 8.60 (d, 1H, *J*=2.4 Hz), 4.81 (m, 1H), 4.51 (m, 1H), 4.31 (m, 1H), 4.10 (m, 1H), 3.40 (m, 1H), 2.18 (s, 6H)

[2247]

[2248] **Example 86**

[2249] **Synthesis of (1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamic acid**

[2250]

[2251] 1-(8-Bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine obtained from *tert*-butyl (1-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (13000.0 mg, 30.3 mmol) in the same way as Example 3 (e) to (f) was purified by column chromatography (DCM:MeOH=90:10) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of (1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamic acid (56.0 mg, 0.5%).

[2252]

[2253] LC/MS ESI (+): 378 (M+1), 380 (M+3)

[2254] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.97 (s, 1H), 9.03 (bs, 1H), 8.95 (d, 1H, *J*=2.2Hz), 8.65 (d, 1H, *J*=2.2Hz), 4.40~4.30 (m, 2H), 4.10~4.00 (m, 1H), 3.90~3.80 (m, 2H), 2.89(m, 3H)

[2255]

[2256] **Example 87**

[2257] **Synthesis of 2-((8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)amino)ethanol**

[2258]

[2259] (a) Sythesis of 2-((2,7-dichloropyrido[2,3-b]pyrazin-3-yl)amino)ethanol

[2260] 2,3,7-Trichloropyrido[2,3-b]pyrazine (500.0 mg, 2.14 mmol) was dissolved in DCM (20.0 mL), and ethanolamine (135.0 μL, 2.25 mmol) and TEA (965.0 μL, 6.42 mmol) were added thereto at 0℃. The reaction mixture was stirred at room temperature for 2 hours, diluted in DCM and then stirred at room temperature for one hour. The formed solid was filtered and dried under reduced pressure to obtain unpurified brown solid compound of 2-((2,7-dichloropyrido[2,3-b]pyrazin-3-yl)amino)ethanol.

[2261]

[2262] LC/MS ESI(+): 259 (M+1), 261 (M+3)

[2263]

[2264] (b) Synthesis of 2-((7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)amino)ethanol

[2265] Hydrazine monohydrate (276.0 μL, 8.79 mmol) was added to the mixture of unpurified 2-((2,7-dichloropyrido[2,3-b]pyrazin-3-yl)amino)ethanol and EtOH (30.0 mL), and it was then stirred at room temperature for 4 hours. The reaction mixture was diluted in Et_2O and then stirred at room temperature for one hour. The formed solid was filtered and then dried under reduced pressure to obtain unpurified brown solid compound of 2-((7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)amino)ethanol.

[2266]

[2267] LC/MS ESI(+): 255 (M+1), 257 (M+3)

[2268]

[2269] (c) Synthesis of 2-((8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)amino)ethanol

[2270] The mixture of unpurified 2-((7-chloro-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)amino)ethanol and trimethyl orthoformate (16.0 mL) was stirred at 80℃ for 4 hours and then cooled to room temperature. The reaction mixture was concentrated under reduced pressure and then dissolved in MeOH. EtOAc was added to the mixture and the mixture was diluted. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. EtOAc (20.0 mL) was added to the residue, and it was stirred for one hour. The formed solid was filtered and dried under reduced pressure to obtain white solid compound of 2-((8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)amino)ethanol (82.0 mg, 14% in 3 steps).

[2271]

[2272] LC/MS ESI(+): 265 (M+1), 267 (M+3)

[2273] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 9.93(s, 1H), 8.82(d, 1H, J=2.7 Hz), 8.64-8.58(brs, 1H), 8.55(d, 1H, J=2.7 Hz), 4.84(m, 1H), 3.70-3.64(m, 4H)

[2274]

[2275] **Example 88**

[2276] **Synthesis of 1-(8-chloroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-N-methylazetidin-3-amine**

[2277]

[2278] (a) Synthesis of *tert* -butyl (1-(7-chloro-2-((2,2-diethoxyethyl)amino)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[2279] *tert*-Butyl (1-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (180.0 mg, 0.47 mmol) was dissolved in 2,2-diethoxyethanamine (2.0 mL), stirred at room temperature for 12 hours, and EtOAc solvent was added thereto. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure to obtain yellow solid compound of *tert*-butyl (1-(7-chloro-2-((2,2-diethoxyethyl)amino)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate.

[2280]

[2281] (b) Synthesis of 1-(8-chloroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine

[2282] Unpurified *tert*-butyl (1-(7-chloro-2-((2,2-diethoxyethyl)amino)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (225.1 mg, 0.47 mmol) and 4-methylbenzene sulfonic acid (1160.0 mg, 6.08 mmol) were dissolved in IPA (3.0 mL), stirred at 100℃ for 2 hours and then cooled to room temperature. Water was added to the reaction mixture. The resulting solution was alkalized with saturated $NaHCO_3$ aqueous solution (pH=9) and then extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=5:95) on silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 1-(8-chloroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine (70.0 mg, 52%).

[2283]

[2284] LC/MS ESI (+): 289 (M+1), 291 (M+3)

[2285] ^{1}H-NMR (300MHz, $CDCl_3$); δ: 8.53 (m, 1H), 7.94-7.89 (m, 2H), 7.66 (m, 1H), 5.12-4.13 (m, 4H), 3.83 (m, 1H), 2.49 (s, 3H)

[2286]

[2287] **Example 89**

[2288] **Synthesis of 1-(8-bromoimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine**

[2289]

[2290] (a) Synthesis of *tert*-butyl (1-(7-bromo-2-((2,2-diethoxyethyl)amino)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[2291] *tert*-Butyl (1-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[2292] (177.0 mg, 0.41 mmol) was dissolved in 2,2-diethoxyethanamine (2.0 mL), and the mixture was stirred at room temperature for 12 hours. EtOAc solvent was then added

to the reaction mixture, and it was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure to obtain yellow solid compound of *tert*-butyl (1-(7-bromo-2-((2,2-diethoxyethyl)amino)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate.

[2293]

[2294] (b) Synthesis of 1-(8-bromoimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine

[2295] Unpurified *tert*-butyl (1-(7-bromo-2-((2,2-diethoxyethyl)amino)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (215.0 mg, 0.41 mmol) and 4-methylbenzene sulfonic acid (1020.0 mg, 5.36 mmol) were dissolved in IPA (3.0 mL), and the mixture was stirred at 100℃ for 2 hours and then cooled to room temperature. Water was added to the reaction mixture, and it was alkalized with saturated $NaHCO_3$ aqueous solution (pH=9) and then extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4, filtered and distilled under reduced pressure, and then purified by column chromatography (MeOH:DCM=5:95) on silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of 1-(8-bromoimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine (65.0 mg, 47%).

[2296]

[2297] LC/MS ESI (+): 333 (M+1), 335 (M+3)

[2298] ^{1}H-NMR (300MHz, $CDCl_3$); δ: 8.60 (d, 1H, *J*=2.1Hz), 8.06 (d, 1H, *J*=2.1Hz), 7.89 (d, 1H, *J*=1.5Hz), 7.65 (d, 1H, *J*=1.5Hz), 5.08-4.20 (m, 4H), 3.82 (m, 1H), 2.48 (s, 3H)

[2299]

[2300] **Example 90**

[2301] **Synthesis of *tert*-butyl (1-(8-chloro-2-methyloxazolo[4,5-c][1,8]naphthylidine-4-yl)azetidin-3-yl)(methyl)carbamate**

[2302]

[2303] (a) Synthesis of methyl 2,5-dichloronicotinate

[2304] 2,5-Dichloronicotine acid (2150.0 mg, 11.20 mmol) was dissolved in mixture solution of DCM (10.0 mL) and MeOH (5.0 mL), and trimethylsilyldiazomethane (2.0M in hexane) (11.2 mL, 22.40 mmol) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for one hour and then distilled under reduced pressure. The residue was purified by column chromatography (EtOAc:*n*-Hex=1:9) on silica. The fractions containing the product were collected and evaporated to obtain white solid compound of methyl 2,5-dichloronicotinate (2020.0 mg, 87%).

[2305]

[2306] LC/MS ESI (+): 206 (M+1)

[2307] ^{1}H-NMR (300MHz, $CDCl_3$); δ: 8.48(d, 1H, *J*=2.6Hz), 8.16(d, 1H, *J*=2.6Hz), 3.98 (s, 3H)

[2308]

[2309] (b) Synthesis of methyl 5-chloro-2-((4-methoxybenzyl)amino)nicotinate

[2310] EtOH (30.0 mL) was added to methyl 2,5-dichloronicotinate (2020.0 mg, 9.79 mmol), and then 4-methoxybenzylamine (2.6 mL, 19.60 mmol) was added thereto. The mixture was stirred at 65℃ for 12 hours and then cooled to room temperature. The reaction mixture was distilled under reduced pressure and the residue was purified by column chromatography (EtOAc:*n*-Hex=1:9) on silica. The fractions containing the product were collected and evaporated to obtain colorless liquid compound of methyl 5-chloro-2-((4-methoxybenzyl)amino)nicotinate (840.0 mg, 28%).

[2311]

[2312] LC/MS ESI (+): 307 (M+1)

[2313]

[2314] (c) Synthesis of 6-chloro-1-(4-methoxybenzyl)-1H-pyrido[2,3-d][1,3]oxazine-2,4-dione

[2315] Methyl 5-chloro-2-((4-methoxybenzyl)amino)nicotinate (205.0 mg, 0.67 mmol) was dissolved in 1,4-dioxane (3.0 mL), and diphosgen (120.0 μL, 1.01 mmol) was slowly added thereto at room temperature. The reaction mixture was stirred at 110℃ for 12 hours. The reaction mixture was then distilled under reduced pressure. The residue was dissolved in toluene (5.0 mL), distilled again under reduced pressure and then dried to obtain pale yellow solid compound of 6-chloro-1-(4-methoxybenzyl)-1*H* -pyrido[2,3-d][1,3]oxazine-2,4-dione.

[2316]

[2317] LC/MS ESI (+): 319 (M+1)

[2318]

[2319] (d) Synthesis of 6-chloro-4-hydroxy-1-(4-methoxybenzyl)-3-nitro-1,8-naphthylidine-2(1 *H*)-one

[2320] DMA (3.0 mL) was added to NaH (40.4 mg: in 60% oil, 1.01 mmol), and ethylnitroacetate (110.0 μL, 1.01 mmol) was then added thereto. The mixture was stirred at room temperature for 30 minutes. Solution of 6-chloro-1-(4-methoxybenzyl)-1*H* -pyrido[2,3-d][1,3]oxazine-2,4-dione dissolved in DMA (1.0 mL) was slowly added to the reaction mixture at room temperature. The reaction mixture was stirred at 110℃ for 12 hours, cooled to room temperature and then filtered through celite. The filtrate was distilled under reduced pressure. The residue was dissolved in toluene (5.0 mL) and it was distilled under reduced pressure. The formed solid was stirred in the mixture of

DCM and Et_2O and then filtered to obtain dark yellow solid compound of 6-chloro-4-hydroxy-1-(4-methoxybenzyl)-3-nitro-1,8-naphthylidine-2(1*H*)-one (232.0 mg, 95% in 2 steps).

[2321]

[2322] LC/MS ESI (+): 362 (M+1)

[2323]

[2324] (e) Synthesis of 8-chloro-5-(4-methoxybenzyl)-2-methyloxazolo[4,5-c][1,8]naphthylidine-4(5H)-one

[2325] The mixture of 6-chloro-4-hydroxy-1-(4-methoxybenzyl)-3-nitro-1,8-naphthylidine-2(1*H*)-one (200.0 mg, 0.55 mmol), Zn (220.0 mg, 3.36 mmol), acetic acid anhydride (2.7 mL, 28.30 mmol) and acetic acid (4.0 mL) was stirred at 120℃ for 12 hours. The reaction mixture was cooled to room temperature and then filtered through celite. The filtrate was concentrated under reduced pressure, and TEA (0.5 mL) was added thereto, and it was purified by column chromatography (EtOAc:*n*-Hex=1:1) on silica. The fractions containing the product were collected and evaporated to obtain white solid compound of 8-chloro-5-(4-methoxybenzyl)-2-methyloxazolo[4,5-c][1,8]naphthylidine-4(5*H*)-one (108.0 mg, 52%).

[2326]

[2327] LC/MS ESI (+): 356 (M+1)

[2328]

[2329] (f) Synthesis of 4,8-dichloro-2-methyloxazolo[4,5-c][1,8]naphthylidine

[2330] 8-Chloro-5-(4-methoxybenzyl)-2-methyloxazolo[4,5-c][1,8]naphthylidine-4(5H)-one (108.0 mg, 0.30 mmol) was dissolved in $POCl_3$ (2.0 mL) and the mixture was stirred at 140℃ for 12 hours. The reaction mixture was cooled to 0℃, poured into saturated Na_2CO_3 aqueous solution with pieces of ice and then extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (EtOAc:*n*-Hex=1:3) on silica. The fractions containing the product were collected and evaporated to pale yellow solid compound of 4,8-dichloro-2-methyloxazolo[4,5-c][1,8]naphthylidine (42.0 mg, 54%).

[2331]

[2332] LC/MS ESI (+): 254 (M+1)

[2333] ^{1}H-NMR (300MHz, $CDCl_3$); δ: 9.04(d, 1H, *J*=2.7Hz), 8.49(d, 1H, *J*=2.7Hz), 2.85 (s, 3H)

[2334]

[2335] g) Synthesis of *tert* -butyl (1-(8-chloro-2-methyloxazolo[4,5-c][1,8]naphthylidine-4-yl)azetidin-3-yl)(methyl)carb

amate

[2336] DMF (2.0 mL) was added to 4,8-Dichloro-2-methyloxazolo[4,5-c][1,8]naphthylidine (19.4 mg, 0.08 mmol), and *tert*-butyl azetidin-3-yl(methyl)carbamate hydrochloride (26.0 mg, 0.12 mmol) and TEA (30.0 μL, 0.23 mmol) were then added thereto. The reaction mixture was stirred for 6 hours and distilled under reduced pressure. The residue was purified by column chromatography (EtOAc:*n*-Hex=1:2) on silica. The fractions containing the product were collected and evaporated to obtain pale yellow solid compound of *tert*-butyl (1-(8-chloro-2-methyloxazolo[4,5-c][1,8]naphthylidine-4-yl)azetidin-3-yl)(methyl)carbamate (30.0 mg, 97%).

[2337]

[2338] LC/MS ESI (+): 404 (M+1)

[2339] ^{1}H-NMR (300MHz, $CDCl_3$); δ: 8.73(d, 1H, J=2.7Hz), 8.19(d, 1H, J=2.7Hz), 5.41-4.91(m, 1H), 4.82-4.68(m, 2H), 4.59-4.47(m, 2H), 2.99 (s, 3H), 2.71 (s, 3H), 1.48(s, 9H)

[2340]

[2341] **Example 91**

[2342] **Synthesis of 1-(8-chloro-2-methyloxazolo[4,5-c][1,8]naphthylidine-4-yl)-*N*-methylazetidin-3-amine**

[2343]

[2344] *tert*-Butyl (1-(8-chloro-2-methyloxazolo[4,5-c][1,8]naphthylidine-4-yl)azetidin-3-yl)(methyl)carbamate (30.0 mg, 0.07 mmol) was dissolved in DCM (2.0 mL), and TFA (1.0 mL, 13.50 mmol) was added thereto. The mixture was stirred for 6 hours. The reaction mixture was distilled under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=1:50) on amine silica. The fractions containing the product were collected and evaporated to obtain pale yellow solid compound of 1-(8-chloro-2-methyloxazolo[4,5-c][1,8]naphthylidine-4-yl)-*N*-methylazetidin-3-amine (20.3 mg, 87%).

[2345]

[2346] LC/MS ESI (+): 304 (M+1)

[2347] ^{1}H-NMR (300MHz, $CDCl_3$); δ: 8.71(d, 1H, *J*=2.7Hz), 8.16(d, 1H, *J*=2.7Hz), 4.78-4.68(m, 2H), 4.29-4.19(m, 2H), 3.87-3.76(m, 1H), 2.71 (s, 3H), 2.48 (s, 3H)

[2348]

[2349] **Example 92**

[2350] **Synthesis of 8-chloro-2-methyl-4-(4-methylpiperazin-1-yl)oxazolo[4,5-c][1,8]naphthylidine**

[2351]

[2352] 4,8-Dichloro-2-methyloxazolo[4,5-c][1,8]naphthylidine (10.0 mg, 0.04 mmol) was added to DMF (1.0 mL), and *N*-methylpiperazine (26.0 mg, 0.12 mmol) and TEA (30.0 μL, 0.23 mmol) were added thereto. The reaction mixture was stirred for 12 hours and then distilled under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=1:10) on silica. The fractions containing the product were collected and evaporated to obtain pale yellow solid compound of 8-chloro-2-methyl-4-(4-methylpiperazin-1-yl)oxazolo[4,5-c][1,8]naphthylidine (7.9 mg, 83%).

[2353]

[2354] LC/MS ESI (+): 318 (M+1)

[2355] ^{1}H-NMR (300MHz, $CDCl_3$); δ: 8.72(d, 1H, *J*=2.7Hz), 8.17(d, 1H, *J*=2.7Hz), 4.51-4.28(m, 4H), 2.72 (s, 3H), 2.62-2.53 (m, 4H), 2.36 (s, 3H)

[2356]

[2357] **Example 93**

[2358] **Synthesis of 1-(8-chloropyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)-*N* -methylazetidin-3-amine**

[2359]

[2360] (a) Synthesis of *tert* -butyl (1-(8-chloropyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[2361] NaN_3 (122.0 mg, 1.87 mmol) was added to suspension of *tert*-butyl (1-(2,7-dichloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (80.0 mg, 0.21 mmol) and EtOH (2.1 mL). The reaction mixture was stirred at 70°C for 12 hours, cooled to room temperature and then concentrated under reduced pressure. Water was added thereto to form a solid, and the formed solid was dried under reduced pressure to obtain white solid compound of *tert*-butyl (1-(8-chloropyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (75.0 mg, 93%).

[2362]

[2363] LC/MS ESI(+): 391 (M+1), 393 (M+3)

[2364] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 8.88 (d, 1H, *J*=2.4 Hz), 8.78 (d, 1H, *J*=2.4 Hz), 5.21-4.85 (m, 2H), 4.82 (m, 1H), 4.46 (m, 1H), 4.45 (m, 1H), 2.93 (s, 3H), 1.42 (s, 9H)

[2365]

[2366] (b) Synthesis of 1-(8-chloropyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)-*N* -methylazetidin-3-amine

[2367] TFA (0.4 mL) was added to a mixture of *tert*-Butyl (1-(8-chloropyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (75.0 mg, 0.19 mmol) and DCM (0.6 mL), and it was stirred at room temperature for one hour. The reaction mixture was purified by column chromatography

(MeOH:DCM=1:60) on amine silica. The fractions containing the product were collected and evaporated. Et_2O was added to the residue to form a solid, and the formed solid was filtered and then dried under reduced pressure to obtain white solid compound of 1-(8-chloropyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)-*N* -methylazetidin-3-amine (42.0 mg, 75%).

[2368]

[2369] LC/MS ESI(+): 291 (M+1), 293 (M+3)

[2370] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 8.83 (d, 1H, *J*=2.4 Hz), 8.76 (d, 1H, *J*=2.4 Hz), 4.90 (m, 1H), 4.60-4.39 (m, 2H), 4.05 (m, 1H), 3.75 (m, 1H), 2.46 (m, 1H), 2.31 (s, 3H)

[2371]

[2372] **Example 94**

[2373] **Synthesis of 8-chloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e]tetrazolo[1,5-a]pyrazine**

[2374]

[2375] NaN_3 (55.0 mg, 0.85 mmol) was added to suspension of 2,7-dichloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (28.0 mg, 0.09 mmol) and EtOH (1.0 mL). The mixture was stirred at 70℃ for 12 hours. The reaction mixture was cooled to room temperature and distilled under reduced pressure. Water was then added thereto to form a solid, and the formed solid was filtered and dried under reduced pressure to obtain orange solid compound of 8-chloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e]tetrazolo[1,5-a]pyrazine (21.0 mg, 75%).

[2376]

[2377] LC/MS ESI(+): 305 (M+1), 307 (M+3)

[2378] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 8.87 (d, 1H, *J*=2.1 Hz), 8.79 (d, 1H, *J*=2.4 Hz), 4.80-3.90 (m, 4H), 2.58-2.50 (m, 4H), 2.26 (s, 3H)

[2379]

[2380] **Example 95**

[2381] **Synthesis of 1-(8-bromopyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)-*N* -methylazetidin-3-amine**

[2382]

[2383] (a) Synthesis of *tert* -butyl (1-(8-bromopyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[2384]

[2385] NaN_3 (71.0 mg 1.09 mmol) was added to a suspension of *tert*-butyl (1-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (52.0 mg, 0.12 mmol) and EtOH (1.2 mL). The mixture was stirred at 70℃ for 12 hours. The

reaction mixture was cooled to room temperature and then distilled under reduced pressure. Water was added thereto to form a solid, and the formed solid was filtered and dried under reduced pressure to obtain white solid compound of *tert*-butyl (1-(8-bromopyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (45.0 mg, 85%).

[2386]

[2387] LC/MS ESI(+): 435 (M+1), 437 (M+3)

[2388] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 8.94 (d, 1H, *J*=2.4 Hz), 8.84 (d, 1H, *J*=2.4 Hz), 5.25-4.90 (m, 2H), 4.82 (m, 1H), 4.65-4.30 (m, 2H), 2.94 (s, 3H), 1.43 (s, 9H)

[2389]

[2390] (b) Synthesis of 1-(8-bromopyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine

[2391] TFA (0.4 mL) was added to the mixture of *tert*-butyl (1-(8-bromopyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (45.0 mg, 0.10 mmol) and DCM (0.6 mL). The reaction mixture was stirred at room temperature for one hour and purified by column chromatography (MeOH:DCM=1:60) on amine silica. The fractions containing the product were collected and evaporated. Et $_2$O was added to the residue to form a solid. The formed solid was filtered and then dried under reduced pressure to obtain white solid compound of 1-(8-bromopyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (28.0 mg, 80%).

[2392]

[2393] LC/MS ESI(+): 335 (M+1), 337 (M+3)

[2394] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 8.92 (bs, 1H), 8.81 (bs, 1H), 4.90 (m, 1H), 4.55-4.38 (m, 2H), 4.04 (m, 1H), 3.76 (m, 1H), 2.31 (s, 3H)

[2395]

[2396] **Example 96**

[2397] **Synthesis of 8-bromo-4-(4-methylpiperazin-1-yl)pyrido[2,3-e]tetrazolo[1,5-a]pyrazine**

[2398]

[2399] NaN_3 (50.0 mg, 0.76 mmol) was added to suspension of 7-bromo-2-chloro-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (29.0 mg, 0.08 mmol) and EtOH (1.0 mL). The reaction mixture was stirred at 70°C for 12 hours, then cooled to room temperature and distilled under reduced pressure. Water was added thereto to form a solid, and the formed solid was filtered and dried under reduced pressure to obtain orange solid compound of 8-bromo-4-(4-methylpiperazin-1-yl)pyrido[2,3-e]tetrazolo[1,5-a]pyrazine (24.0 mg, 80%).

[2400]

[2401] LC/MS ESI(+): 349 (M+1), 351 (M+3)

[2402] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 8.95 (d, 1H, *J*=2.4 Hz), 8.85 (d, 1H, *J*=2.4 Hz), 4.65-4.05 (m, 4H), 2.60-2.50 (m, 4H), 2.26 (s, 3H)

[2403]

[2404] **Example 97**

[2405] **Synthesis of 1-(8-chloro-2-methylpyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine**

[2406]

[2407] (a) Synthesis of 5-chloro-3-fluoro-2-nitropyridine

[2408] 5-Chloro-3-fluoropyridin-2-amine (500.0 mg, 3.41 mmol) was dissolved in H_2SO_4 (1.5 mL), and $Na_2S_2O_8$ (406.1 mg, 1.71 mmol) was added thereto. The mixture was stirred at room temperature for 12 hours and water was then poured into the reaction mixture. The resulting solution was alkalized with saturated $NaHCO_3$ aqueous solution (pH=9) and then extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (EtOAc:*n*-Hex=10:90) on silica. The fractions containing the product were collected and evaporated to obtain white solid compound of 5-chloro-3-fluoro-2-nitropyridine (200.0 mg, 33%).

[2409]

[2410] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 8.21 (d, 1H, *J*=1.8Hz), 8.17 (m, 1H)

[2411]

[2412] (b) Synthesis of 5-chloro-3-hydrazinyl-2-nitropyridine

[2413] 5-Chloro-3-fluoro-2-nitropyridin (190.0 mg, 1.08 mmol) and hydrazine monohydrate (80.0 μL, 1.61 mmol) were dissolved in EtOH (3.0 mL) and the mixture was stirred at room temperature for 2 hours. Et_2O was added thereto to form a solid, and the formed solid was filtered to obtain orange solid compound of 5-chloro-3-hydrazinyl-2-nitropyridine (170.0 mg, 84%).

[2414]

[2415] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.06 (brs, 1H), 8.10 (m, 1H), 7.76 (d, 1H, *J* =2.4Hz)

[2416]

[2417] (c) Synthesis of (Z)-*N*'-(5-chloro-2-nitropyridin-3-yl)acetohydrazone amide

[2418] 5-Chloro-3-hydrazinyl-2-nitropyridine (100.0 mg, 0.53 mmol) and ethyl acetimidate hydrochloride (102.2 mg, 0.80 mmol) were added to pyridine (1.8 mL), and it was stirred at room temperature for 3 hours. Saturated Na_2CO_3 aqueous solution was added to the reaction mixture, and it was then extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The

residue was purified by column chromatography (EtOAc:*n*-Hex=50:50) on silica. The fractions containing the product were collected and evaporated to obtain red solid compound of (Z)-*N*'-(5-chloro-2-nitropyridin-3-yl)acetohydrazone amide (77.0 mg, 63%).

[2419]

[2420] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.53 (brs, 1H), 7.88 (d, 1H, *J*=2.4Hz), 7.78 (d, 1H, *J*=2.4Hz), 6.62 (brs, 2H), 1.92 (s, 3H)

[2421]

[2422] (d) Synthesis of ethyl 1-(5-chloro-2-nitropyridin-3-yl)-3-methyl-1H-1,2,4-triazole-5-carboxylate

[2423] (Z)-*N*'-(5-chloro-2-nitropyridin-3-yl)acetohydrazone amid (60.0 mg, 0.26 mmol) and ethyl 2-chloro-2-oxoacetate (54.0 μL, 0.52 mmol) were dissolved in Et_2O (0.6 mL), stirred at room temperature for one hour, and toluene (6.0 mL) was then added thereto. The mixture was stirred at 80℃ for one hour, stirred at 180℃ for 2 hours and then cooled to room temperature, and water and EtOAc were added thereto, and it was then alkalized with KOH aqueous solution (pH=12) and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and distilled under reduced pressure. The residue was purified by column chromatography (EtOAc:*n*-Hex=50:50) on silica. The fractions containing the product were collected and evaporated to obtain red solid compound of ethyl 1-(5-chloro-2-nitropyridin-3-yl)-3-methyl-1H-1,2,4-triazole-5-carboxylate (78.0 mg, 56%).

[2424]

[2425] LC/MS ESI(+): 312 (M+1), 314 (M+3)

[2426] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 8.95 (d, 1H, *J*=2.4Hz), 8.83 (d, 1H, *J*=2.4Hz), 4.28-4.21(m, 2H), 2.40 (s, 3H), 1.20-1.15 (m, 3H)

[2427]

[2428] (e) Synthesis of 8-chloro-2-methylpyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazin-4(5H)-one

[2429] Ethyl 1-(5-chloro-2-nitropyridin-3-yl)-3-methyl-1H-1,2,4-triazole-5-carboxylate (62.0 mg, 0.20 mmol) and Fe (166.6 mg, 2.98 mmol) were added to acetic aicd (13.0 mL), stirred at 90℃ for 2 hours and then cooled to room temperature. 1N of HCl aqueous solution was added to the reaction mixture to dissolve completely and then extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=5:95) on silica. The fractions containing the product were collected and evaporated white solid compound of 8-chloro-2-methylpyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazin-4(5H)-one (40.0 mg,

86%).

[2430]

[2431] LC/MS ESI(+): 236 (M+1), 238 (M+3)

[2432] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 12.89 (brs, 1H), 8.52 (d, 1H, *J*=2.4Hz), 8.44 (d, 1H, *J*=2.4Hz), 2.53 (s, 3H)

[2433]

[2434] (f) Synthesis of 4,8-dichloro-2-methylpyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazine

[2435] 8-Chloro-2-methylpyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazin-4(5H)-one (40.0 mg, 0.17 mmol) was dissolved in $POCl_3$ (1.0 mL), and DIPEA (60.0 μL, 0.34 mmol) was added thereto. The reaction mixture was refluxed for 5 hours and then cooled to room temperature. The reaction mixture was poured into ice water, neutralized with saturated $NaHCO_3$ aqueous solution, and it was then extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then distilled under reduced pressure to obtain ivory solid compound of 4,8-dichloro-2-methylpyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazine (43.0 mg, 100%).

[2436]

[2437] LC/MS ESI(+): 254 (M+1), 256 (M+3)

[2438] ^{1}H-NMR (300MHz, DMSO-d_6); δ: 9.03 (m, 1H), 8.94 (m, 1H), 2.67 (s, 3H)

[2439]

[2440] (g) Synthesis of 1-(8-chloro-2-methylpyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine

[2441] 4,8-Dichloro-2-methylpyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazine (10.0 mg, 0.04 mmol) and TFA (16.5 μL, 0.12 mmol) were dissolve in DMF (0.2 mL), and *tert*-butyl azetidin-3-yl(methyl)carbamate hydrochloride (13.0 mg, 0.06 mmol) was added thereto. The reaction mixture was stirred at room temperature for 2 hours, then concentrated and purified by column chromatography (MeOH:DCM=5:95) on silica. The fractions containing the product were collected and evaporated to obtain white solid compound of *tert*-butyl (1-(8-chloro-2-methylpyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate. Unpurified *tert*-butyl (1-(8-chloro-2-methylpyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate was dissolved in DCM (1.0 mL), and TFA (0.4 mL) was added thereto. The reaction mixture was stirred at room temperature for one hour and then purified by column chromatography (MeOH:DCM=5:95) on amine silica. The fractions containing the product were collected and evaporated to obtain white solid compound of 1-(8-chloro-2-methylpyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (7.0 mg, 45%).

[2442]

[2443] LC/MS ESI(+): 304 (M+1), 306 (M+3)

[2444] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 8.60 (d, 1H, *J*=2.4 Hz), 8.45 (d, 1H, *J*=2.4 Hz), 4.83 (m, 1H), 4.50-4.30 (m, 2H), 4.00 (m, 1H), 3.69 (m, 1H), 2.57 (s, 3H), 2.30 (brs, 3H)

[2445]

[2446] **Example 98**

[2447] **Synthesis of 8-chloro-2-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazine**

[2448]

[2449] 4,8-Dichloro-2-methylpyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazine (10.0 mg, 0.04 mmol) and TFA (16.5 μL, 0.12 mmol) were dissolved in DMF (0.2 mL), and *N*-methylpiperazine (6.5 μL, 0.06 mmol) was added thereto. The reaction mixture was stirred at room temperature for 2 hours, then concentrated and purified by column chromatography (MeOH:DCM=5:95) on silica. The fractions containing the product were collected and evaporated to obtain white solid compound of 8-chloro-2-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazine (8.0 mg, 66%).

[2450]

[2451] LC/MS ESI(+): 318 (M+1), 320 (M+3)

[2452] ^{1}H-NMR (300 MHz, DMSO-d_6); δ: 8.65 (d, 1H, *J*=2.4 Hz), 8.49 (d, 1H, *J*=2.4 Hz), 4.45-4.18 (m, 4H), 2.59 (s, 3H), 2.52 (m, 4H), 2.25 (s, 3H)

[2453]

[2454] **Example 99**

[2455] **Synthesis of 1-(8-bromo-7-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine**

[2456]

[2457] (a) Synthesis of 7-bromo-6-methylpyrido[2,3-b]pyrazine-2,3-diol

[2458] The mixture of 5-bromo-6-methylpyridine-2,3-diamine (500.0 mg, 2.47 mmol) and diethyloxalate (3.0 mL) was stirred at 100℃ for 12 hours and then cooled to room temperature. Et_2O was added to the reaction mixture to form a solid. The formed solid was then filtered and dried under reduced pressure to obtain light brown solid compound of 7-bromo-6-methylpyrido[2,3-b]pyrazine-2,3-diol (611.0 mg, 97%).

[2459]

[2460] LC/MS ESI (+): 256 (M+1), 258 (M+3)

[2461] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 12.40 (s, 1H), 11.94 (s, 1H), 7.53 (s, 1H), 2.48 (s,

3H)

[2462]

[2463] (b) Synthesis of 7-bromo-2,3-dichloro-6-methylpyrido[2,3-b]pyrazine

[2464] The mixture of 7-bromo-6-methylpyrido[2,3-b]pyrazine-2,3-diol (300.0 mg, 1.17 mmol) and $POCl_3$ (6.0 mL) was stirred at 95℃ for 12 hours and then cooled to room temperature. The reaction mixture was poured into ice water to form a solid. The formed solid was filtered and dried under reduced pressure to obtain black solid compound of 7-bromo-2,3-dichloro-6-methylpyrido[2,3-b]pyrazine (340.0 mg, 99%).

[2465]

[2466] LC/MS ESI (+): 292 (M+1), 294 (M+3), 296 (M+5)

[2467] ^{1}H-NMR (400 MHz, $CDCl_3$); δ: 8.53 (s, 1H), 2.95 (s, 3H)

[2468]

[2469] (c) Synthesis of *tert* -butyl (1-(7-bromo-2-chloro-6-methylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[2470] TEA (140.0 μL, 1.02 mmol) was added to a mixture of 7-bromo-2,3-dichloro-6-methylpyrido[2,3-b]pyrazine (100.0 mg, 0.34 mmol), *tert* -butyl azetidin-3-yl(methyl)carbamate hydrochloride salt (76.0 mg, 0.34 mmol) and DCM (3.4 mL) at 0℃, and it was then stirred for 1 hour. The reaction mixture was purified by column chromatography (EtOAc:*n*-Hex=1:4) on silica. The fractions containing the product were collected and evaporated to obtain red solid compound of *tert*-butyl (1-(7-bromo-2-chloro-6-methylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (43.0 mg, 28%).

[2471]

[2472] LC/MS ESI (+): 442 (M+1), 444 (M+3)

[2473] ^{1}H-NMR (400 MHz, $CDCl_3$); δ: 8.23 (s, 1H), 5.02-4.90 (m, 1H), 4.78-4.68 (m, 2H), 4.50-4.49 (m, 2H), 2.96 (s, 3H), 2.836 (s, 3H), 1.48 (s, 9H)

[2474]

[2475] (d) Synthesis of *tert* -butyl (1-(8-bromo-7-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[2476] Hydrazine monohydrate (15.0 μL, 0.49 mmol) was added to suspension of *tert*-butyl (1-(7-bromo-2-chloro-6-methylpyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (43.0 mg, 0.10 mmol) and EtOH (1.0 mL). The reaction mixture was stirred at room temperature for 1 hour and then concentrated under reduced pressure. The residue was dissolved in trimethyl orthoformate (1.0 mL), and it was stirred at 85℃ for 1 hour. The reaction mixture was cooled to room temperature and then concentrated

under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=1:40) on silica. The fractions containing the product were collected and evaporated to obtain light brown solid compound of *tert*-butyl (1-(8-bromo-7-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (35.0 mg, 80%).

[2477]

[2478] LC/MS ESI (+): 448 (M+1), 450 (M+3)

[2479]

[2480] (e) Synthesis of 1-(8-bromo-7-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine

[2481] TFA (0.4 mL) was added to a mixture of *tert*-butyl (1-(8-bromo-7-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (35.0 mg, 0.08 mmol) and DCM (0.6 mL), and then stirred at room temperature for 1 hour. The reaction mixture was purified by column chromatography (MeOH:DCM=1:40) on amine silica. The fractions containing the product were collected and evaporated. Et_2O was added to the residue to form a solid. The formed solid was filtered and then dried under reduced pressure to obtain yellow solid compound of 1-(8-bromo-7-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (12.0 mg, 43%).

[2482]

[2483] LC/MS ESI (+): 348 (M+1), 350 (M+3)

[2484] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 9.93 (s, 1H), 8.63 (s, 1H), 4.90 (m, 1H), 4.45-4.35 (m, 2H), 3.97 (m, 1H), 3.71 (m, 1H), 2.60 (s, 3H), 2.30 (s, 3H)

[2485]

[2486] **Example 100**

[2487] **Synthesis of 8-bromo-7-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine**

[2488]

[2489] (a) Synthesis of 7-bromo-2-chloro-6-methyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine

[2490] TEA (140.0 μL, 1.02 mmol) was added to a mixture of 7-bromo-2,3-dichloro-6-methylpyrido[2,3-b]pyrazine (100.0 mg, 0.34 mmol) obtained from the step (b) of Example 99, *N*-methylpiperazine (38.0 μL, 0.34 mmol) and DCM (3.4 mL) at 0°C, and then stirred for 1 hour. The reaction mixture was purified by column chromatography (EtOAc:*n*-Hex=1:4) on amine silica. The fractions containing the product were collected and evaporated to obtain red solid compound of

7-bromo-2-chloro-6-methyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (23.0 mg, 19%).

[2491]

[2492] LC/MS ESI (+): 356 (M+1), 358 (M+3), 360 (M+5)

[2493] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 8.32 (s, 1H), 3.79-3.70 (m, 4H), 2.87 (s, 3H), 2.65-2.62 (m, 4H), 2.38 (s, 3H)

[2494]

[2495] (b) Synthesis of 8-bromo-7-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine

[2496] Hydrazine monohydrate (10.0 μL, 0.32 mmol) was added to suspension of 7-bromo-2-chloro-6-methyl-3-(4-methylpiperazin-1-yl)pyrido[2,3-b]pyrazine (23.0 mg, 0.06 mmol) and EtOH (1.0 mL). The reaction mixture was stirred at room temperature for 1 hour and then concentrated under reduced pressure. The residue was dissolved in trimethyl orthoformate (1.0 mL), and it was stirred at 85℃ for 1 hour. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=1:40) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of compound of 8-bromo-7-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (1.1 mg, 4%).

[2497]

[2498] LC/MS ESI (+): 362 (M+1), 364 (M+3)

[2499] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 9.99 (s, 1H), 8.93 (s, 1H), 4.46-4.30 (m, 4H), 3.32 (s, 3H), 2.63 (s, 3H) 2.54-2.50 (m, 4H)

[2500]

[2501] **Example 101**

[2502] **Synthesis of 8-chloro-4-(3-(methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-7-ol HCl salt**

[2503]

[2504] (a) Synthesis of *tert* -butyl (1-(8-chloro-7-hydroxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[2505] CsF (32.2 mg, 0.21 mmol) was added to a mixture of *tert*-butyl (1-(7,8-dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (30.0 mg, 0.07 mmol) obtained from the step (b) of Example 27 and NMP (1.0 mL). The reaction mixture was stirred at 135℃ for 12 hours and then cooled to

room temperature. CsF (161.0 mg, 1.06 mmol) was further added thereto and stirred at 145℃ for 12 hours. The reaction mixture was cooled to room temperature and purified by column chromatography (MeOH:DCM=1:40) on silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of *tert*-butyl (1-(8-chloro-7-hydroxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (10.0 mg, 35%).

[2506]

[2507] LC/MS ESI (+): 406 (M+1), 408 (M+3)

[2508]

[2509] (b) Synthesis of 8-chloro-4-(3-(methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-7-ol HCl salt

[2510] Suspension of *tert*-butyl (1-(8-chloro-7-hydroxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (9.0 mg, 0.02 mmol) and 4N HCl in 1,4-dioxane (0.5 mL) was stirred at room temperature for 1 hour. Et_2O was added to the reaction mixture to form a solid. The formed solid was filtered and dried under reduced pressure to obtain yellow solid compound of 8-chloro-4-(3-(methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-7-ol HCl salt (3.2 mg, 43%).

[2511]

[2512] LC/MS ESI (+): 306 (M+1), 308 (M+3)

[2513] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 13.00-12.30 (m, 1H), 9.80 (s, 1H), 9.75-9.65 (m, 2H), 8.76 (s, 1H), 5.02 (m, 1H), 4.89 (m, 1H), 4.53 (m, 2H), 4.23 (m, 1H), 2.63 (s, 3H)

[2514]

[2515] **Example 102**

[2516] **Synthesis of *N* -(1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)-*N* -methylhydroxylamine**

[2517]

[2518] (a) Synthesis of *O*-benzoyl-*N* -(1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)-*N*-methylhydroxylamine

[2519] $CHCl_3$ (5.0 mL) was added to a mixture of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (120.0 mg, 0.36 mmol), Benzoyl peroxide (116.0 mg, 0.36 mmol) and K_2CO_3 (174.0 mg, 1.26 mmol), and stirred at 65℃ for 12 hours. The reaction mixture was cooled to room temperature, filtered through celite and then concentrated under reduced

pressure. The residue was purified by column chromatography (DCM:MeOH=98:2 to 93:7) on silica. The fractions containing the product were collected and evaporated to obtain gray solid compound of O-benzoyl-*N*-(1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)-*N*-methylhydroxylamine (150.0 mg, 92%).

[2520]

[2521] LC/MS ESI (+): 454 (M+1), 456 (M+3)

[2522]

[2523] (b) Synthesis of *N*-(1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)-*N*-methylhydroxylamine

[2524] NaOH (24.0 mg, 0.60 mmol) was dissolved in MeOH (8.0 mL), and *O*-benzoyl-*N*-(1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)-*N*-methylhydroxylamine (120.0 mg, 0.26 mmol) was added thereto. The mixture was stirred for 12 hours and purified by column chromatography (DCM:MeOH=91:9) on silica. The fractions containing the product were collected and evaporated. The residue was dissolved in DMSO, and it was then purified by reverse phase high performance chromatography (ACN:H_2O=65:35). The fractions containing the product were collected and evaporated to obtain beige solid. The obtained solid was stirred in Et_2O for 30 minutes and then filtered to obtain beige solid compound of *N*-(1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)-*N*-methylhydroxylamine (71.0 mg, 77%).

[2525]

[2526] LC/MS ESI (+): 350 (M+1), 352 (M+3)

[2527] ^{1}H-NMR (400MHz, DMSO-d_6); δ: 9.95 (s, 1H), 8.90 (d, 1H, *J*=2.2Hz), 8.59 (d, 1H, *J*=2.2Hz), 4.76 (m, 2H), 4.30 (m, 2H), 3.77 (m, 1H), 2.51 (s, 3H)

[2528]

[2529] **Example 103**

[2530] **Synthesis of 1-(2-bromopyrido[3,2-e]pyrrolo[1,2-c]pyrimidin-6-yl)-*N*-methylazetidin-3-amine**

[2531]

[2532] (a) Synthesis of 2-bromopyrido[3,2-e]pyrrolo[1,2-c]pyrimidin-6-ol

[2533] $Pd(PPh_3)_4$ (193.0 mg, 0.17 mmol) was added to suspension of 5-bromo-3-iodopyridin-2-amine (500.0 mg, 1.67 mmol), (1-(*tert*-butoxycarbonyl)-1H-pyrrol-2-yl)boronic acid (423.0 mg, 2.00 mmol), Cs_2CO_3 (1600.0 mg, 5.01 mmol), H_2O (4.0 mL) and DME (16.0 mL). The mixture was allowed to react in microwave under conditions of 100W, 110℃ for 2 hours and then cooled to room temperature. Et_2O was added to the reaction mixture to form a solid. The formed solid

was filtered and then dried under reduced pressure to form white solid compound of 2-bromopyrido[3,2-e]pyrrolo[1,2-c]pyrimidin-6-ol (180.0 mg, 41%).

[2534]

[2535] LC/MS ESI (+): 264 (M+1), 266 (M+3)

[2536] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 12.11 (s, 1H), 8.66 (d, 1H, *J*=1.5 Hz), 8.39 (d, 1H, *J*=1.5 Hz), 7.66 (m, 1H), 7.23 (m, 1H), 6.72 (m, 1H)

[2537]

[2538] (b) Synthesis of *tert* -butyl (1-(2-bromopyrido[3,2-e]pyrrolo[1,2-c]pyrimidin-6-yl)azetidin-3-yl)(methyl)carbamate

[2539] DIPEA (24.0 μL, 0.14 mmol) was added to suspension of 2-bromopyrido[3,2-e]pyrrolo[1,2-c]pyrimidin-6-ol (30.0 mg, 0.11 mmol) and $POCl_3$ (1.1 mL), and it was then stirred at 120℃ for 20 hours. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was dissolved in DCM (1.1 mL), and *tert*-butyl azetidin-3-yl(methyl)carbamate HCl salt (50.0 mg, 0.23 mmol) and DIPEA (200.0 μL, 1.13 mmol) were added thereto. The mixture was stirred at room temperature for 12 hours. The reaction mixture was purified by column chromatography (MeOH:DCM=1:50) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of *tert*-butyl (1-(2-bromopyrido[3,2-e]pyrrolo[1,2-c]pyrimidin-6-yl)azetidin-3-yl)(methyl)carbamate (28.0 mg, 57%).

[2540]

[2541] LC/MS ESI (+): 433 (M+1), 435 (M+3)

[2542] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 8.65 (d, 1H, J=1.8 Hz), 8.46 (d, 1H, J=1.8 Hz), 7.60 (m, 1H), 7.25 (m, 1H), 6.84 (m, 1H), 5.01-4.90 (m, 1H), 4.68 (m, 2H), 4.54 (m, 2H), 2.93 (s, 3H), 1.41 (s, 9H)

[2543]

[2544] (c) Synthesis of 1-(2-bromopyrido[3,2-e]pyrrolo[1,2-c]pyrimidin-6-yl)-*N* -methylazetidin-3-amine

[2545] TFA (0.4 mL) was added to a mixture of *tert*-butyl (1-(2-bromopyrido[3,2-e]pyrrolo[1,2-c]pyrimidin-6-yl)azetidin-3-yl)(methyl)carbamate (28.0 mg, 0.06 mmol) and DCM (0.6 mL), and it was stirred at room temperature for 1 hour. The reaction mixture was purified by column chromatography (MeOH:DCM=1:40) on amine silica and the fractions containing the product were collected and evaporated. Et_2O was added to the residue to form a solid. The formed solid was filtered and then dried under reduced pressure to obtain yellow solid compound of 1-(2-bromopyrido[3,2-e]pyrrolo[1,2-c]pyrimidin-6-yl)-*N* -

methylazetidin-3-amine (14.0 mg, 64%).

[2546]

[2547] LC/MS ESI (+): 332 (M+1), 334 (M+3)

[2548] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 8.62 (d, 1H, *J*=1.8 Hz), 8.44 (d, 1H, *J*=1.8 Hz), 7.60 (m, 1H), 7.25 (m, 1H), 6.82 (m, 1H), 4.61 (m, 2H), 4.17 (m, 2H), 3.60 (m, 1H), 2.38 (m, 1H), 2.37 (s, 3H)

[2549]

[2550] **Example 104**

[2551] **Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine 2,2,2-trifluoroacetate**

[2552]

[2553] Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine 2,2,2-trifluoroacetate

[2554] *tert*-Butyl (1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (300.0 mg, 0.69 mmol) was dissolved in DCM (1.8 mL), and TFA (0.9 mL) was slowly added thereto at room temperature. The reaction mixture was stirred at room temperature for 30 minutes and then concentrated under reduced pressure. MeOH (1.84 mL) was added thereto to form a solid. The formed solid was filtered and dried to obtain white solid compound of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine 2,2,2-trifluoroacetate (270.0 mg, 90%).

[2555]

[2556] LC/MS ESI (+): 334 (M+1)

[2557] ^{1}H-NMR (400MHz, DMSO-d_6); δ: 10.03 (s, 1H), 9.31 (s, 1H), 8.99 (d, 1H, *J*=1.5Hz), 8.67 (d, 1H, *J*=1.5Hz), 5.04 (m, 1H), 4.85 (m, 1H), 4.59 (m, 1H), 4.42 (m, 1H), 4.27 (m, 1H), 2.69 (s, 3H)

[2558]

[2559] **Example 105**

[2560] **Synthesis of (S)-1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine**

[2561]

[2562] (a) Synthesis of (S)-*tert*-butyl (1-(7-bromo-2-((1-hydroxypropan-2-yl)amino)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[2563] The mixture of *tert*-butyl (1-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

(500.0 mg, 1.17 mmol) and (S)-2-aminopropan-1-ol (193.0 mg, 2.57 mmol) in EtOH (20.0 mL) was stirred at 80℃ for 8 hours. The reaction mixture was then concentrated under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=98:2 to 95:5) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of (S)-*tert*-butyl (1-(7-bromo-2-((1-hydroxypropan-2-yl)amino)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl) (methyl)carbamate (349.0 mg, 64%).

[2564]

[2565] LC/MS ESI (+): 467 (M+1), 469 (M+3)

[2566] ^{1}H-NMR (400MHz, DMSO-d_6); δ: 8.40 (d, 1H, *J*=2.4Hz), 7.97 (d, 1H, *J*=2.4Hz), 6.18 (d, 1H, *J*=7.8Hz), 4.85 (brs, 1H), 4.80 (t, 1H, *J*=5.6Hz), 4.48 (q, 2H, *J*=8.4Hz), 4.20-4.35 (m, 3H), 3.50 (m, 2H), 2.88 (s, 3H), 1.40 (s, 9H), 1.19 (d, 3H, *J*=6.6Hz)

[2567]

[2568] (b) Synthesis of (S)- *tert* -butyl (1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[2569] The mixture of (S)-*tert*-butyl (1-(7-bromo-2-((1-hydroxypropan-2-yl)amino)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl) (methyl)carbamate (199.0 mg, 0.43 mmol), MsCl (63.0 mg, 0.56 mmol) and TEA (129.0 mg, 1.29 mmol) in DCM (10.0 mL) was stirred at room temperature for 2 hours and then concentrated under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=98:2 to 95:5) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of (S)-*tert* -butyl (1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (211.0 mg, quant.).

[2570]

[2571] LC/MS ESI (+): 449 (M+1), 451 (M+3)

[2572]

[2573] (c) Synthesis of (S)-1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)- *N* -methylazetidin-3-amine

[2574] (S)-*tert*-Butyl (1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (100.0 mg, 0.22 mmol) was dissolved in DCM (1.0 mL), and TFA (1.0 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was neutralized with TEA and was purified by column chro-

matography (DCM:MeOH=90:10) on amine silica and silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of (S)-1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine (42.0 mg, 54%).

[2575]

[2576] LC/MS ESI (+): 349 (M+1), 351 (M+3)

[2577] ^{1}H-NMR (400MHz, DMSO-d_6); δ: 7.95 (d, 1H, *J*=2.2Hz), 7.27 (d, 1H, *J*=2.2Hz), 4.68 (m, 1H), 4.35 (m, 1H), 4.23 (m, 1H), 4.04 (t, 2H, *J*=10.6Hz), 3.80 (m, 1H), 3.45-3.57 (m, 2H), 2.23 (s, 3H), 1.25 (d, 3H, *J*=6.7Hz)

[2578]

[2579] **Example 106**

[2580] **Synthesis of (R)-1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl) -*N*-methylazetidin-3-amine**

[2581]

[2582] (a) Synthesis of (R)- *tert* -butyl (1-(7-bromo-2-((1-hydroxypropan-2-yl)amino)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[2583] The mixture of tert-Butyl (1-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (500.0 mg, 1.17 mmol) and (R)-2-aminopropan-1-ol (193.0 mg, 2.57 mmol) in EtOH (20.0 mL) was stirred at 80℃ for 8 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=98:2 to 95:5) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of (R)-*tert*-butyl (1-(7-bromo-2-((1-hydroxypropan-2-yl)amino)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (378.0 mg, 69%).

[2584]

[2585] LC/MS ESI (+): 467 (M+1), 469 (M+3)

[2586]

[2587] (b) Synthesis of (R)- *tert* -butyl (1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[2588] The mixture of (R)-*tert*-butyl (1-(7-bromo-2-((1-hydroxypropan-2-yl)amino)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (378.0 mg, 0.81 mmol), MsCl (120.0 mg, 1.05 mmol) and TEA (246.0 mg, 2.43 mmol) in DCM (10.0 mL) was stirred at room temperature for 12 hours and concentrated under reduced pressure. The residue was purified by column

chromatography (DCM:MeOH=98:2 to 95:5) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of (R)-*tert* -butyl (1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (320.0 mg, 88%).

[2589]

[2590] LC/MS ESI (+): 449 (M+1), 451 (M+3)

[2591]

[2592] (c) Synthesis of (R)-1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)- *N* -methylazetidin-3-amine

[2593] (R)-*tert*-Butyl (1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (150.0 mg, 0.33 mmol) was dissolved in DCM (1.5 mL), and TFA (1.5 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 3 hours and then concentrated under reduced pressure. The residue was neutralized with TEA and it was purified by column chromatography (DCM:MeOH=90:10) on amine silica and silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of (R)-1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine (75.0 mg, 64%).

[2594]

[2595] LC/MS ESI (+): 349 (M+1), 351 (M+3)

[2596] ^{1}H-NMR (400MHz, DMSO-d_6); δ: 7.95 (d, 1H, *J*=2.2Hz), 7.27 (d, 1H, *J*=2.2Hz), 4.68 (m, 1H), 4.35 (m, 1H), 4.22 (m, 1H), 4.03 (t, 2H, *J*=10.6Hz), 3.80 (m, 1H), 3.44-3.58 (m, 2H), 2.24 (s, 3H), 1.25 (d, 3H, *J*=6.7Hz)

[2597]

[2598] **Example 107**

[2599] **Synthesis of 1-(8-bromo-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)- *N* -methylazetidin-3-amine**

[2600]

[2601] (a) Synthesis of *tert* -butyl (1-(7-bromo-2-((2-hydroxyethyl)amino)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[2602] The mixture of *tert*-butyl (1-(7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (500.0 mg, 1.17 mmol) and 2-aminoethanol (157.0 mg, 2.57 mmol) in EtOH (20.0 mL) was stirred at 90℃ for 12 hours. The reaction mixture was then concentrated under

reduced pressure. The residue was purified by column chromatography (DCM:MeOH=98:2 to 95:5) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of *tert*-butyl (1-(7-bromo-2-((2-hydroxyethyl)amino)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (481.0 mg, 91%).

[2603]

[2604] LC/MS ESI (+): 453 (M+1), 455 (M+3)

[2605]

[2606] (b) Synthesis of *tert* -butyl (1-(8-bromo-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[2607] The mixture of *tert*-butyl (1-(7-bromo-2-((2-hydroxyethyl)amino)pyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (481.0 mg, 1.06 mmol), MsCl (158.0 mg, 1.38 mmol) and TEA (322.0 mg, 3.18 mmol) in DCM (10.0 mL) was strirred at room temperature for 6 hours and then concentrated under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=98:2) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of *tert*-butyl (1-(8-bromo-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (435.0 mg, 94%).

[2608]

[2609] LC/MS ESI (+): 435(M+1), 437 (M+3)

[2610] ^{1}H-NMR (400MHz, DMSO-d_6); δ: 7.96 (d, 1H, *J*=2.2Hz), 7.31 (d, 1H, *J*=2.2Hz), 4.83 (brs, 1H), 4.74 (m, 1H), 4.57 (m, 1H), 4.31 (m, 1H), 4.20 (m, 1H), 4.04 (m, 2H), 3.92 (m, 2H), 2.87 (s, 3H), 1.41 (s, 9H)

[2611]

[2612] (c) Synthesis of 1-(8-bromo-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine

[2613] *tert*-Butyl (1-(8-bromo-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (435.0 mg, 1.00 mmol) was dissolved in DCM (1.0 mL), and TFA (2.0 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 3 hours and then concentrated under reduced pressure. The residue was neutralized with TEA and then purified by column chromatography (DCM:MeOH=90:10) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of 1-(8-bromo-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine (186.0 mg, 56%).

[2614]

[2615] LC/MS ESI (+): 335(M+1), 337 (M+3)

[2616] ^{1}H-NMR (400MHz, DMSO-d_6); δ: 7.95 (d, 1H, *J*=2.2Hz), 7.28 (d, 1H, *J*=2.2Hz), 4.67 (m, 1H), 4.23 (m, 2H), 4.03 (m, 2H), 3.91 (m, 2H), 3.81 (m, 1H), 3.53 (m, 1H), 2.32 (brs, 1H), 2.23 (s, 3H)

[2617]

[2618] **Example 108**

[2619] **Synthesis of 1-(8-bromo-2-methylimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine**

[2620]

[2621] (a) Synthesis of *tert*-butyl (1-(8-bromo-2-methylimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[2622] The mixture of (S)-*tert*-butyl (1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (139.0 mg, 0.31 mmol) and DDQ (140.0 mg, 0.62 mmol) in xylene (5.0 mL) is stirred at 90℃ for 8 hours and the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=98:2) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound which is the mixture of (S)-*tert*-butyl (1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate and *tert*-butyl (1-(8-bromo-2-methylimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate.

[2623]

[2624] LC/MS ESI (+): 447(M+1), 449 (M+3)

[2625]

[2626] (b) Synthesis of 1-(8-bromo-2-methylimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine

[2627] The mixture of (S)-*tert*-butyl (1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate and *tert*-butyl (1-(8-bromo-2-methylimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate was dissolved in DCM (1.0 mL), and TFA (2.0 mL) was slowly added thereto at 0℃. The reaction mixture was stirred at room temperature for 2 hours and concentrated under reduced pressure. The residue was neutralized with TEA (pH=7) and purified by column chromatography (DCM:MeOH=98:2 to 90:10) on silica. The fractions containing the product were collected and evaporated to obtain yellow solid

compound of 1-(8-bromo-2-methylimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine (14.0 mg, 13% in two steps).

[2628]

[2629] LC/MS ESI (+): 347(M+1), 349 (M+3)

[2630] ^{1}H-NMR (400MHz, DMSO-d_6); δ: 8.75 (d, 1H, *J*=2.1Hz), 8.53 (d, 1H, *J*=2.1Hz), 8.43 (s, 1H), 4.85 (m, 1H), 4.38 (m, 2H), 3.96 (m, 1H), 3.63 (m, 1H), 2.38 (s, 3H), 2.30 (s, 3H)

[2631]

[2632] **Example 109**

[2633] **Synthesis of 1-(9-bromo-2-methylpyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-yl)-*N*-methylazetidin-3-amine**

[2634]

[2635] (a) Synthesis of 5-bromo-3-(3-methyl-1H-pyrazol-5-yl)pyridin-2-amine

[2636] $Pd(PPh_3)_4$ (190.0 mg, 0.17 mmol) was added to suspension of 5-bromo-3-iodopyridin-2-amine (500.0 mg, 1.67 mmol), (1-(*tert*-butoxycarbonyl)-3-methyl-1H-pyrazol-5-yl)boronic acid (755.0 mg, 3.34 mmol), Cs_2CO_3 (1600.0 mg, 5.01 mmol), H_2O (3.0 mL) and DME (12.0 mL). The reaction mixture was allowed to react in microwave under conditions of 100W and 130℃ for 2 hours and 30 minutes, followed by 100W and 150℃ for 2 hours and then cooled to room temperature. Water was added to the reaction mixture, and it was extracted 2 times with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and then concentrated under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=1:40) on silica. The fractions containing the product were collected and evaporated to obtain brown solid compound which is the mixture of 5-bromo-3-(3-methyl-1H-pyrazol-5-yl)pyridin-2-amine and 9-bromo-2-methylpyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-ol (78.0 mg).

[2637]

[2638] (b) Synthesis of 9-bromo-2-methylpyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-ol

[2639] Diphosgene (0.05 mL) was added to a suspension of mixture (78.0 mg) of 5-bromo-3-(3-methyl-1H-pyrazol-5-yl)pyridin-2-amine and 9-bromo-2-methylpyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-ol and 1,4-dioxane (1.0 mL). The reaction mixture was stirred at 110℃ for 1 hour and then cooled to room temperature. Et_2O was added thereto to form a solid. The formed solid was filtered and dried under reduced pressure to obtain ivory compound of 9-bromo-2-methylpyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-ol (57.0 mg, 12% in 2 steps).

[2640]

[2641] LC/MS ESI (+): 279 (M+1), 281 (M+3)

[2642] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 12.34 (s, 1H), 8.76 (m, 1H), 8.57 (m, 1H), 7.17 (s, 1H), 2.38 (s, 3H)

[2643]

[2644] (c) Synthesis of *tert* -butyl (1-(9-bromo-2-methylpyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-yl)azetidin-3-yl)(methyl)carbamate

[2645] DIPEA (22.0 μL, 0.13 mmol) was added to suspension of 9-bromo-2-methylpyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-ol (30.0 mg, 0.11 mmol) and $POCl_3$ (2.0 mL), and it was stirred at 120℃ for 20 hours. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was dissolved in DCM (1.0 mL). *tert*-Butyl azetidin-3-yl(methyl)carbamate HCl salt (119.0 mg, 0.54 mmol) and DIPEA (400.0 μL, 2.14 mmol) were added thereto. The mixture was then stirred at room temperature for 12 hours. The reaction mixture was purified by column chromatography (MeOH:DCM=1:50) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of *tert*-butyl (1-(9-bromo-2-methylpyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-yl)azetidin-3-yl)(methyl)carbamate (32.0 mg, 67%).

[2646]

[2647] LC/MS ESI (+): 448 (M+1), 450 (M+3)

[2648] ^{1}H-NMR (400 MHz, $CDCl_3$); δ: 8.65 (m, 1H), 8.17 (m, 1H), 6.67 (s, 1H), 5.20-5.10 (m, 1H), 4.86 (m, 2H), 4.65 (m, 2H), 2.99 (s, 3H), 2.46 (m, 3H), 1.48 (s, 9H)

[2649]

[2650] (d) Synthesis of 1-(9-bromo-2-methylpyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-yl)- *N* -methylazetidin-3-amine

[2651] TFA (0.4 mL) was added to the mixture of *tert*-butyl (1-(9-bromo-2-methylpyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-yl)azetidin-3-yl)(methyl)carbamate (32.0 mg, 0.07 mmol) and DCM (0.6 mL), and it was stirred at room temperature for 30 minutes. The reaction mixture was purified by column chromatography (MeOH:DCM=1:40) on amine silica. The fractions containing the product were collected and evaporated. Et_2O was added to the residue and form a solid. The formed solid was filtered and dried under reduced pressure to obtain ivory compound of 1-(9-bromo-2-methylpyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-yl)-*N*-methylazetidin-3-amine (15.0 mg, 60%).

[2652]

[2653] LC/MS ESI (+): 347 (M+1), 349 (M+3)

[2654] ^{1}H-NMR (400 MHz, $CDCl_3$); δ: 8.64 (d, 1H, *J*=1.8 Hz), 8.15 (d, 1H, *J*=1.8 Hz), 6.65 (s, 1H), 4.82 (m, 2H), 4.37 (m, 2H), 3.75 (m, 1H), 2.48 (s, 3H), 2.47 (s, 3H)

[2655]

[2656] **Example 110**

[2657] **Synthesis of 1-(9-bromopyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-yl)-*N* -methylazetidin-3-amine**

[2658]

[2659] (a) Synthesis of 5-bromo-3-(1H-pyrazol-5-yl)pyridin-2-amine

[2660] $Pd(PPh_3)_4$ (39.0 mg, 0.03 mmol) was added to suspension of 5-bromo-3-iodopyridin-2-amine (100.0 mg, 0.34 mmol), (1-(*tert* -butoxycarbonyl)-1H-pyrazol-5-yl)boronic acid (99.0 mg, 0.47 mmol), Cs_2CO_3 (327.0 mg, 1.01 mmol), H2O (0.5 mL) and DME (2.0 mL). The reaction mixture was allowed to react in microwave under conditions of 100W and 120°C for 1 hour and 30 minutes, then cooled to room temperature and $Pd(PPh_3)_4$ (20.0 mg, 0.02 mmol) and (1-(*tert* -butoxycarbonyl)-1H-pyrazol-5-yl)boronic acid (50.0 mg, 0.24 mmol) were further added thereto. The reaction mixture was allowed to react in microwave under conditions of 100W and 130°C for 2 hours and then cooled to room temperature. Water was added to the reaction mixture, and it was extracted 2 times with DCM. The organic layer was dried over anhydrous Na_2SO_4, filtered and then concentrated under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=1:50) on amine silica. The fractions containing the product were collected and evaporated to obtain brown solid compound which is the mixture of 5-bromo-3-(1H-pyrazol-5-yl)pyridin-2-amine and 9-bromopyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-ol (39.0 mg).

[2661]

[2662] (b) Synthesis of 9-bromopyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-ol

[2663] Diphosgene (0.05 mL) was added to a suspension of mixture of 5-bromo-3-(1H-pyrazol-5-yl)pyridin-2-amine and 9-bromopyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-ol and 1,4-dioxane (1.0 mL). The reaction mixture was stirred at 110°C for 1 hour and then cooled to room temperature. Et_2O was added thereto to form a solid. The formed solid was filtered and dried under reduced pressure to obtain yellow solid compound of 9-bromopyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-ol (32.0 mg, 36% in 2 steps).

[2664]

[2665] LC/MS ESI (+): 265 (M+1), 267 (M+3)

[2666] ^{1}H-NMR (400 MHz, $CDCl_3$+DMSO-d_6); δ: 8.51 (d, 1H, *J*=1.5 Hz), 8.43 (d, 1H, *J* =1.5 Hz), 8.04 (m, 1H), 7.11 (m, 1H)

[2667]

[2668] (c) Synthesis of *tert* -butyl (1-(9-bromopyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-yl)azetidin-3-yl)(methyl)carbama

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[2669] DIPEA (25.0 μL, 0.15 mmol) was added to suspension of 9-bromopyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-ol (32.0 mg, 0.12 mmol) and $POCl_3$ (2.0 mL), and it was stirred at 120℃ for 24 hours. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was dissolved in DCM (1.2 mL), and *tert*-butyl azetidin-3-yl(methyl)carbamate HCl salt (135.0 mg, 0.61 mmol) and DIPEA (420.0 μL, 2.42 mmol) were added thereto. The reaction mixture was stirred at room temperature for 12 hours and then purified by column chromatography (EtOAc:*n*-Hex=1:5) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of *tert* -butyl (1-(9-bromopyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-yl)azetidin-3-yl)(methyl)carbamate (32.0 mg, 62%).

[2670]

[2671] LC/MS ESI (+): 433 (M+1), 435 (M+3)

[2672] ^{1}H-NMR (400 MHz, $CDCl_3$); δ: 8.68 (m, 1H), 8.24 (m, 1H), 7.97 (m, 1H), 6.89 (m, 1H), 5.20-5.10 (m, 1H), 4.89 (m, 2H), 4.68 (m, 2H), 2.99 (s, 3H), 1.48 (s, 9H)

[2673]

[2674] (d) Synthesis of 1-(9-bromopyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-yl)- *N* -methylazetidin-3-amine

[2675] TFA (0.4 mL) was added to the mixture of *tert*-butyl (1-(9-bromopyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-yl)azetidin-3-yl)(methyl)carbamate (32.0 mg, 0.07 mmol) and DCM (0.6 mL), and it was stirred at room temperature for 30 minutes. The reaction mixture was purified by column chromatography (MeOH:DCM=1:40) on amine silica. The fractions containing the product were collected and evaporated. Et_2O was added to the residue and form a solid. The formed solid was filtered and dried under reduced pressure to obtain ivory solid compound of 1-(9-bromopyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-yl)-*N*-methylazetidin-3-amine (16.0 mg, 64%).

[2676]

[2677] LC/MS ESI (+): 333 (M+1), 335 (M+3)

[2678] ^{1}H-NMR (400 MHz, $CDCl_3$); δ: 8.67 (d, 1H, *J*=1.8 Hz), 8.22 (d, 1H, *J*=1.8 Hz), 7.97 (d, 1H, *J*=1.5 Hz), 6.88 (d, 1H, *J*=1.5 Hz), 4.86 (m, 2H), 4.40 (m, 2H), 3.76 (m, 1H), 2.48 (s, 3H)

[2679]

[2680]

[2681] **Example 111**

[2682] **Synthesis of N-**

methyl-1-(8-nitropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine

[2683]

[2684] (a) Synthesis of 5-nitropyridine-2,3-diamine

[2685] 3,5-Dinitropyridin-2-amine (300.0 mg, 1.63 mmol) and ammonium sulfide solution (2.4 mL, 8.15 mmol) was dissolved in MeOH (11.3 mL), and it was stirred at 75℃ for 30 minutes and then cooled to room temperature. The formed solid was filtered and then dried under reduced pressure to obtain red solid compound of 5-nitropyridine-2,3-diamine (250.0 mg, 99%).

[2686]

[2687] LC/MS ESI (+): 155 (M+1)

[2688] ^{1}H-NMR (400MHz, DMSO-d_6);δ:8.29 (d, 1H, J=1.8Hz), 7.36 (d, 1H, J=1.8Hz), 6.99 (s, 2H), 5.32 (s, 2H)

[2689]

[2690] (b) Synthesis of 7-nitropyrido[2,3-b]pyrazine-2,3-diol

[2691] 5-Nitropyridine-2,3-diamine (25.0 mg, 1.63 mmol) was added to diethyloxalate (5.0 mL) and the reaction mixture was stirred at 180℃ for 72 hours and then cooled to room temperature. Et_2O was added to the reaction mixture to form a solid. The formed solid was filtered and dried under reduced pressure to obtain light brown solid compound of 7-nitropyrido[2,3-b]pyrazine-2,3-diol (167.0 mg, 49%).

[2692]

[2693] ^{1}H-NMR (400MHz, DMSO-d_6);δ:12.95 (s, 1H), 12.23 (s, 1H), 8.93 (d, 1H, J =1.8Hz), 8.11 (d, 1H, J=1.8Hz)

[2694]

[2695] (c) Synthesis of 2,3-dichloro-7-nitropyrido[2,3-b]pyrazine

[2696] The mixture of 7-nitropyrido[2,3-b]pyrazine-2,3-diol (167.0 mg, 0.80 mmol) and $POCl_3$ (2.6 mL) was stirred at 150℃ for 48 hours and then cooled to room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (n-Hex:EtOAc=80:20) on silica. The fractions containing the product were collected and evaporated to obtain white solid compound of 2,3-dichloro-7-nitropyrido[2,3-b]pyrazine (68.0 mg, 35%).

[2697]

[2698] LC/MS ESI (+): 245 (M+1), 247 (M+3)

[2699]

[2700] (d) Synthesis of *tert* -butyl (1-(2-chloro-7-nitropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[2701] 2,3-Dichloro-7-nitropyrido[2,3-b]pyrazine (68.0 mg, 0.28 mmol) and *tert*-butyl azetidin-3-yl(methyl)carbamate HCl salt (61.8 mg, 0.28 mmol) were added to DCM (6.0 mL), and TEA (0.12 mL, 0.84 mmol) was slowly added thereto at 0℃. The

reaction mixture was stirred at room temperature for 1 hour and then concentrated under reduced pressure. The residue was purified by column chromatography (*n*-Hex:EtOAc=70:30) on silica. The fractions containing the product were collected and evaporated to obtain white solid compound of *tert*-butyl (1-(2-chloro-7-nitropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (95.0 mg, 87%).

[2702]

[2703] LC/MS ESI (+): 395 (M+1)

[2704]

[2705] (e) Synthesis of *tert*-butyl (1-(2-hydrazinyl-7-nitropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate

[2706] *tert*-Butyl (1-(2-chloro-7-nitropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate (90.0 mg, 0.23 mmol) and hydrazine hydrate (24.0 μL, 0.68 mmol) were dissolved in EtOH (2.3 mL), and it was stirred at room temperature for 1 hour and then concentrated under reduced pressure. Et_2O was added to the reaction mixture and form a solid. The formed solid was filtered and dried under reduced pressure to obtain yellow solid compound of *tert*-butyl (1-(2-hydrazinyl-7-nitropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate. The mixture of unpurified *tert*-butyl (1-(2-hydrazinyl-7-nitropyrido[2,3-b]pyrazin-3-yl)azetidin-3-yl)(methyl)carbamate and trimethyl orthoformate (2.5 mL) was stirred at 75°C for 5 hours and then cooled to room temperature. Et_2O was added thereto to form a solid. The formed solid was filtered and purified by column chromatography (DCM:MeOH=95:5) on amine silica. The fractions containing the product were collected and evaporated to obtain ivory solid compound of *tert*-butyl methyl(1-(8-nitropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)carbamate (64.0 mg, 66%).

[2707]

[2708] LC/MS ESI (+): 401 (M+1)

[2709] ^{1}H-NMR (400MHz, DMSO-d_6); δ: 10.23 (s, 1H), 9.47 (d, 1H, *J*=1.8Hz), 9.32 (d, 1H, *J*=1.8Hz), 5.00 (m, 3H), 4.52 (m, 1H), 2.95 (s, 3H), 1.44 (s, 9H)

[2710]

[2711] (f) Synthesis of N-methyl-1-(8-nitropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine

[2712] *tert*-Butyl methyl(1-(8-nitropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)carbamate (30.0 mg, 0.08 mmol) was dissolved in DCM (1.0 mL), and TFA (0.5 mL) was

slowly added thereto at 0°C. The reaction mixture was stirred at room temperature for 1 hour and then concentrated under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=95:5) on amine silica. The fractions containing the product were collected and evaporated to obtain yellow solid compound of *N*-methyl-1-(8-nitropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine (20.0 mg, 89%).

[2713]

[2714] LC/MS ESI (+): 301 (M+1)

[2715] ^{1}H-NMR (400MHz, DMSO-d_6); δ: 10.22 (s, 1H), 9.44 (d, 1H, *J*=1.8Hz), 9.30 (d, 1H, *J*=1.8Hz), 4.97 (m, 1H), 4.53 (m, 2H), 4.09 (m, 1H), 3.77 (m, 1H), 2.32 (s, 3H)

[2716]

[2717] **Example 112**

[2718] **Synthesis of 4-(3-(methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-amine**

[2719]

[2720] (a) Synthesis of *tert*-butyl (1-(8-aminopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate

[2721] *tert*-Butyl methyl(1-(8-nitropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)carbamate (35.0 mg, 0.09 mmol) and 10% Pd/C (9.0 mg) were dissolved in MeOH (3.0 mL). The flask was substituted with hydrogen and then stirred at room temperature for 40 minutes. The reaction mixture was filtered with celite and then concentrated under reduced pressure to obtain *tert*-butyl (1-(8-aminopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (32.4 mg).

[2722]

[2723] LC/MS ESI (+): 371 (M+1)

[2724]

[2725] (b) Synthesis of 4-(3-(methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-amine

[2726] Unpurified *tert*-butyl (1-(8-aminopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate (32.4 mg, 0.09 mmol) was dissolved in DCM (1.5 mL), and TFA (0.5 mL) was slowly added thereto at room temperature. The reaction mixture was stirred at room temperature for 1 hour and then concentrated under reduced pressure. The residue was purified by column chromatography (*n*-Hex:EtOA:MeOH=40:40:20) on amine silica.

The fractions containing the product were collected and evaporated to obtain yellow solid compound of 4-(3-(methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-amine (5.0 mg, 21% in 2 steps).

[2727]

[2728] LC/MS ESI (+): 271 (M+1)

[2729] ^{1}H-NMR (400MHz, DMSO-d_6); δ: 9.83 (s, 1H), 8.05 (d, 1H, *J*=1.8Hz), 7.56 (d, 1H, *J*=1.8Hz), 5.63 (s, 2H), 4.55 (m, 2H), 4.11 (m, 2H), 3.68 (m, 1H), 2.29 (s, 3H)

[2730]

[2731] **Example 113**

[2732] **Synthesis of N-methyl-1-(8-phenylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine**

[2733] $Pd(PPh_3)_4$ (17.0 mg, 0.02 mmol) was added to a suspension of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (50.0 mg, 0.15 mmol), phenylboronic acid (27.0 mg, 0.22 mmol), Cs_2CO_3 (122.0 mg, 0.38 mmol), H_2O (0.3 mL) and DME (1.2 mL). The reaction mixture was reacted with microwave under conditions of 50W and 80°C for 30 minutes and then cooled to room temperature. The reaction mixture was purified by column chromatography (MeOH:DCM=1:40) on amine silica. The fractions containing the product were collected and concentrated. Et_2O was added to the residue and a solid was formed. The formed solid was filtered and dried under reduced pressure to obtain yellow solid compound of N-methyl-1-(8-phenylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine (42.0 mg, 85%).

[2734]

[2735] LC/MS ESI (+): 332 (M+1)

[2736] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 10.08 (s, 1H), 8.91 (m, 2H), 7.87 (m, 2H), 7.55 (m, 2H), 7.44 (m, 1H), 4.91 (m, 1H), 4.45 (m, 2H), 4.02 (m, 1H), 3.72 (m, 1H), 2.45 (m, 1H), 2.31 (s, 1H)

[2737]

[2738] **Example 114**

[2739] **Synthesis of 1-(8-(furan-2-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine**

[2740] $Pd(PPh_3)_4$ (17.0 mg, 0.02 mmol) was added to a suspension of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (50.0 mg, 0.15 mmol), furan-2-ylboronic acid (34.0 mg, 0.30 mmol), Cs_2CO_3 (122.0

mg, 0.38 mmol), H_2O (0.3 mL) and DME (1.2 mL). The reaction mixture was reacted with microwave under conditions of 50W and 80℃ for 30 minutes and then cooled to room temperature. The reaction mixture was purified by column chromatography (MeOH:DCM=1:40) on amine silica. The fractions containing the product were collected and concentrated. Et_2O was added to the residue and a solid was formed. The formed solid was filtered and dried under reduced pressure to obtain yellow solid compound of 1-(8-(furan-2-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (31.0 mg, 65%).

[2741]

[2742] LC/MS ESI (+): 322 (M+1)

[2743] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 10.07 (s, 1H), 8.91 (s, 1H), 8.82 (s, 1H), 7.87 (s, 1H), 7.12 (m, 1H), 6.70 (m, 1H), 4.91 (m, 1H), 4.44 (m, 2H), 4.02 (m, 1H), 3.72 (m, 1H), 2.31 (s, 3H)

[2744]

[2745] **Example 115**

[2746] **Synthesis of 1-(2-bromopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6-yl)-N-methylazetidin-3-amine**

[2747] (a) Synthesis of 5-bromo-3-(1H-pyrrol-1-yl)pyridin-2-amine

[2748] A mixture of 5-bromopyridine-2,3-diamine (2000.0 mg, 10.6 mmol) and 2,5-dimethoxytetrahydrofuran (1.5 mL, 11.7 mmol) in AcOH (10.0 mL) was stirred at 90℃ for 4 hours. The reaction mixture was poured into water, neutralized with 10% NaOH aqueous solution (pH=7) and then extracted with EtOAc (200.0 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then concentrated. The residue was purified by column chromatography (EtOAc:*n*-Hex=1:4) on silica. The fractions containing the product were collected and concentrated to obtain yellow solid compound of 5-bromo-3-(1H-pyrrol-1-yl)pyridin-2-amine (614.0 mg, 24%).

[2749]

[2750] LC/MS ESI (+): 238 (M+1), 240 (M+3)

[2751] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 8.13 (d, 1H, *J*=2.1 Hz), 7.53 (d, 1H, *J*=2.1 Hz), 6.83 (m, 2H), 6.37 (m, 2H), 4.63 (brs, 2H)

[2752]

[2753] (b) Synthesis of 2-bromopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6(5H)-one

[2754] The mixture of 5-bromo-3-(1H-pyrrol-1-yl)pyridin-2-amine (200.0 mg, 0.84 mmol) and triphosgene (374.0 mg, 1.26 mmol) in anhydrous toluene (8.0 mL) was stirred at 110℃ for 3 hours, cooled to room temperature and then concentrated under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=30:1) on

silica. The fractions containing the product were collected and concentrated to obtain dark green solid compound of 2-bromopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (178.0 mg, 80%).

[2755]

[2756] LC/MS ESI (+): 264 (M+1), 266 (M+3)

[2757] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 11.86 (s, 1H), 8.81 (m, 1H), 8.37 (m, 1H), 8.28 (m, 1H), 7.08 (m, 1H), 6.74 (m, 1H)

[2758]

[2759] (c) Synthesis of *tert* -butyl (1-(2-bromopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6-yl)azetidin-3-yl)(methyl)carbamate

[2760] 2-Bromopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (178.0 mg, 0.67 mmol) was dissolved in $POCl_3$ (3.0 mL), and then DIPEA (141.0 μL, 0.81 mmol) was added thereto. The reaction mixture was stirred at 120°C for 12 hours, cooled to room temperature and then concentrated under reduced pressure. Unpurified 2-bromo-6-chloropyrido[2,3-e]pyrrolo[1,2-a]pyrazine and TEA (0.5 mL, 3.35 mmol) were dissolved in DMA (7.0 mL), and *tert*-butyl azetidin-3-yl(methyl)carbamate hydrochloride (164.0 mg, 0.74 mmol) was added thereto. The reaction mixture was stirred at 110°C for 12 hours, cooled to room temperature and then concentrated under reduced pressure. The residue was purified by column chromatography (DCM:MeOH=97:3) on amine silica. The fractions containing the product were collected and concentrated to obtain brown solid compound of *tert*-butyl (1-(2-bromopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6-yl)azetidin-3-yl)(methyl)carbamate (179.0 mg, 62% in 2 steps).

[2761]

[2762] LC/MS ESI (+): 432 (M+1), 434 (M+3)

[2763]

[2764] (d) Synthesis of 1-(2-bromopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6-yl)-N-methylazetidin-3-amine

[2765] *tert*-Butyl (1-(2-bromopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6-yl)azetidin-3-yl)(methyl)carbamate (179.0 mg, 0.41 mmol) was dissolved in DCM (2.0 mL), and TFA (2.0 mL) was slowly added thereto at 0°C. The reaction mixture was stirred at room temperature for 2 hours and then concentrated under reduced pressure. The residue was neutralized with NEt_3 and purified by column chromatography (DCM:MeOH=100:0 to 90:10) on amine silica. The fractions containing the product were collected and concentrated to obtain brown solid compound of 1-(2-bromopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6-yl)-N-methylazetidin-3-amine (91.0 mg, 66%).

[2766]

[2767] LC/MS ESI (+): 332(M+1), 334 (M+3)

[2768] ^{1}H-NMR (400MHz, DMSO-d_6); δ: 8.75 (m, 1H), 8.39 (m, 2H), 6.90 (m, 1H), 6.82 (m, 1H), 4.54 (m, 2H), 4.09 (m, 2H), 3.65 (m, 1H), 2.28 (s, 3H)

[2769]

[2770] **Example 116**

[2771] **Synthesis of 1-(2-chloropyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazin-6-yl)-N-methylazetidin-3-amine**

[2772] (a) Synthesis of 6-bromo-3-nitropyridin-2-amine

[2773] 2,6-Dibromo-3-nitropyridine (700.0 mg, 2.48 mmol) was added to 2M ammonia solution in EtOH (25.0 mL, 49.66 mmol). The mixture stirred at room temperature for 12 hours and concentrated under reduced pressure to obtain yellow solid compound of 6-bromo-3-nitropyridin-2-amine (526.0 mg, 97%).

[2774]

[2775] ^{1}H-NMR (400MHz, DMSO-d_6); δ: 8.26 (m, 3H), 6.91 (d, 1H, *J*=8.4Hz)

[2776]

[2777] (b) Synthesis of 6-bromopyridine-2,3-diamine

[2778] 6-Bromo-3-nitropyridin-2-amine (520.0 mg, 2.39 mmol) and $SnCl_2$ $2H_2O$ (2140.0 mg, 9.54 mmol) were added to DMF (8.6 mL), and the reaction mixture was stirred at 80℃ for 2 hours. The reaction mixture was cooled to room temperature, basified with 1N NaOH (pH=9) and then extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain brown solid compound of 6-bromopyridine-2,3-diamine (238.0 mg, 44%).

[2779]

[2780] ^{1}H-NMR (400MHz, DMSO-d_6); δ: 6.62 (d, 1H, *J*=8.4Hz), 6.48 (d, 1H, *J*=8.4Hz), 5.81 (brs, 2H), 4.79 (brs, 2H)

[2781]

[2782] (c) Synthesis of 6-bromopyrido[2,3-b]pyrazine-2,3-diol

[2783] 6-Bromopyridine-2,3-diamine (238.0 mg, 1.26 mmol) was added to diethyl oxalate (4.0 mL). The mixture was stirred at 150℃ for 4 hours and then cooled to room temperature. Et_2O was added to form a solid. The formed solid was filtered and then dried under reduced pressure to obtain brown solid compound of 6-bromopyrido[2,3-b]pyrazine-2,3-diol (250.0 mg, 82%).

[2784]

[2785] ^{1}H-NMR (400MHz, DMSO-d_6); δ: 12.50 (brs, 1H), 12.06 (brs, 1H), 7.36(m, 2H)

[2786]

[2787] (d) Synthesis of 2,3,6-trichloropyrido[2,3-b]pyrazine

[2788] A mixture of 6-bromopyrido[2,3-b]pyrazine-2,3-diol (250.0 mg, 1.03 mmol) and $POCl_3$ (4.0 mL) was stirred at 150°C for 10 hours and then cooled to room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (*n*-Hex:EtOAc=70:30) on silica. The fractions containing the product were collected and concentrated to obtain white solid compound of 2,3,6-trichloropyrido[2,3-b]pyrazine (180.0 mg, 63%).

[2789]

[2790] LC/MS ESI (+): 234(M+1), 236 (M+3)

[2791] ^{1}H-NMR (400MHz, DMSO-d_6); δ: 8.65 (d, 1H, *J*=8.8 Hz), 8.08 (d, 1H, *J*=8.8 Hz)

[2792]

[2793] (e) Synthesis of 2,6-dichloropyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine

[2794] Hydrazine monohydrate (18.0 μL, 0.51 mmol) was added to a suspension of 2,3,6-trichloropyrido[2,3-b]pyrazine (80.0 mg, 0.34 mmol) and EtOH (1.4 mL). The reaction mixture was stirred at room temperature for 90 minutes. Et_2O was added thereto to form a solid. The formed solid was filtered and dried under reduced pressure to obtain yellow solid compound of 2,6-dichloro-3-hydrazinylpyrido[2,3-b]pyrazine. Unpurified 2,6-dichloro-3-hydrazinylpyrido[2,3-b]pyrazine (60.0 mg, 0.26 mmol) was dissolved in trimethyl orthoformate (3.0 mL) and then stirred at 85°C for 12 hours. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was purified by column chromatography (*n*-Hex:EtOAc=70:30) on silica. The fractions containing the product were collected and concentrated to obtain beige solid compound of 2,6-dichloropyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine (35.0 mg, 56% in 2 steps).

[2795]

[2796] ^{1}H-NMR (400MHz, DMSO-d_6); δ: 10.14 (s, 1H), 8.60 (d, 1H, *J*=8.4Hz), 7.96 (d, 1H, *J*=8.4Hz)

[2797]

[2798] (f) Synthesis of 1-(2-chloropyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazin-6-yl)-N-methylazetidin-3-amine

[2799] 2,6-Dichloropyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine (35.0 mg, 0.12 mmol) and *tert*-butyl azetidin-3-yl(methyl)carbamate hydrochloride (41.0 mg, 0.18 mmol) were added to DCM (1.0 mL), and TEA (51.0 μL, 0.37 mmol) was slowly added thereto at room temperature. The reaction mixture was stirred at room temperature for 30 minutes and then concentrated under reduced pressure. The residue was purified column chromatography (*n*-Hex:EtOAc=70:30) on silica. The fractions containing the product were collected and concentrated to obtain yellow solid compound of *tert*-butyl (1-(2-chloropyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazin-6-yl)azetidin-3-yl)(methyl)carbamate. TFA (0.4 mL) was added to a mixture of *tert*-butyl

(1-(2-chloropyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazin-6-yl)azetidin-3-yl)(methyl)carbamate and DCM (1.0 mL), and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=5:95) on amine silica. The fractions containing the product were collected and concentrated to obtain beige solid compound of 1-(2-chloropyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazin-6-yl)-N-methylazetidin-3-amine (30.0 mg, 86% in 2 steps).

[2800]

[2801] LC/MS ESI (+): 290 (M+1)

[2802] ^{1}H-NMR (400MHz, DMSO-d_6); δ: 9.31 (s, 1H), 8.02 (d, 1H, *J*=8.4 Hz), 7.61 (d, 1H, *J*=8.4 Hz), 4.90 (m, 1H), 4.43 (m, 2H), 4.00 (m, 1H), 3.73 (m, 1H), 2.30 (s, 3H)

[2803]

[2804] **Example 117**

[2805] **Synthesis of 1-(8-chloropyrido[3,4-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine**

[2806] (a) Synthesis of 6-bromopyridine-3,4-diamine

[2807] 2-Bromo-5-nitropyridin-4-amine (300.0 mg, 2.48 mmol) and Fe (300.0 mg, 5.37 mmol) were added to AcOH, and the reaction mixture was stirred at 75℃ for 4 hours and then cooled to room temperature. The reaction mixture was filtered through celite and then concentrated under reduced pressure. The residue was purified by column chromatography (*n*-Hex:EtOAc=50:50) on amine silica. The fractions containing the product were collected and concentrated to obtain brown solid compound of 6-bromopyridine-3,4-diamine (200.0 mg, 78%).

[2808]

[2809] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 7.39 (s, 1H), 6.42 (s, 1H), 5.74 (brs, 2H), 4.66 (brs, 2H)

[2810]

[2811] (b) Synthesis of 7-bromopyrido[3,4-b]pyrazine-2,3-diol

[2812] 6-Bromopyridine-3,4-diamine (200.0 mg, 1.06 mmol) was added to diethyl oxalate (3.0 mL). The mixture was stirred at 130℃ for 12 hours and then cooled to room temperature. Et_2O was added thereto to form a solid. The formed solid was filtered and dried under reduced pressure to obtain brown solid compound of 7-bromopyrido[3,4-b]pyrazine-2,3-diol (195.0 mg, 76%).

[2813]

[2814] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 12.23 (brs, 1H), 12.11 (brs, 1H), 8.09 (s, 1H), 7.05 (s, 1H)

[2815]

[2816] (c) Synthesis of 2,3,7-trichloropyrido[3,4-b]pyrazine

[2817] A mixture of 7-bromopyrido[3,4-b]pyrazine-2,3-diol (190.0 mg, 0.79 mmol) and $POCl_3$ (3.0 mL) was stirred at 150°C for 12 hours and then cooled to room temperature. Et_2O was added thereto to form a solid and the formed solid was filtered. The resulting solid was purified by column chromatography (*n*-Hex:EtOAc=50:50) on silica. The fractions containing the product were collected and concentrated to obtain white solid compound of 2,3,7-trichloropyrido[3,4-b]pyrazine (1.0 mg, 5%).

[2818]

[2819] LC/MS ESI (+): 234(M+1), 236 (M+3)

[2820] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 9.39 (s, 1H), 8.31 (s, 1H)

[2821]

[2822] (d) Synthesis of 4,8-dichloropyrido[3,4-e][1,2,4]triazolo[4,3-a]pyrazine

[2823] Hydrazine monohydrate (1.9 μL, 0.05 mmol) was added to a suspension of 2,3,7-trichloropyrido[3,4-b]pyrazine (10.0 mg, 0.03 mmol) and EtOH (0.5 mL) at 0°C. The reaction mixture was stirred at room temperature for 3 hours. Et_2O was added thereto to form a solid. The formed solid was filtered and dried under reduced pressure to obtain red solid compound of 3,7-dichloro-2-hydrazinylpyrido[3,4-b]pyrazine. Unpurified 3,7-dichloro-2-hydrazinylpyrido[3,4-b]pyrazine was dissolved in trimethyl orthoformate (0.3 mL), and the reaction mixture was stirred at 80°C for 5 hours. The reaction mixture was cooled to room temperature. Et_2O was added thereto to form a solid. The formed solid was filtered and dried under reduced pressure to form orange solid compound of 4,8-dichloropyrido[3,4-e][1,2,4]triazolo[4,3-a]pyrazine (3.5 mg, 42% in 2 steps).

[2824]

[2825] LC/MS ESI (+): 240 (M+1)

[2826] ^{1}H-NMR (400MHz, $CDCl_3$); δ: 9.35 (s, 1H), 9.19 (s, 1H), 7.90 (s, 1H)

[2827]

[2828] (e) Synthesis of 1-(8-chloropyrido[3,4-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine

[2829] 4,8-Dichloropyrido[3,4-e][1,2,4]triazolo[4,3-a]pyrazine (3.5 mg, 0.01 mmol) and *tert*-butyl azetidin-3-yl(methyl)carbamate hydrochloride(4.1 mg, 0.02 mmol) were added to DCM (0.2 mL), and TEA (5.0 μL, 0.04 mmol) was added thereto at room temperature. The reaction mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure to obtain *tert*-butyl (1-(8-chloropyrido[3,4-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamate. TFA (0.2 mL) was added to a mixture of unpurified *tert*-butyl (1-(8-chloropyrido[3,4-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carba

mate and DCM (1.0 mL), and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (MeOH:DCM=5:95) on amine silica. The fractions containing the product were collected and concentrated to obtain beige solid compound of 1-(8-chloropyrido[3,4-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (2.0 mg, 57% in 2 steps).

[2830]

[2831] LC/MS ESI (+): 290 (M+1)

[2832] ^{1}H-NMR (400 MHz, $CDCl_3$); δ: 9.12 (s, 1H), 8.77 (s, 1H), 7.62 (s, 1H), 5.07 (m, 1H), 4.59 (m, 2H), 4.18 (m, 1H), 3.88 (m, 1H), 2.50 (s, 3H)

[2833]

[2834] **Example 118**

[2835] **Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine methanesulfonic acid salt**

[2836] Methanesulfonic acid (38.9 μL, 0.60 mmol) was slowly added to a suspension of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (200.0 mg, 0.60 mmol) and ethanol (3.0 mL). The reaction mixture was stirred at room temperature for 20 hours to form a solid. The formed solid was filtered under reduced pressure, washed with ethanol and then dried under reduced pressure to obtain ivory solid compound of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine methanesulfonic acid salt (226.0 mg, 88%).

[2837]

[2838] LC/MS ESI (+): 334(M+1), 336(M+3)

[2839] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 10.02 (s, 1H), 9.14 (brs, 2H), 8.99 (d, 1H, *J*=2.3 Hz), 8.67 (d, 1H, *J*=2.3 Hz), 5.03 (m, 1H), 4.84 (m, 1H), 4.58 (m, 1H), 4.40 (m, 1H), 4.27 (m, 1H), 2.68 (s, 3H), 2.30 (s, 3H)

[2840]

[2841] **Example 119**

[2842] **Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine maleic acid salt**

[2843] Maleic acid (139.0 mg, 1.20 mmol) was slowly added to a suspension of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (200.0 mg, 0.60 mmol) and ethanol (3.0 mL). The reaction mixture was stirred at room temperature for 20 hours. The formed solid was filtered under reduced pressure,

washed with ethanol and then dried under reduced pressure to obtain white solid compound of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine maleic acid salt (242.0 mg, 90%).

[2844]

[2845] LC/MS ESI (+): 334 (M+1), 336 (M+3)

[2846] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 10.02 (s, 1H), 8.99 (brs, 2H), 8.98 (d, 1H, *J*=2.3 Hz), 8.66(d, 1H, *J*=2.3 Hz), 6.02 (s, 2H), 5.03 (m, 1H), 4.82 (m, 1H), 4.58 (m, 1H), 4.38 (m, 1H), 4.23 (m, 1H), 2.66 (s, 3H)

[2847]

[2848] **Example 120**

[2849] **Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine 2-hydroxypropane-1,2,3-tricarboxylic acid salt**

[2850] 2-Hydroxypropane-1,2,3-tricarboxylic acid (230.0 mg, 1.20 mmol) was slowly added to a suspension of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (200.0 mg, 0.60 mmol) and THF (6.0 mL). The reaction mixture was stirred at room temperature for 20 hours. The formed solid was filtered under reduced pressure, washed with ethanol and then dried under reduced pressure to obtain white solid compound of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine 2-hydroxypropane-1,2,3-tricarboxylic acid salt (246.0 mg, 78%).

[2851]

[2852] LC/MS ESI (+): 334 (M+1), 336 (M+3)

[2853] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 9.98 (s, 1H), 8.94 (d, 1H, *J*=2.3 Hz), 8.63 (d, 1H, *J*=2.3 Hz), 4.96 (m, 1H), 4.62 (m, 1H), 4.50 (m, 1H), 4.18 (m, 1H), 3.95 (m, 1H), 2.55 (m, 4H), 2.47 (s, 3H)

[2854]

[2855] **Example 121**

[2856] **Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine nitric acid salt**

[2857] 70% Nitric acid (13.0 μL, 0.30 mmol) was added to a suspension of 1-(8-Bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (50.0 mg, 0.15 mmol) and ethanol (1.5 mL). The reaction mixture was stirred at room temperature for 12 hours. The formed solid was filtered under reduced pressure, washed with ethanol and then dried under reduced pressure to obtain white solid

compound of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine nitric acid salt (55.8 mg, 94%).

[2858]

[2859] LC/MS ESI (+): 334 (M+1), 336 (M+3)

[2860] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 10.02 (s, 1H), 9.15 (brs, 2H), 8.98 (d, 1H, *J*=2.4 Hz), 8.66 (d, 1H, *J*=2.4 Hz), 5.03 (m, 1H), 4.83 (m, 1H), 4.58 (m, 1H), 4.40 (m, 1H), 4.27 (m, 1H), 2.69 (s, 3H)

[2861]

[2862] **Example 122**

[2863] **Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine hydroiodic acid salt**

[2864] 55% HI (41.0 μL, 0.30 mmol) was added to a suspension of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (50.0 mg, 0.15 mmol) and ethanol (1.5 mL). The reaction mixture was stirred at room temperature for 12 hours. The formed solid was filtered under reduced pressure, washed with ethanol and then dried under reduced pressure to obtain yellow solid compound of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine hydroiodic acid salt (60.0 mg, 87%).

[2865]

[2866] LC/MS ESI (+): 334 (M+1), 336 (M+3)

[2867] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 10.02 (s, 1H), 9.11 (brs, 2H), 8.99 (d, 1H, *J*=2.0 Hz), 8.67 (d, 1H, *J*=2.0 Hz), 5.03 (m, 1H), 4.83 (m, 1H), 4.58 (m, 1H), 4.40 (m, 1H), 4.26 (m, 1H), 2.69 (s, 3H)

[2868]

[2869] **Example 123**

[2870] **Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine phosphoric acid salt**

[2871] 85% phosphoric acid (25.9 μL, 0.22 mmol) was slowly added to a suspension of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (50.0 mg, 0.15 mmol) and ethanol (2.0 mL). The reaction mixture was stirred at room temperature for 20 hours. The formed solid was filtered under reduced pressure, washed with ethanol and then dried under reduced pressure to obtain white solid compound of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine

phosphoric acid salt (59.0 mg, 91%).

[2872]

[2873] LC/MS ESI (+): 334 (M+1), 336 (M+3)

[2874] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 9.97 (s, 1H), 8.93 (d, 1H, *J*=2.3 Hz), 8.61 (d, 1H, *J*=2.3 Hz), 4.94 (m, 1H), 4.59 (m, 1H), 4.48 (m, 1H), 4.15 (m, 1H), 3.90 (m, 1H), 2.42 (s, 3H)

[2875]

[2876] **Example 124**

[2877] **Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine 4,4'-methylenebis(3-hydroxy-2-naphthoic acid) salt**

[2878] Pamoic acid (87.2 mg, 0.22 mmol) was added to a suspension of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (50.0 mg, 0.15 mmol) and ethanol (2.0 mL). The reaction mixture was stirred at room temperature for 20 hours. The formed solid was filtered under reduced pressure, washed with ethanol and then dried under reduced pressure to obtain green solid compound of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine 4,4'-methylenebis(3-hydroxy-2-naphthoic acid) salt (95.0 mg, 88%).

[2879]

[2880] LC/MS ESI (+): 334 (M+1), 336 (M+3)

[2881] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 9.98 (s, 1H), 8.91 (d, 1H, *J*=2.3 Hz), 8.63 (d, 1H, *J*=2.3 Hz), 8.35 (s, 2H), 8.14 (m, 2H), 7.79 (m, 2H), 7.30 (m, 2H), 7.15 (m, 2H), 5.04 (m, 1H), 4.91 (m, 1H), 4.74 (s, 2H), 4.59 (m, 1H), 4.47 (m, 1H), 4.29 (m, 1H), 2.72 (s, 3H)

[2882]

[2883] **Example 125**

[2884] **Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine hydrobromic acid salt**

[2885] 33% Hydrogen bromide in acetic acid (41.3μL, 0.23mmol) was slowly added to a suspension of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (50.0 mg, 0.15 mmol) and ethanol (1.5 mL). The reaction mixture was stirred at room temperature for 20 hours. The formed solid was filtered under reduced pressure, washed with ethanol and dried under reduced pressure to obtain white solid compound of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine

hydrobromic acid salt (54.3 mg, 87%).

[2886]

[2887] LC/MS ESI (+): 334 (M+1), 336 (M+3)

[2888] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 10.04 (s, 1H), 9.23 (brs, 2H), 9.00 (d, 1H, *J*=2.2 Hz), 8.67 (d, 1H, *J*=2.2 Hz), 5.05 (m, 1H), 4.87 (m, 1H), 4.59 (m, 1H), 4.43 (m, 1H), 4.29 (m, 1H), 2.69 (s, 3H)

[2889]

[2890] **Example 126**

[2891] **Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine sulfuric acid salt**

[2892] Sulfuric acid solution (22.5 mg, 0.23 mmol) in ethanol (0.5 mL) was slowly added to a suspension of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (50.0 mg, 0.15 mmol) and ethanol (1.0 mL). The reaction mixture was stirred at room temperature for 20 hours. The formed solid was filtered under reduced pressure, washed with ethanol and dried under reduced pressure to obtain white solid compound of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine sulfuric acid salt (64.6 mg, 99%).

[2893]

[2894] LC/MS ESI (+): 334 (M+1), 336 (M+3)

[2895] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 10.03 (s, 1H), 9.20 (brs, 2H), 9.01 (d, 1H, *J*=2.2 Hz), 8.67 (d, 1H, *J*=2.2 Hz), 5.05 (m, 1H), 4.86 (m, 1H), 4.60 (m, 1H), 4.43 (m, 1H), 4.29 (m, 1H), 2.69 (t, 3H, *J*=5.0 Hz)

[2896]

[2897] **Example 127**

[2898] **Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (2R,3R)-2,3-dihydroxysuccinic acid salt**

[2899] (2R,3R)-2,3-Dihydroxysuccinic acid solution (45mg, 0.30mmol) in ethanol (0.5 mL) was slowly added to a suspension of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (50.0 mg, 0.15 mmol) and ethanol (1.0 mL). The reaction mixture was stirred at room temperature for 48 hours. The formed solid was filtered under reduced pressure, washed with ethanol and dried under reduced pressure to obtain white solid compound of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine

(2R,3R)-2,3-dihydroxysuccinic acid salt (62.9 mg, 86%).

[2900]

[2901] LC/MS ESI (+): 334 (M+1), 336 (M+3)

[2902] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 9.97 (s, 1H), 8.92 (d, 1H, *J*=2.2 Hz), 8.60 (d, 1H, *J*=2.2 Hz), 4.94 (m, 1H), 4.57 (m, 1H), 4.47 (m, 1H), 4.14 (m, 1H), 4.13 (s, 2H), 3.90 (m, 1H), 2.42 (s, 3H)

[2903]

[2904] **Example 128**

[2905] **Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (1S)-(+)-10-Camphorsulfonic acid salt**

[2906] (1S)-(+)-10-Camphorsulfonic acid (69.5 mg, 0.30mmol) was added to a suspension of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (50.0 mg, 0.15 mmol) and ethanol (1.5 mL). The reaction mixture was stirred at room temperature for 12 hours. The formed solid was filtered under reduced pressure, washed with ethanol and dried under reduced pressure to obtain white solid compound of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (1S)-(+)-10-Camphorsulfonic acid salt (39.0 mg, 46%).

[2907]

[2908] LC/MS ESI(+): 334(M+1), 336(M+3)

[2909] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 10.03(s, 1H), 9.03(brs, 2H), 8.99(d, 1H, *J*=2.0 Hz), 8.67(d, 1H, *J*=2.0 Hz), 5.04(m, 1H), 4.84(m, 1H), 4.59(m, 1H), 4.40(m, 1H), 4.25(m, 1H), 2.86(d, 1H, *J*=14.8 Hz), 2.71(m, 1H), 2.68(S, 3H), 2.36(d, 1H, *J*=14.8 Hz), 2.23(m, 1H), 1.93(m, 1H), 1.85(1H, m), 1.80(d, 1H, *J*=18.4 Hz), 1.27(m, 2H), 1.05(S, 3H), 0.75(S, 3H)

[2910]

[2911] **Example 129**

[2912] **Synthesis of 8-bromo-N-(1-methylpyrrolidin-3-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-amine**

[2913] (a) Synthesis of 7-bromo-2-chloro-N-(1-methylpyrrolidin-3-yl)pyrido[2,3-b]pyrazin-3-amine

[2914] TEA (150.0 μL, 1.07 mmol) was added to a mixture of 7-bromo-2,3-dichloropyrido[2,3-b]pyrazine (100.0 mg, 0.36 mmol), 1-methylpyrrolidin-3-amine (43.0 mg, 0.43 mmol) and DCM (1.8 mL), and the reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was

purified by column chromatography (MeOH:DCM=1:40) on amine silica. The fractions containing the product were collected and concentrated to obtain yellow solid compound of 7-bromo-2-chloro-N-(1-methylpyrrolidin-3-yl)pyrido[2,3-b]pyrazin-3-amine (30.0 mg, 24%).

[2915]

[2916] LC/MS ESI (+): 342 (M+1), 344 (M+3)

[2917]

[2918] (b) Synthesis of 8-bromo-N-(1-methylpyrrolidin-3-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-amine

[2919] Hydrazine monohydrate (5.5 μL, 0.18 mmol) was added to a suspension of 7-bromo-2-chloro-N-(1-methylpyrrolidin-3-yl)pyrido[2,3-b]pyrazin-3-amine (26.0 mg, 0.06 mmol) and EtOH (1.0 mL). The reaction mixture was stirred at room temperature for 1 hour and then concentrated under reduced pressure. The residue was dissolved in trimethyl orthoformate (1.0 mL), and the reaction mixture was stirred at 100℃ for 5 hours. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was purified by column chromatography (MeOH:DCM=1:40) on amine silica. The fractions containing the product were collected and concentrated. Et_2O was added to the residue to form a solid. The formed solid was filtered and dried under reduced pressure to obtain yellow solid compound of 8-bromo-N-(1-methylpyrrolidin-3-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-amine (6.0 mg, 30%).

[2920]

[2921] LC/MS ESI (+): 348 (M+1), 350 (M+3)

[2922] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 9.95 (s, 1H), 8.92 (d, 1H, J=2.0 Hz), 8.78 (m, 1H), 8.61 (d, 1H, J=2.0 Hz), 4.72 (m, 1H), 2.86 (m, 1H), 2.68-2.50 (m, 3H), 2.33-2.10 (m, 4H), 2.01 (m, 1H)

[2923]

[2924] **Example 130**

[2925] **Synthesis of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (S)-2-hydroxypropanoic acid salt**

[2926] (S)-2-Hydroxypropanoic acid solution (135.0 mg, 1.50 mmol) in water (0.8 mL) was added to a suspension of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (50.0 mg, 0.15 mmol) and ethanol (0.8 mL). The reaction mixture was stirred at room temperature for 3 hours and then concentrated under reduced pressure. EtOH and Et_2O

were added to the residue to form a solid. The resulting solid was filtered, washed with Et_2O and dried under reduced pressure to obtain yellow solid compound of 1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (S)-2-hydroxypropanoic acid salt (34.0 mg, 53%).

[2927]

[2928] LC/MS ESI (+): 334 (M+1), 336 (M+3)

[2929] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 9.96 (s, 1H), 8.91 (d, 1H, *J*=2.0 Hz), 8.60 (d, 1H, *J*=2.0 Hz), 4.91 (m, 1H), 4.45 (m, 2H), 4.02 (m, 2H), 3.75 (m, 1H), 2.33 (s, 3H), 1.22 (m, 3H)

[2930]

[2931] **Example 131**

[2932] **Synthesis of N-(azetidin-3-ylmethyl)-8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-amine trifluoroacetic acid salt**

[2933] (a) Synthesis of *tert* -butyl 3-(((7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)amino)methyl)azetidine-1-carboxylate

[2934] 7-Bromo-2,3-dichloropyrido[2,3-b]pyrazine (100.0 mg, 0.56 mmol) was dissolved in DCM (5.6 mL), and *tert*-butyl 3-(aminomethyl)azetidine-1-carboxylate (104.1 mg, 0.56 mmol) and TEA (0.23 mL, 1.68 mmol) were slowly added thereto at 0°C. The reaction mixture was stirred at room temperature for 48 hours and then concentrated under reduced pressure. The residue was purified by column chromatography (*n* -Hex:EtOAc=70:30) on silica. The fractions containing the product were collected and concentrated to obtain yellow solid compound of *tert*-butyl 3-(((7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)amino)methyl)azetidine-1-carboxylate (72.0 mg, 30%).

[2935]

[2936] LC/MS ESI (+): 428 (M+1)

[2937] ^{1}H-NMR (400 MHz, DMSO-d_6); ?: 8.85 (d, 1H, *J*=2.4 Hz), 8.48 (d, 1H, *J*=2.4 Hz), 8.20 (t, 1H, *J*=5.6 Hz), 3.90 (m, 2H), 3.70 (m, 4H), 2.92 (m, 1H), 1.38 (s, 9H)

[2938]

[2939] (b) Synthesis of *tert* -butyl 3-(((7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)amino)methyl)azetidine-1-carboxylate

[2940] *tert*-Butyl 3-(((7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)amino)methyl)azetidine-1-carboxylate (50.0 mg, 0.12 mmol) and hydrazine monohydrate (12.0 μL, 0.35 mmol) were dissolved in EtOH (0.6 mL), and the reaction mixture was stirred at room temperature

for 1 hour. Et_2O was added thereto to form a solid. The formed solid was filtered and dried under reduced pressure to obtain yellow solid compound of *tert*-butyl 3-(((7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)amino)methyl)azetidine-1-carboxylate (48.0 mg, 98%).

[2941]

[2942] LC/MS ESI (+): 424 (M+1)

[2943]

[2944] (c) Synthesis of N-(azetidin-3-ylmethyl)-8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-amine trifluoroacetic acid salt

[2945] A reaction mixture of *tert*-butyl 3-(((7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)amino)methyl)azetidine-1-carboxylate (50.0 mg, 0.12 mmol) and trimethyl orthoformate (1.5 mL) was stirred at 70℃ for 12 hours, cooled to room temperature and then dried under reduced pressure to obtain *tert*-butyl 3-(((8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)amino)methyl)azetidine-1-carboxylate. TFA (0.3 mL) was added to mixture of unpurified *tert*-butyl 3-(((8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)amino)methyl)azetidine-1-carboxylate and DCM (1.0 mL), and the reaction mixture was then stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (MeOH:DCM=5:95) on amine silica. The fractions containing the product were collected and concentrated to obtain beige solid compound of N-(azetidin-3-ylmethyl)-8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-amine trifluoroacetic acid salt (1.5 mg, 3% in 2 steps).

[2946]

[2947] LC/MS ESI (+): 334 (M+1)

[2948] ^{1}H-NMR (400 MHz, MeOH-d_4); δ: 9.77 (s, 1H), 8.80 (d, 1H, *J*=2.0 Hz), 8.64 (m, 1H), 3.94 (m, 2H), 3.76 (m, 2H), 3.63 (m, 2H), 3.35 (s, 1H)

[2949]

[2950] **Example 132**

[2951] **Synthesis of 4-(azetidin-3-ylmethoxy)-8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine hydrochloric acid salt**

[2952] (a) Synthesis of *tert* -butyl 3-(((7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)oxy)methyl)azetidine-1-carboxylate

[2953] 60% NaH (10mg, 0.25mmol) was added to a solution of *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (47.9 mg, 0.25 mmol) dissolved in THF

(2.5mL) under nitrogen at room temperature. The mixture was stirred at room temperature for 30 minutes, and 7-bromo-2,3-dichloropyrido[2,3-b]pyrazine (60.0 mg, 0.25 mmol) was then added thereto at room temperature. The reaction mixture was stirred at room temperature for 2 hours and diluted with EtOAc. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered and then concentrated under reduced pressure. The residue was purified by column chromatography (n-Hex:EtOAc=2:1) on silica. The fractions containing the product were collected and concentrated to obtain white solid compound of *tert*-butyl 3-(((7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)oxy)methyl)azetidine-1-carboxylate (65.8 mg, 61%).

[2954]

[2955] LC/MS ESI (+): 429 (M+1), 431 (M+3), 451 (M+23), 453 (M+25)

[2956] ^{1}H-NMR (400 MHz, $CDCl_3$); δ: 9.00 (d, 1H, *J*=2.3Hz), 8.45 (d, 1H, *J*=2.3 Hz), 4.79 (d, 2H, *J*=6.6 Hz), 4.13 (t, 2H, *J*=8.5 Hz), 3.85 (dd, 2H, *J*=5.2, 3.6 Hz), 3.13(m, 1H), 1.45(s, 9H)

[2957]

[2958] (b) Synthesis of *tert* -butyl 3-(((8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)oxy)methyl)azetidine-1-carboxylate

[2959] Hydrazine monohydrate (14.1 μL, 0.45 mmol) was added to a mixture of *tert*-butyl 3-(((7-bromo-2-chloropyrido[2,3-b]pyrazin-3-yl)oxy)methyl)azetidine-1-carboxylate (63.8 mg, 0.15 mmol) and EtOH (1.5 mL), and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure, and unpurified *tert*-butyl 3-(((7-bromo-2-hydrazinylpyrido[2,3-b]pyrazin-3-yl)oxy)methyl)azetidine-1-carboxylate was dissolved in trimethyl orthoformate (1.5 mL). The reaction mixture was stirred at 80℃ for 4 hours and concentrated under reduced pressure to obtain unpurified brown solid compound of *tert*-butyl 3-(((8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)oxy)methyl)azetidine-1-carboxylate.

[2960]

[2961] LC/MS ESI (+): 435 (M+1), 437 (M+3), 457 (M+23), 459 (M+25)

[2962]

[2963] (c) Synthesis of 4-(azetidin-3-ylmethoxy)-8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine hydrochloride

[2964] Unpurified *tert*-butyl 3-(((8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)oxy)methyl)azetidine-1-ca

rboxylate was dissolved in DCM (1.5 mL), and then 4N HCl of 1,4-dioxane solution (75.0 μL, 0.30 mmol) was slowly added thereto at room temperature. The mixture was stirred at room temperature for 2 hours and then concentrated under reduced pressure. The residue was dissolved in DMSO (0.5 mL) and then purified by prep. HPLC (YL9110S YoungLin, acetonitrile:water=8:92). The fractions containing the product were collected and freeze-dried to obtain white solid compound of 4-(azetidin-3-ylmethoxy)-8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine hydrochloric acid salt (6.4 mg, 11% in 3 steps).

[2965]

[2966] LC/MS ESI (+): 335 (M+1), 337 (M+3)

[2967] ^{1}H-NMR (400 MHz, DMSO-d_6); δ: 10.05 (s, 1H), 9.15 (d, 1H, *J*=2.0 Hz), 8.97 (brs, 2H), 8.78 (d, 1H, *J*=2.0 Hz), 4.79 (d, 2H, J=6.64Hz), 4.04 (m, 2H), 3.90 (m, 2H), 3.33 (m, 1H)

[2968]

[2969]

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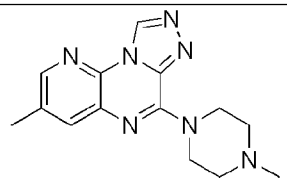
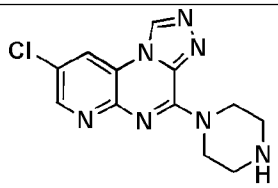
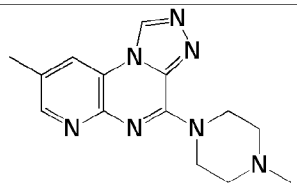
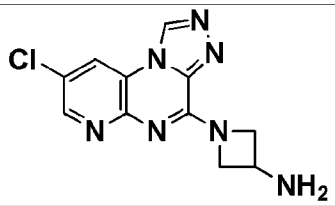
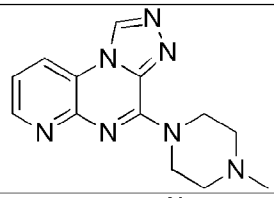
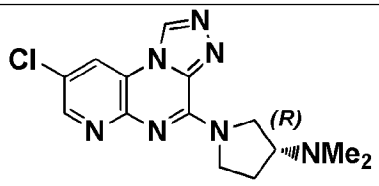
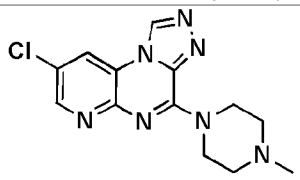
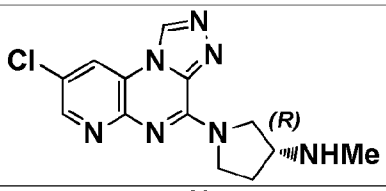
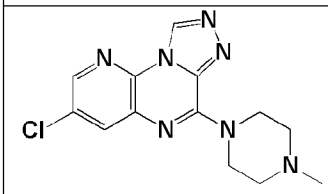
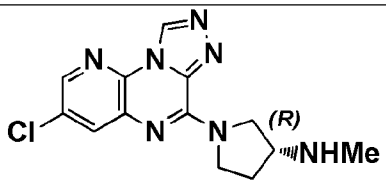
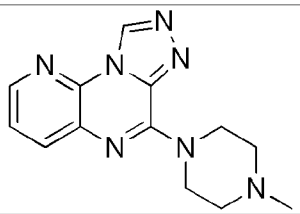
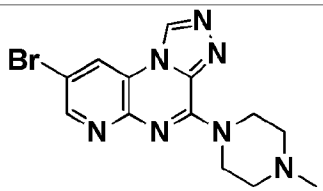
	1		7
	2		8
	3		9
	4		10
	5		11
	6		12

[2970]

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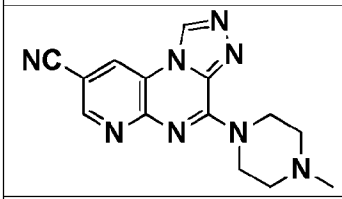
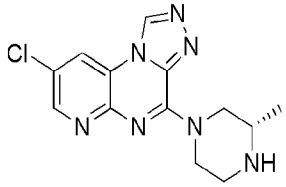
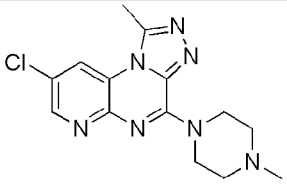
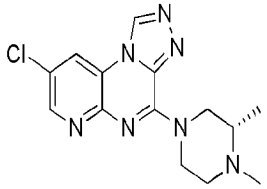
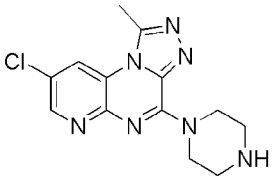
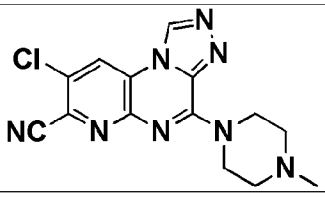
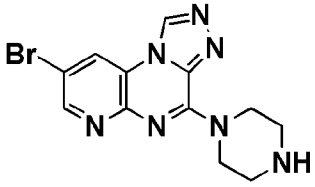
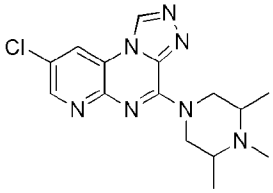
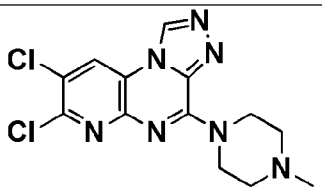
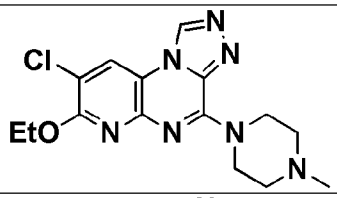
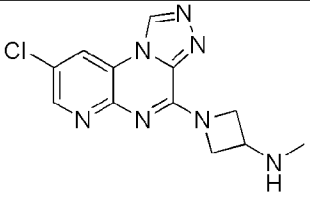
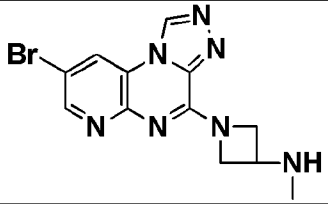
	13		19
	14		20
	15		21
	16		22
	17		23
	18		24

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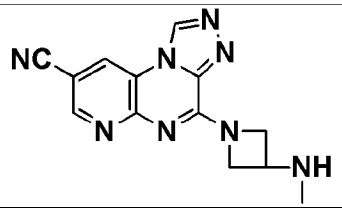
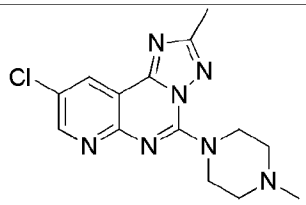
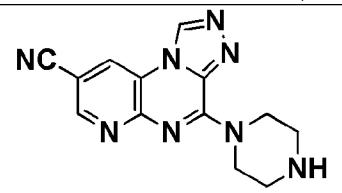
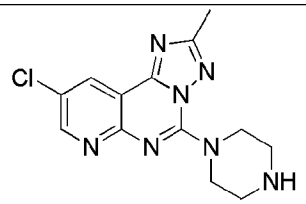
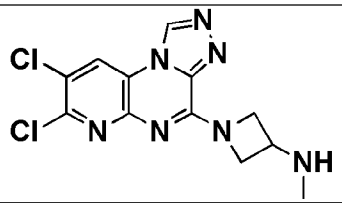
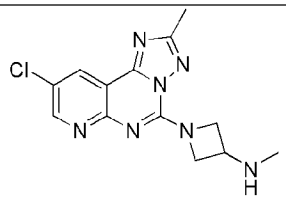
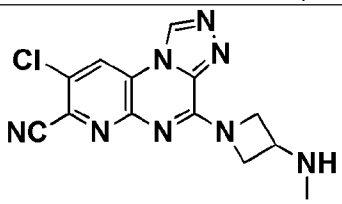
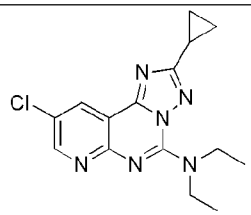
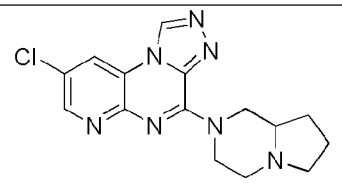
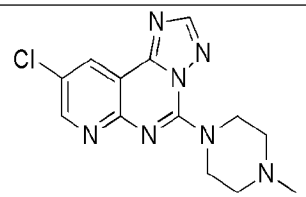
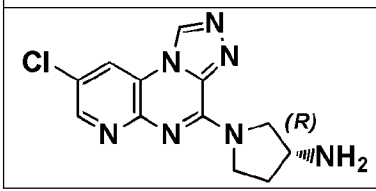
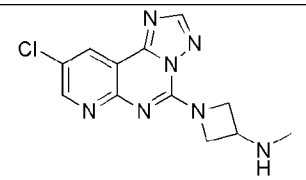
	25		31
	26		32
	27		33
	28		34
	29		35
	30		36

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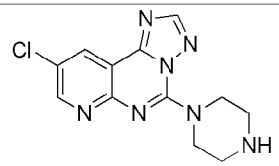
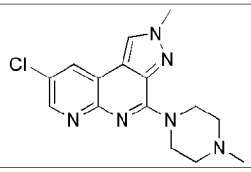
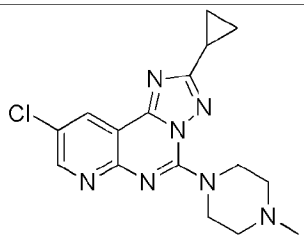
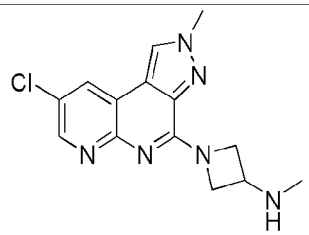
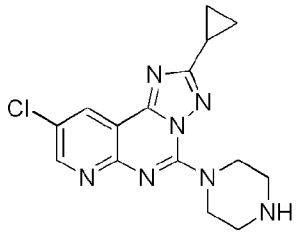
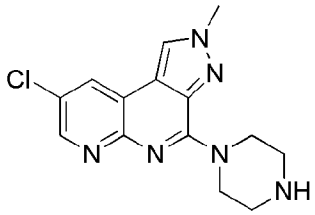
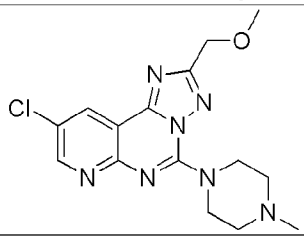
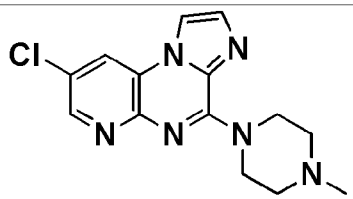
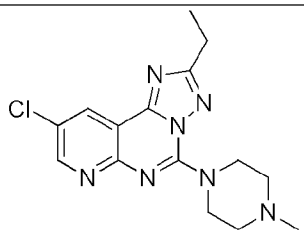
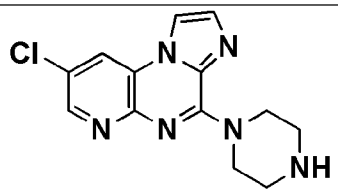
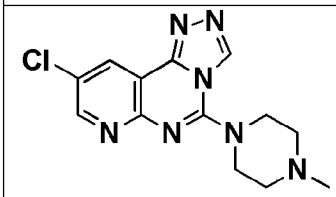
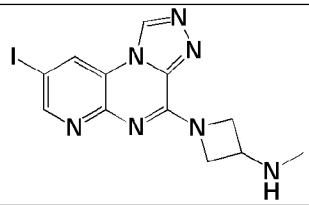
	37		43
	38		44
	39		45
	40		46
	41		47
	42		48

[2973]

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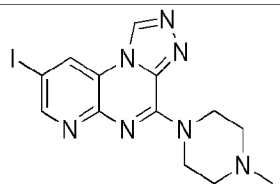
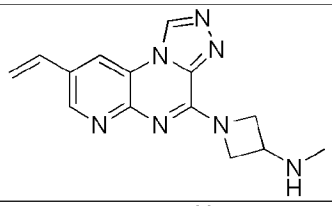
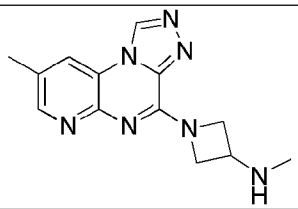
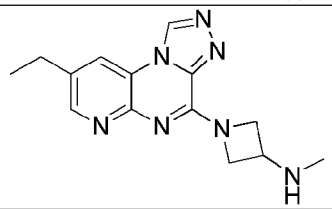
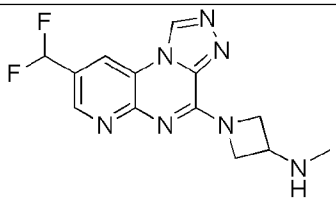
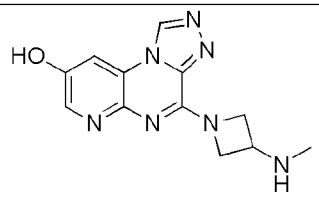
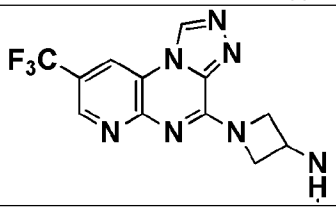
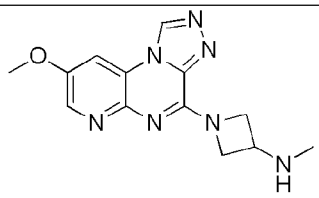
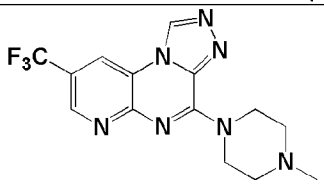
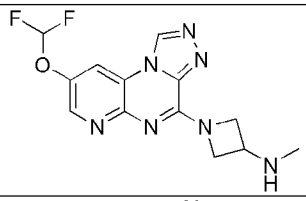
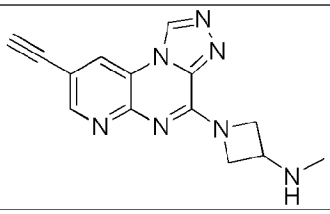
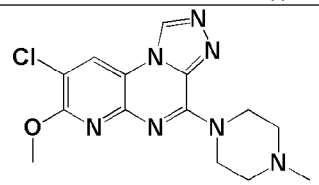
	49		55
	50		56
	51		57
	52		58
	53		59
	54		60

[2974]

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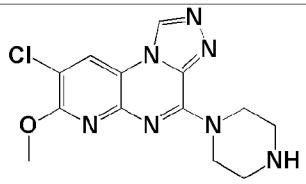
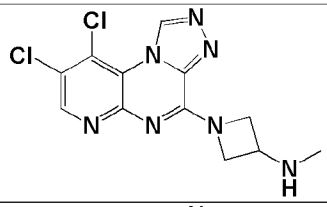
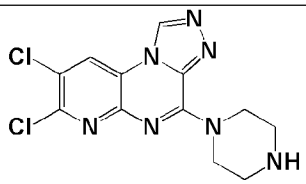
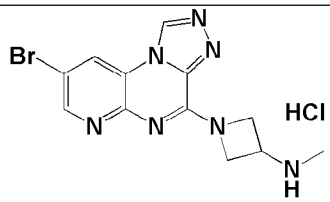
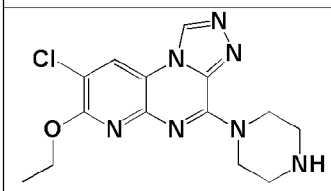
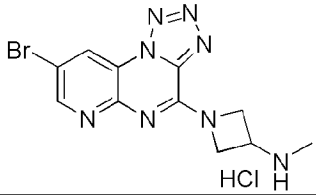
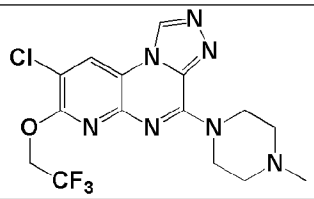
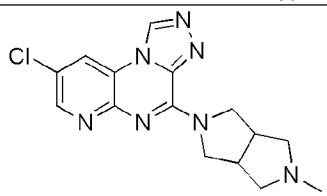
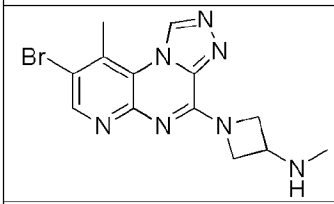
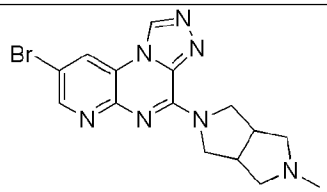
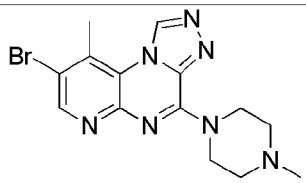
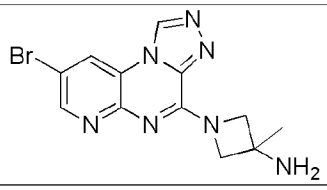
	61		67
	62		68
	63		69
	64		70
	65		71
	66		72

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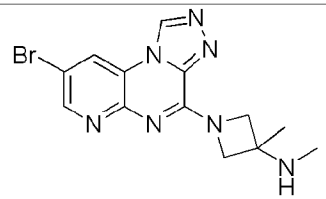
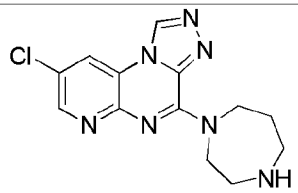
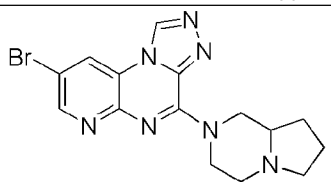
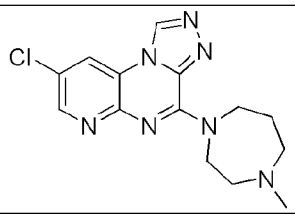
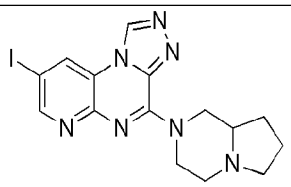
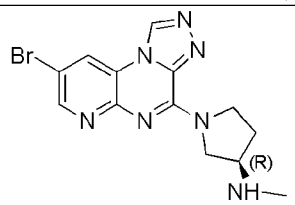
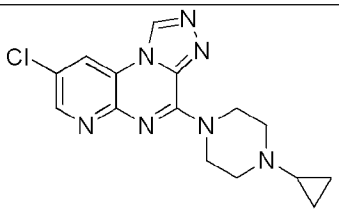
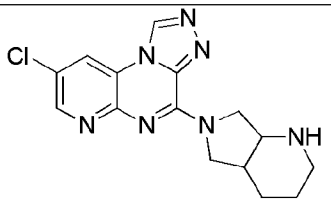
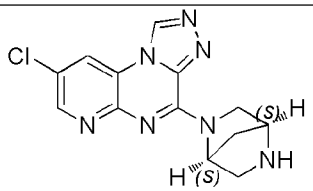
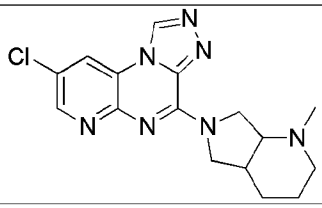
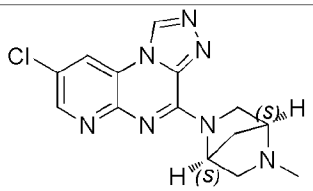
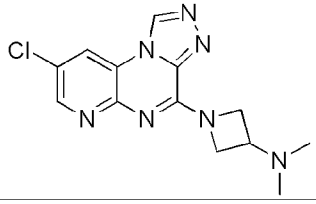
	73		79
	74		80
	75		81
	76		82
	77		83
	78		84

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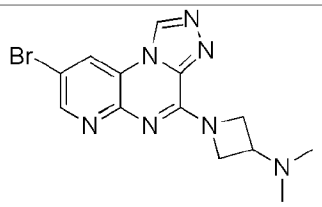
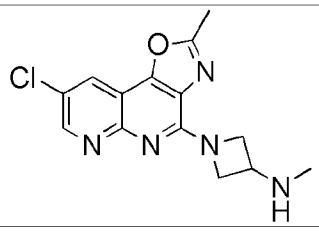
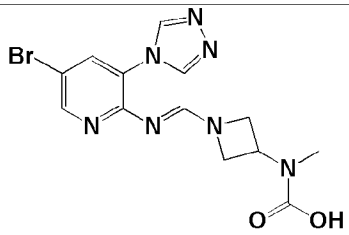
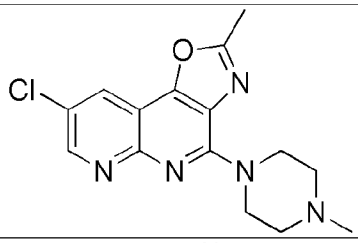
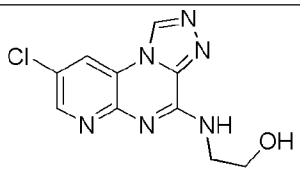
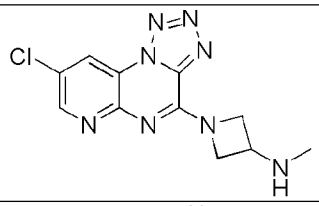
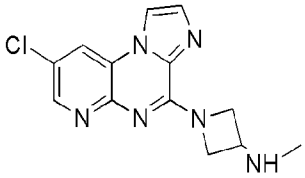
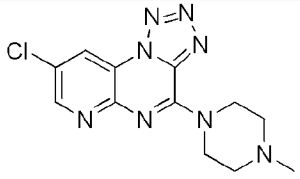
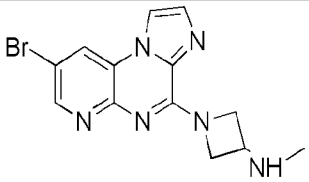
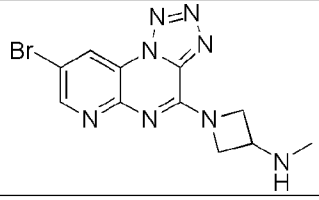
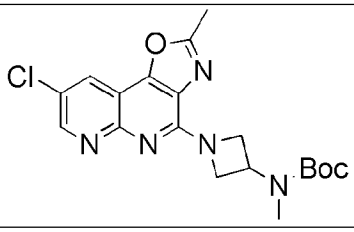
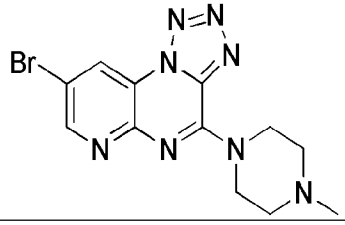
	85		91
	86		92
	87		93
	88		94
	89		95
	90		96

[2977]

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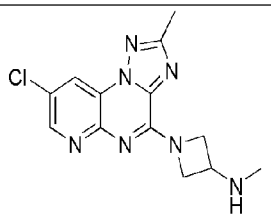
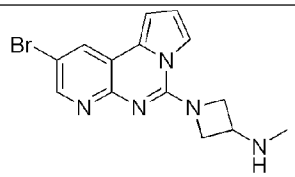
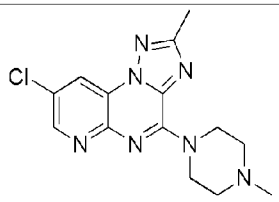
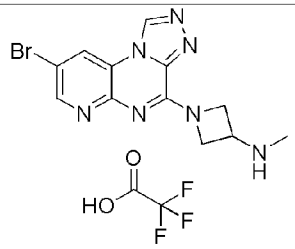
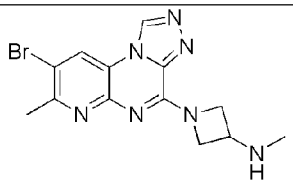
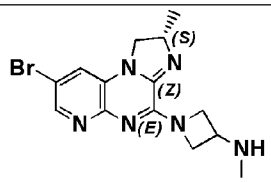
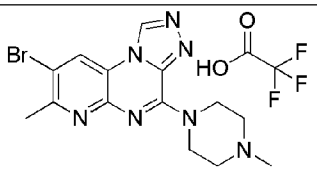
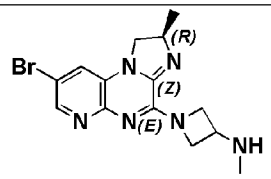
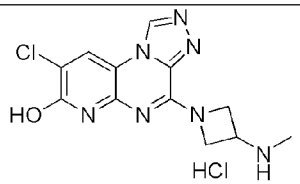
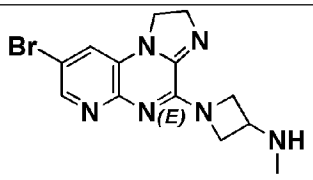
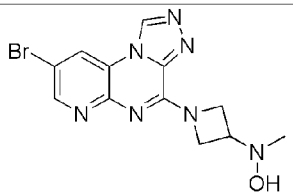
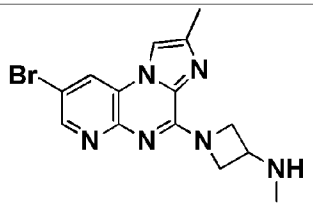
	97		103
	98		104
	99		105
	100		106
	101		107
	102		108

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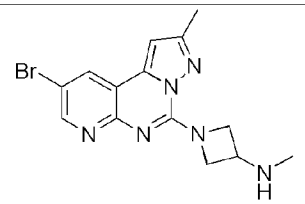
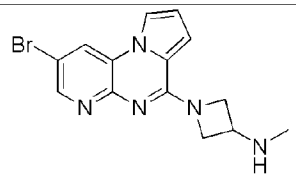
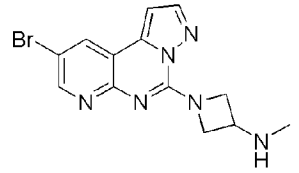
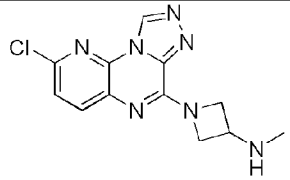
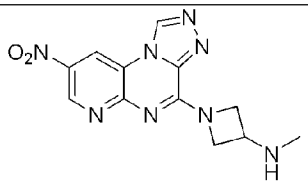
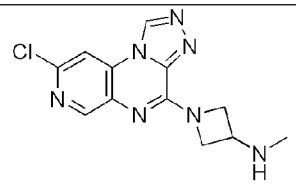
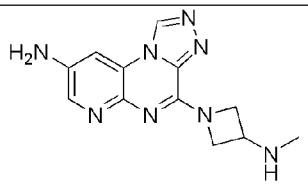
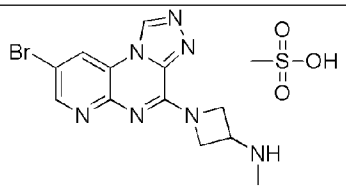
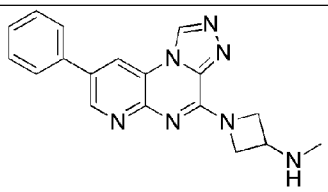
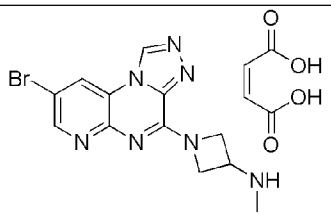
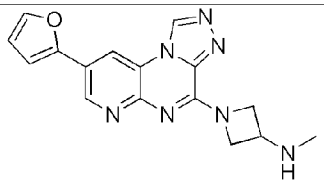
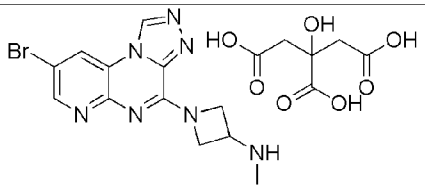
	109		115
	110		116
	111		117
	112		118
	113		119

[2979]

	114		120
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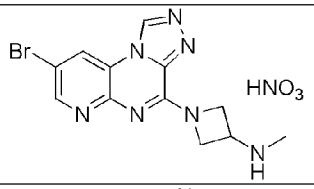
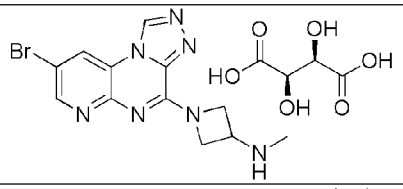
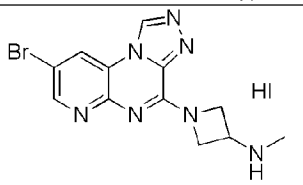
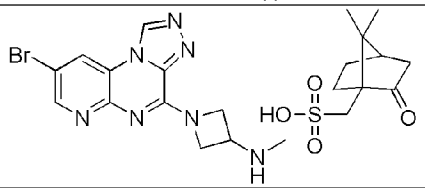
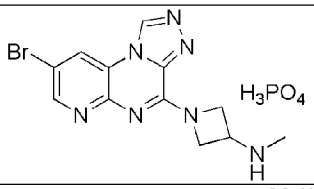
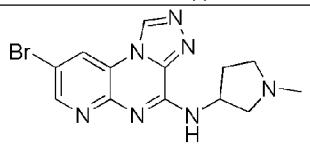
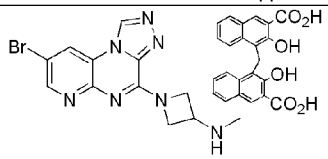
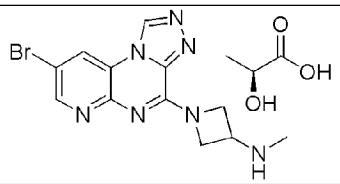
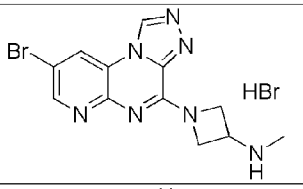
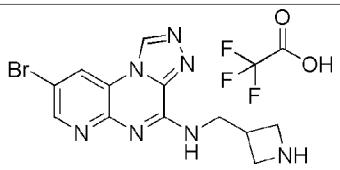
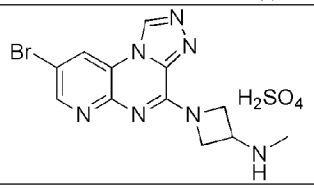
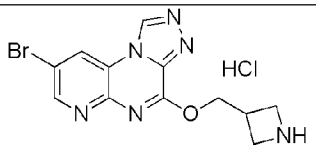
	121		127
	122		128
	123		129
	124		130
	125		131
	126		132

[2980]

[2981] **Experimental Example 1: Analysis for binding affinity of human histamine 4 receptor (hH4R)**

[2982] Each compound of the present invention prepared in the examples was diluted by 1000 fold (v/w) with DMSO, and then 1 μL of the diluted compound solution was mixed with 99 μL of the analysis buffer solution (50 mM tris-HCl pH 7.4, 5 mM EDTA) to obtain concentrations of 0.1, 0.3, 1, 3, 10 and 100 μM. 20 μL of the

prepared compound solution was transferred to each well of a 96-well plate, and then 20 μL of 100 μM histamine diluted with analysis buffer solution and 1% DMSO were transferred to each well to calculate non-specific binding and total binding degree. 25 μg of human histamine 4 receptor-overexpressed cell membrane (PerkinElmer) was diluted into 160 μL of analysis buffer solution and that was transferred to each well. [^{3}H] labeled histamine (PerkinElmer) was diluted into 1 μM concentration, 20 μL was allocated in each well, and then it was kept in a 27℃ incubator for 30 minutes. After the reaction, 200 μL of the mixture was transferred to a glass fiber plate in which 0.5% polyethylene amine was presoaked, and then non-binding [^{3}H] labeled histamine was removed in vacuum. After 4 times washing with 200 μL of washing buffer solution (50 mM tris-HCl, pH 7.4), the plate was dried in a 37℃ oven for 18 hours. 100 μL of betascint cocktail solution was added to each well, and after 1 hour CPM (count per minute) value of [^{3}H] labeled histamine was measured by using Wallac beta-counter TriLux. The binding affinity (IC50) of the human histamine 4 receptor for the present invention was analyzed by an Excel program, and the results of analysis are shown in Table 1.

[2983]

[2984] Table 1

[Table 1]

Compound	Binding affinity (IC50) of human histamine 4 receptor (hH4R)
Compound 2	506 nM
Compound 4	40 nM
Compound 7	133 nM
Compound 12	67 nM
Compound 13	238 nM
Compound 16	65 nM
Compound 17	177 nM
Compound 18	55 nM
Compound 19	760 nM
Compound 20	380 nM
Compound 21	270 nM
Compound 23	140 nM
Compound 24	36 nM

[2985]

Compound 25	100 nM
Compound 26	220 nM
Compound 28	490 nM
Compound 29	49 nM
Compound 31	16 nM
Compound 32	73 nM
Compound 35	170 nM
Compound 39	130 nM
Compound 43	70 nM
Compound 46	154 nM
Compound 47	618 nM
Compound 48	65 nM
Compound 49	34 nM
Compound 50	190 nM
Compound 51	710 nM
Compound 52	220 nM
Compound 53	280 nM
Compound 54	200 nM
Compound 55	260 nM
Compound 58	210 nM
Compound 59	890 nM
Compound 60	610 nM
Compound 62	510 nM
Compound 63	580 nM
Compound 64	240 nM
Compound 65	730 nM
Compound 66	300 nM
Compound 67	314 nM
Compound 68	130 nM
Compound 69	35 nM
Compound 74	60 nM
Compound 75	64 nM
Compound 77	490 nM
Compound 78	430 nM
Compound 88	260 nM
Compound 89	360 nM
Compound 92	42 nM
Compound 93	65 nM

[2986]

Compound 94	62 nM
Compound 95	44 nM
Compound 96	28 nM
Compound 98	11 nM
Compound 100	231 nM
Compound 104	30 nM
Compound 107	620 nM
Compound 110	160 nM
Compound 111	240 nM
Compound 116	240 nM
Compound 117	210 nM
Compound disclosed in WO 2010030785, Example 55	22 nM

[2987]

[2988] **Experimental Example 2: Analysis for binding affinity of human histamine 3 receptor (hH3R)**

[2989] Each compound of the present invention prepared in the examples was prepared in DMSO into concentrations of 0.02, 0.06, 0.3 and 2 mM. 10 μL of the prepared compound solution was allocated in each well of a 96-well plate, and then 10 μL of 200 μM (R)(-)-α-methylhistamine (RaMH) diluted with analysis buffer and 1% of DMSO were transferred to each well to calculate non-specific binding and total binding degree. 15 μg of human histamine 3 receptor-overexpressed cell membrane (PerkinElmer) was diluted with 180 μL of analysis buffer solution (50 mM tris-HCl pH 7.4, 5 mM $MgCl_2$), and that was transferred to each well. [^{3}H] labeled N-α-methylhistamine (PerkinElmer) was diluted into 20 μM concentration, 10 μL of that was added to each well, and then it was kept in a 27℃ incubator for 30 minutes. After the reaction, 200 μL of the mixture was transferred to a glass fiber plate in which 0.5% polyethylene amine was presoaked, and then non-binding [^{3}H] labeled N-α-methylhistamine was removed in vacuum. After 5 times washing with 200 μL of washing buffer solution (50 mM tris-HCl, pH 7.4), the plate was dried in a 37℃ oven for 18 hours. 100 μL of betascint cocktail solution was added to each well, and after 1 hour CPM of [^{3}H] labeled N-α-methylhistamine was measured by using Wallac beta-counter TriLux. The binding affinity (IC50) of the human histamine 3 receptor for the present invention was analyzed by an Excel program, and the results of analysis are shown in Table 2.

[2990]

[2991] Table 2

[Table 2]

Compound	Binding affinity (IC50) of human histamine 3 receptor (hH3R)
Compound 1	>100 μM
Compound 2	>100 μM
Compound 3	>100 μM
Compound 4	90 μM
Compound 5	>100 μM
Compound 6	>100 μM
Compound 7	>100 μM
Compound 8	>100 μM
Compound 9	>100 μM
Compound 10	>100 μM
Compound 11	>100 μM
Compound 13	>100 μM
Compound 14	>100 μM
Compound 15	>100 μM
Compound 16	>100 μM
Compound 17	>100 μM
Compound 18	>100 μM
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Compound 32	>100 μM
Compound 33	>100 μM
Compound 36	>100 μM
Compound 37	>100 μM
Compound 38	>100 μM
Compound 39	>100 μM
Compound 40	>100 μM
Compound 41	>100 μM
Compound 43	97 μM

[2992]

Compound 44	>100 μM
Compound 45	>100 μM
Compound 48	>100 μM
Compound 49	>100 μM
Compound 50	>100 μM
Compound 51	>100 μM
Compound 52	>100 μM
Compound 54	>100 μM
Compound 55	>100 μM
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Compound 81	>100 μM
Compound 82	>100 μM
Compound 83	>100 μM
Compound 84	>100 μM
Compound 85	>100 μM
Compound 87	>100 μM
Compound 88	>100 μM
Compound 89	>100 μM

[2993]

Compound 90	>100 μM
Compound 91	>100 μM
Compound 92	>100 μM
Compound 93	>100 μM
Compound 95	>100 μM
Compound 97	87 μM
Compound 99	>100 μM
Compound 100	>100 μM
Compound 101	>100 μM
Compound 102	>100 μM
Compound 104	>100 μM
Compound 105	>100 μM
Compound 106	>100 μM
Compound 107	>100 μM
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Compound 109	>100 μM
Compound 110	>100 μM
Compound 111	>100 μM
Compound 112	>100 μM
Compound 113	>100 μM
Compound 114	>100 μM
Compound 115	>100 μM
Compound 116	>100 μM
Compound 117	>100 μM
Compound disclosed in WO 2010030785, Example 55	9.0 μM

[2994]

[2995] **Experimental Example 3: Analysis for binding affinity of human serotonin 3 receptor (human 5-HT3 receptor)**

[2996] The binding assays of the human serotonin 3 receptor for present invention were performed at Cerep (Poitiers, France), and the results of analysis are shown in Table 3.

[2997]

[2998] Table 3

[Table 3]

Compound	Binding affinity (IC50) of human serotonin 3 receptor (h5-HT3R)
Compound 18	2.9 μM
Compound 24	9.1 μM
Compound 25	>10 μM (0 %*)
Compound 48	>10 μM (28 %*)
Compound 93	>10 μM (18 %*)
Compound 95	>10 μM (25 %*)

*: indicates % inhibition degree at 10 μM

[2999]

[3000] **Experimental Example 4: Test for solubility in artificial gastrointestinal tract solution**

[3001] [First solution]

[3002] 2.0 g of sodium chloride was added in 7.0 mL of 37% of hydrochloric acid and water to make the total volume of 1L. The pH was adjusted to exactly 1.2 with 1N sodium hydroxide or 1N hydrchlroic acid. A small amount (20 mL) of this solution was taken and added in 25 μL of triton X-100 to make the total volume of 25 mL.

[3003] [Second solution]

[3004] 0.348 g sodium hydroxide, 3.438 g NaH_2PO_4, 6.186 g sodium chloride and water were added to make the total volume of 1L. The pH was adjusted to exactly 6.5 with 1N sodium hydroxide or 1N hydrchlroic acid. A small amount (20 mL) of this solution was taken and 41.25 mg of sodium taurocholate hydrate and 25 μL of 750 mM lecithin dissolved in ethanol was added to make the total volume of 25mL.

[3005] [Experiment]

[3006] For the compound of the present invention prepared in the examples, the test samples were prepared in each of the first and second solutions with 2 mg/mL concentration, and then they were agitated for 1 minute, sonicated for 1 minute and heated at 37℃ for 1 hour for the first solution and 2 hours for the second solution. The heated test sample solutions were filtered to remove undissolved compounds therein. Finally, 100 μL of the completely compound-dissolved solution was sampled and 100 μL of CH_3CN was added thereto to make the test sample solution. For each analysis of the test sample solution, the solubility was measured by using liquid chromatography. The results of the solubility test in the first and second solutions are shown in Table 4.

[3007]

[3008] Table 4

[Table 4]

Compound	Solubility (μg/mL)	
	First solution (pH=1.2)	Second solution (pH=6.5)
Compound 4	2008.9	1243.6
Compound 7	1373.7	1151.2
Compound 12	1928.6	679.2
Compound 16	1932.6	758.0
Compound 18	1593.9	791.2
Compound 19	1975.0	1695.5
Compound 20	2067.6	1645.0
Compound 24	1690.2	939.0
Compound 25	1926.5	1385.0
Compound 29	1558.4	1993.3
Compound 31	2010.3	1978.8
Compound 32	1346.4	1151.5
Compound 46	1912.7	1102.8
Compound 48	1608.2	676.6
Compound 50	1986.8	1872.6
Compound 52	1674.4	1464.6
Compound 68	1820.3	1755.5
Compound 69	1813.0	1924.9
Compound 74	1527.2	646.5
Compound 75	2003.2	722.8
Compound 88	1821.3	1576.7
Compound 91	1836.1	1944.6
Compound 93	1971.8	1305.9
Compound 95	1790.7	1126.0
Compound 98	1702.7	1092.0
Compound 104	1506.8	1559.8
Compound 107	1415.2	1569.6
Compound 110	1871.9	708.1
Compound 111	1900.7	1065.4
Compound 116	1939.9	960.4
Compound disclosed in WO 2010030785, Example 55	1708.3	320.1

[3009]

[3010] **Experimental Example 5: Test for metabolic stability**

[3011] [Preparation of microsome solution]

[3012] The microsome of 20 mg/mL protein concentration (human, mouse, rat) was diluted with 0.1 M phosphate buffer (pH: 7.4) and prepared into a concentration of 1.316 mg/mL. The compound of the present invention prepared in the examples was dissolved in

DMSO to make a 2.5 mM solution, and diluted with distilled water to make a 125 μM solution. The microsome-diluted solution prepared above and the compound-diluted solution was mixed to make the microsome solution in 1.25 mg/mL protein concentration and 6.25 μM compound concentration.

[3013] [Preparation of NADPH solution]

[3014] NADPH was dissolved in 0.1 M phosphate buffer to make a 5 mM solution.

[3015] [Experiment]

[3016] The microsome solution in 6.25 μM concentration of the compound of the present invention prepared in the examples was allocated for each 80 μL, placed in a 37℃ bath and kept for 5 minutes, and then reaction was initiated by adding 20 μL of 5 mM NADPH to make final concentrations of 1 mg/mL microsome protein, 5 μM compound and 1 mM NADPH. The reaction was terminated by adding 100 μL of acetonitrile at 0, 10, 20 and 30 minutes, centrifuged, and then supernatant was analyzed by using liquid chromatography. The half-life was determined using the peak area of the remaining compound at 0, 10, 20 and 30 minutes, and $CL_{h.int}$ parameter representing metabolism stability was then calculated therefrom. The results of the metabolic stability test are shown in Table 5.

[3017]

[3018] Table 5

[Table 5]

Compound	Metabolic stability ($CL_{h,int}$)(mL/min/mg)	
	Mouse	Human
Compound 4	10.22	2.20
Compound 7	6.90	NC[y]
Compound 12	14.42	3.73
Compound 13	3.07	2.71
Compound 16	10.42	4.08
Compound 17	17.13	5.88
Compound 18	1.76	4.20
Compound 19	26.16	0.96
Compound 20	7.57	1.62
Compound 21	7.13	4.87
Compound 24	3.05	1.33
Compound 25	4.59	4.16
Compound 26	6.74	2.45
Compound 27	7.27	1.24
Compound 29	12.07	3.95
Compound 31	28.63	5.19
Compound 32	8.39	1.03
Compound 38	14.90	7.18
Compound 39	5.09	2.84
Compound 45	12.99	3.26
Compound 48	5.31	0.40
Compound 50	9.08	1.90
Compound 52	2.05	1.32
Compound 53	3.38	2.34

[3019]

Compound 54	0.68	1.16
Compound 58	12.74	2.80
Compound 59	1.23	1.32
Compound 62	7.98	4.17
Compound 65	6.49	3.21
Compound 68	3.93	0.30
Compound 69	14.04	5.69
Compound 77	0.32	1.33
Compound 78	1.46	2.36
Compound 88	11.77	2.87
Compound 89	10.71	3.19
Compound 93	9.47	4.48
Compound 95	18.10	5.50
Compound 102	6.78	1.99
Compound 107	8.15	5.16
Compound 110	1.78	3.88
Compound 111	5.23	4.20
Compound disclosed in WO 2010030785, Example 55	111.63	10.99

NC[y]: Not calculable (99.8% remaining in 30 minutes)

[3020]

[3021] **Experimental Example 6: Test for pharmacokinetics**

[3022] [Preparation of drug]

[3023] The compound of the present invention prepared in the examples was dissolved in 20% hydroxypropyl-β-cyclodextrine solution to make 5mg/mL administration solution for mice, and DMSO (5%), 5% dextrose solution (94.75%) and 2N hydrochloric acid (0.25%) were added sequentially to make 2mg/mL administration solution for rats.

[3024] [Experiment]

[3025] The weight of each ICR mouse and SD rat was properly 20~30g and 200~300g, and dosage of the compound of the present invention was 10mL/kg for mice and 5mL/kg for rats, and administered orally using Zonde. Blood collection was performed at 0.25, 0.5, 1, 2, 4, 6, 8 and 24 hours by orbital venous blood collection using a capillary tube coated with an anticoagulant, and then plasma was isolated using a centrifuge and kept in a freezer.

[3026] [Analysis]

[3027] Plasma collected from animals and standard concentration material were pretreated using solid-phase extraction, and concentration of the compound of the invention was determined using a liquid chromatography mass spectrometer (Agilent HPLC, API-3000).

[3028] According to the resulting concentration value, the pharmacokinetics parameter was found using WinNonlin (Version 6.2) and half-life ($t_{1/2}$), maximum blood concentration (C_{max}) and infinite area under the curve (AUC_{inf}) are shown in Tables 6 and 7 below.

[3029]

[3030] Table 6

[Table 6]

Compound	Mouse pharmacokinetics		
	$t_{1/2}$ (h)	C_{max}(μg/mL)	AUC_{inf} (μg·hr/mL)
Compound 4	2.21	14.87	35.58
Compound 7	1.28	6.57	16.49
Compound 16	1.18	8.27	15.90
Compound 18	1.32	12.29	23.71
Compound 24	0.96	18.87	32.17
Compound 25	1.17	9.76	13.98
Compound 31	1.79	11.66	22.36
Compound 32	5.39	10.07	74.90
Compound 48	1.46	10.21	21.62
Compound 93	15.56	10.85	121.23
Compound 95	4.03	15.43	98.33
Compound disclosed in WO 2010030785, Example 55	3.49	3.84	6.65

[3031] Table 7

[Table 7]

Compound	Rat pharmacokinetics		
	$t_{1/2}$ (h)	C_{max}(μg/mL)	AUC_{inf} (μg·hr/mL)
Compound 4	1.88	1.95	7.74
Compound 7	1.62	1.33	3.11
Compound 18	1.04	2.59	4.56
Compound 24	1.30	2.42	4.51
Compound 25	2.21	0.97	2.92
Compound disclosed in WO 2010030785, Example 55	1.09	0.49	1.06

[3032]

[3033] **Experimental Example 7: Histamine-induced mast cell migration**

[3034] [Animal]

[3035] Female, Balb/c mice (7 weeks old, 20±3g) were purchased from OrientBio Co., Ltd. The animals were housed under conditions of controlled temperature (23±3℃), humidity (50±5%) and lighting with food and water available ad libitum.

[3036] [Experiment]

[3037] Mice were dosed with either vehicle (20% cyclodextrin in second distilled water) or the compound by orally adminstration. The Compound (20mg/kg) dissolved in a vehicle and administered orally at a volume of 10 mL/kg. After 15 minutes, mice were challenged by a 20 min aerosol inhalation of PBS (phosphate buffered saline) or 0.1 M histamine (dissolving in PBS). This process was repeated for 2 days. After a final challenge, the tracheae were cleared of blood via perfusion of PBS and tracheae were extracted, the tracheae were fixed in 10% (w/v) formaldehyde for subsequent paraffin cross-sectioning and toluidine blue staining. Total mast cells were calculated, and a mean was reported. (The Journal of Pharmacology and Experimental Therapeutics, 2004, 309, 404-413). The inhibitory effects of the compound are shown in Table 8. Statistical analysis was analyzed using one-way ANOVA with Dunnett test. Values of $p<0.05$ were considered statistically significant.

[3038]

[3039] $$\text{Inhibitory effect of the compound (\%)} = \frac{(\text{mast cell No. of control group.} - \text{mast cell No. of normal group}) - (\text{mast cell No. of experimental group} - \text{mast cell No. of normal group}}{(\text{mast cell No. of control group} - \text{mast cell No. of normal group})} \times 100$$

[3040]

[3041] Table 8

[Table 8]

Compound	Mast cell migration (% change from control group)
Compound 4	70.3[1]
Compound 7	43.1[1]
Compound 24	60.0[1]
Compound 25	48.4[1]
Compound disclosed in WO 2010030785, Example 55	23.1[1]

"1" means statistical significance.

[3042]

[3043] **Experimental Example 8: Histamine-induced itching model in ICR mice**

[3044] [Animal]

[3045] Female, ICR mice (8 weeks old) were purchased from OrientBio Co., Ltd. The animals were housed under conditions of controlled temperature (23±3℃), humidity (50±5%) and lighting with food and water available ad *libitum*.

[3046] [Experiment: Itch-inducement and its measurement]

[3047] The hair was clipped using clippers (8000AD, THRIVE) over the rostral part of the back 24 hours before the experiment under anesthesia with isoflurane. Histamine (300nmol) was dissolved in saline and a volume of 40 μL injected intradermally into

the rostral part of the back. Mice were dosed with either vehicle (20% cyclodextrin in second distilled water) or the compound by orally adminstration. The Compound (50mg/kg) dissolved in a vehicle (20% cyclodextrin in second distilled water) and administered orally at a volume of 10 mL/kg.

[3048] Mice (n=10 per group) were divided into 3 groups (normal group, control group and experimental group). The animals were randomized for similar body weight distribution. A vehicle or the compound was administered 20 minutes before injection of histamine or saline. Immediately after intradermal injection, the animals were returned to an acrylic cage (approximately 30 x 30 x 30 cm, access production) composed of four cells, to which they had been acclimated for at least 1 hour before the experiment, for observation of itch responses. A camera (Samsung, VLUUNV30) was positioned above the mice to record their response. Itch was measured by blinded counting of the number of scratching in the 20 min period immediately after the intradermal injection. A number of scratching was defined as 3 or more individual rapid scratch movements with the hind paws around the injection site (J. Allergy Clin. Immunol. 2007, 19(1), 176-183). All data were analyzed by using Excel and Prism, and all values are expressed as the mean ± S.E.M.. The inhibitory effect of compounds is shown as a percentage of the maximal response to histamine (100 % control group).

[3049] Statistical analysis was analyzed using one-way ANOVA with Dunnett test. Values of $p<0.05$ were considered statistically significant. The inhibitory effects of the compound are shown in Table 9.

[3050]

[3051]

$$\text{Inhibitory effect of the compound (\%)} = \frac{\text{Number of scratching of control group} - \text{Number of scratching of experimental group}}{\text{Number of scratching of control group}} \times 100$$

[3052]

[3053] Table 9

[Table 9]

Compound	Number of scratching (% changes from control group)
Compound 4	94.3[1]
Compound 7	61.2[1]
Compound 18	84.3[1]
Compound 24	93.6[1]
Compound 31	89.3[1]
Compound 48	67.3[1]
Compound 95	98.2[1]

"1" means statistical significance.

[3054]

[3055] **Experimental Example 9: Substance P-induced itching model in ICR mice**

[3056] [Animal]

[3057] Female, ICR mice (8 weeks old) were purchased from OrientBio Co., Ltd. The animals were housed under conditions of controlled temperature (23±3℃), humidity (50±5%) and lighting with food and water available ad libitum.

[3058] [Experiment: Itch-inducement and its measurement]

[3059] The hair was clipped using clippers (8000AD, THRIVE) over the rostral part of the back 24 hours before the experiment under anesthesia with isoflurane. Substance P (100nmol) was dissolved in saline and a volume of 40 μL injected intradermally into the rostral part of the back. Mice were dosed with either vehicle (20% cyclodextrin in second distilled water) or the compound by orally adminstration. The Compound (50mg/kg) dissolved in a vehicle (20% cyclodextrin in second distilled water) and administered orally at a volume of 10 mL/kg.

[3060] Mice (n=10 per group) were divided into 3 groups (normal group, control group and experimental group). The animals were randomized for similar body weight distribution. A Vehicle or the compound was administered 20 minutes before injection of substance P or saline. Immediately after intradermal injection, the animals were returned to an acrylic cage (approximately 30 x 30 x 30 cm, access production) composed of four cells, to which they had been acclimated for at least 1 hour before the experiment, for observation of itch responses. A camera (Samsung, VLUUNV30) was positioned above the mice to record their response. Itch was measured by blinded counting of the number of scratching in the 20 min period immediately after the intradermal injection. A number of scratching was defined as 3 or more individual rapid scratch movements with the hind paws around the injection site (J. Toxicol. Sci. 2009, 34(4), 427-431; J. Pharmacol. Sci. 2006, 100, 285-288). All data were analyzed by using Excel and Prism, and all values are expressed as the mean ± S.E.M. The inhibitory effect of compounds is shown as a percentage of the maximal response to histamine (100 % control group). Statistical analysis was analyzed using one-way ANOVA with Dunnett test. Values of $p<0.05$ were considered statistically significant. The inhibitory effects of the compound are shown in Table 10.

[3061]

[3062]

$$\text{Inhibitory effect of the compound (\%)} = \frac{\text{Number of scratching of control group} - \text{Number of scratching of experimental group}}{\text{Number of scratching of control group}} \times 100$$

[3063]

[3064] Table 10

[Table 10]

Compound	Number of scratching (% change from control group)
Compound 4	50.8
Compound 7	60.5[1]
Compound 18	42.6
Compound 24	74.5[1]
Compound 48	33.5
Compound 95	80.7[1]

"1" means statistical significance.

[3065]

[3066] **Experimental Example 10: Compound 48/80-induced itching model in ICR mice**

[3067] [Animal]

[3068] Female, ICR mice (8 weeks old) were purchased from OrientBio Co., Ltd. The animals were housed under conditions of controlled temperature (23±3℃), humidity (50±5%) and lighting with food and water available ad libitum.

[3069] [Experiment: Itch-inducement and its measurement]

[3070] The hair was clipped using clippers (8000AD, THRIVE) over the rostral part of the back 24 hours before the experiment under anesthesia with isoflurane. Compound 48/80 (100μg) were dissolved in saline and a volume of 40 μL injected intradermally into the rostral part of the back. Mice were dosed by orally with either vehicle (20% cyclodextrin in second distilled water) or the compound by orally adminstration. The Compound (50mg/kg) dissolved in a vehicle (20% cyclodextrin in second distilled water) and administered orally at a volume of 10 mL/kg.

[3071] Mice (n=8-10 per group) were divided into 3 groups (normal group, control group and experimental group). The animals were randomized for similar body weight distribution. A vehicle or the compound was administered 20 minutes before injection of compound 48/80 or saline. Immediately after intradermal injection, the animals were returned to an acrylic cage (approximately 30 x 30 x 30 cm, access production) composed of four cells, to which they had been acclimated for at least 1 hour before the experiment, for observation of itch responses. A camera (Samsung, VLUUNV30) was positioned above the mice to record their response. Itch was measured by blinded counting of the number of bouts in the 20 min period immediately after the intradermal injection. A number of scratching was defined as 3 or more individual rapid scratch movements with the hind paws around the injection site (J. Pharmacol. Sci. 2006, 100, 285-288; European J. of Pharmacol. 2002, 448, 175-183). All data were analyzed by using Excel and Prism, and all values are expressed as the mean ± S.E.M. The inhibitory effect of compounds is shown as a percentage of the maximal response to histamine (100 % control group). Statistical analysis was analyzed using one-way

ANOVA with Dunnett test. Values of $p<0.05$ were considered statistically significant. The inhibitory effects of the compound are shown in Table 11.

[3072]

[3073]

$$\text{Inhibitory effect of the compound (\%)} = \frac{\text{Number of scratching of control group} - \text{Number of scratching of experimental group}}{\text{Number of scratching of control group}} \times 100$$

[3074] Table 11

[Table 11]

Compound	Number of scratching (% change from control group)
Compound 4	49.6[1]
Compound 18	50.9[1]
Compound 24	47.9[1]
Compound 48	30.3
Compound 95	93.6[1]

"1" means statistical significance.

[3075]

[3076] **Experimental Example 11: Oxazolone-induced atopic dermatitis model in Balb/c mice**

[3077] [Animal]

[3078] Female, Balb/c mice (6 weeks old, 20±3 g) were purchased from OrientBio Co., Ltd. The animals were housed under conditions of controlled temperature (23±3°C), humidity (50±5%) and lighting with food and water available ad libitum.

[3079] [Experiment]

[3080] On the beginning day (day 1), mice were sensitized by the topical application of 50 μL of 1% oxazolone in acetone and olive oil (4:1 ratio) on the abdominal skin. On day 8, 10, 12, 15, 17, 19, 22, 24 and 26, 25 μL of 0.2% oxazolone was applied topically on the inner side of right ear of each mouse. Between days 8 and 28, the compound of the invention was administered orally (10 mL/kg) twice a day in the morning and afternoon, and on days 12, 19 and 27, the thickness of the right ear of the mouse was measured. On day 28, the ear tissue of the mouse was extracted, fixed in 10% formalin solution, and then a tissue slide was prepared, stained with H&E (hematoxylin & eosin), and then the thickness of the ear was observed (Journal of Investigative Dermatology, 2008, *128*, 79-86). Statistical analysis was analyzed using one-way ANOVA with Dunnett test. Values of $p<0.05$ were considered statistically significant. The inhibitory effects of the compounds of are shown in Table 12.

[3081]

[3082]

$$\text{Inhibitory effect of the compound (\%)} = \frac{\text{(Ear thickness of control group – Ear thickness of normal group) – (Ear thickness of experimental group – Ear thickness of normal group)}}{\text{(Ear thickness of conrol group – Ear thickness of normal group)}} \times 100$$

[3083] Table 12

[Table 12]

Compound	Ear epidermis thickness (% change from control group)
Compound 4 (100 mg/kg, BID)	47.2
Compound 24 (100 mg/kg, BID)	51.2[1]
Compound 95 (50 mg/kg, BID)	34.9
Compound disclosed in WO 2010030785, Example 55 (100 mg/kg, BID)	8.0

"1" means statistical significance.

[3084]

[3085] **Experimental Example 12: Determination of pharmacological effect in Dermatophagoides farina external application-induced atopic dermatis NC/Nga mouse**

[3086] [Animal]

[3087] Female, NC/Nga mice (3 weeks old, 15-17 g) were purchased from Central Lab. Animal Inc. The animals were housed in conditions of controlled temperature (23±3℃), humidity (50±5%) and lighting with food and water available ad libitum.

[3088]

[3089] [Experiment]

[3090] The hair of back of the mice was shaved with clipper, and the remaining hair was removed completely using shaving cream.For barrier disruption, 150 μL of 4% sodium dodecyl sulfate (SDS) was applied to the shaved back skin The Df ointment (100mg/mouse) was applied twice a week for 3 weeks. The compound were administered orally twice a day in the morning and afternoon for 3 weeks, and then the severity of dermatitis was evaluated on days 2, 7, 10, 14 and 21. The development of (1) erythema / haemorrhage, (2) scarring / dryness, (3) oedema, (4)excoriation / erosion was scored as 0 (none), 1 (mild), 2 (moderate) and 3 (severe). The total skin score was defined as the sum of the individual scores. (Scandinavian Journal of Immunol. 2011, 73, 536-545). Statistical analysis was analyzed using one-way ANOVA with Dunnett test. Values of $p<0.05$ were considered statistically. Skin lesions improvement effects are shown in Table 13.

[3091]

[3092] Table 13

[Table 13]

Compound	Scoring of Skin lesions (day 21)
Normal group (non-Df)	0.0
Control group (Df)	9.0
Compound 24 (25 mg/kg, BID)	7.2
Compound 24 (50 mg/kg, BID)	4.4[1]

"1" means statistical significance.

[3093]

[3094] As indicated above, the compound of the present invention was substantially improved in solubility and metabolic stability as compared with conventional drugs. As results of comparative analysis of pharmacokinetics using ICR mouse and SD rat animal models as compared with the compound disclosed in WO 2010/030785, the compound of the present invention showed superior effects in pharmacokinetic profile such as AUC and maximum blood concentration, 7-8 times as much as the comparison compound. It was found that the histamine-induced migration of inflammatory cells such as mast cells and eosinophils is mediated by the histamine 4 receptor (The Journal of Pharmacology and Experimental Therapeutics, 2003, *305*, 1212-1221), and histamine 4 receptor antagonists could have an anti-inflammatory effect by a suppression of the increase of inflammatory cells. According to the improvement of the pharmacokinetic profile, the compound of the present invention showed superior pharmacological effects, 3 times as much as the compound disclosed in WO 2010/030785 as the result of an experiment for suppression of migration into the trachea of mast cells by histamine. The compound of the present invention showed strong anti-pruritic effects in the histamine-induced itch model and the like, and strong anti-inflammatory effects in oxazolone-induced atopic model which is one of the human mimics (J. Invest. Dermatol. 2008, *128*, 79-86) compared with the compound disclosed in WO 2010/030785.

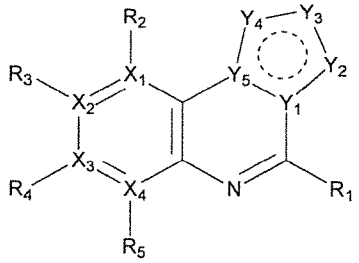
[3095]

[3096] In addition, the compound of the present invention showed the same or stronger effects on skin appearance improvement in NC/Nga mice atopic model which is the human mimics (J. Clin. Invest. 1999, *104*, 1097-1105), as compared with Tacrolimus which is currently used as an atopy drug. Accordingly, it is expected to be very effective for treating atopy patients.

Claims

[Claim 1] A heterocyclic compound of formula 1

[Formula 1]



or a racemate, isomer or pharmaceutically acceptable salt thereof:

wherein

each of X_1, X_2, X_3 and X_4 is independently C or N, provided that at least one of X_1, X_2, X_3 and X_4 is N,

R_1 is a saturated or unsaturated 3-12 membered mono- or poly-heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S), where R_1 is unsubstituted or substituted with 1-3 substituents selected from $-NR_6R_7$, $-C_1$-C_6alkyl-NR_6R_7 and R_8; or R_1 is selected from -H, $-NR_6R_7$ and R_8,

R_2, R_3, R_4 and R_5 may be the same or different; and each of them is independently selected from -H; $-C_1$-C_6alkyl; $-C_1$-C_6haloalkyl; $-C_1$-C_6 perhaloalkyl; -amino-C_1-C_6alkyl; $-C_3$-C_8cycloalkyl; -halogen (-F, -Cl, -Br, -I); -CN; $-C_1$-C_6alkoxy; $-C_1$-C_6haloalkoxy; $-C_1$-C_6perhaloalkoxy; $-C_2$-C_7 alkenyl; $-C_2$-C_8alkynyl; -amino; -amido; $-C_1$-C_6alkylcarboxyl; -carboxyl (-COOH); $-C_1$-C_6acyl; -OH; -nitro ($-NO_2$); $-C_6$-C_{10}aryl; -heterocyclyl; and -O-C_1-C_6alkyl-heterocyclyl, where the heterocyclyl is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S),

provided that when X_1 is N, R_2 does not exist; when X_2 is N, R_3 does not exist; when X_3 is N, R_4 does not exist; and when X_4 is N, R_5 does not exist,

each of Y_1, Y_2, Y_3, Y_4 and Y_5 is independently C or a heteroatom (preferably a heteroatom independently selected from N, O and S),

provided that at least one of Y_1, Y_2, Y_3, Y_4 and Y_5 is a heteroatom independently selected from N, O and S,

each of Y_2 and Y_3 may be independently substituted with R_9,

Y_4 may be substituted with -H or $-C_1$-C_6alkyl,

each of R_6 and R_7 is independently selected from -H; $-C_1$-C_6alkyl; $-C_3$-C

$_8$cycloalkyl; -heterocyclyl; -amino-C_1-C_6mono- or di-alkyl; -C_1-C_6 alkyl-amino-C_1-C_6mono- or di-alkyl; -C_1-C_6alkyl-heterocyclyl; -C_1-C_6 alkyl-carboxyl; -carboxyl (-COOH); and phenyl, where the heterocyclyl is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S),

R_8 is -C_1-C_6alkyl; -C_1-C_6alkoxy; -OH; -amino; -C_1-C_6alkyl-amino; -C_3-C_8cycloalkyl; -S-C_1-C_6alkyl-amino-C_1-C_6mono- or di-alkyl; -S-C_1-C_6 alkyl-heterocyclyl; -O-heterocyclyl; or -O-C1-C6alkyl-heterocyclyl, where the heterocyclyl is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S), and

R_9 is selected from -H; -OH; -C_1-C_6alkyl; -C_1-C_6haloalkyl; -C_1-C_6 perhaloalkyl; -amino-C_1-C_6mono- or di-alkyl; -C_3-C_7cycloalkyl; -heterocyclyl; -C_6-C_{10}aryl; 5-12 membered heteroaryl; -C_1-C_6alkoxy; -C_1-C_6haloalkoxy; -halogen (-F, -Cl, -Br, -I); -amino; -amido; -C_1-C_6acyl; -CN; -carboxyl (-COOH); -C_1-C_6alkylcarboxyl; and -nitro (-NO_2), with proviso that when Y_4 is N and Y_1, Y_2, Y_3 and Y_5 is C, Y_3 is not substituted with a substituent having -C(=O)- moiety,

wherein each of the alkyl, cycloalkyl, heterocyclyl, alkoxy, alkenyl, alkynyl, acyl and aryl groups may be independently unsubstituted or substituted with one or more substituents (for example, 1-3 substituents) selected from the group consisting of -C_1-C_4alkyl, -halogen (-F, -Cl, -Br, -I), -CN, -C_1-C_4alkoxy, -amino, -amido, -carboxyl (-COOH), -C_1-C_6acyl, -OH, -nitro (-NO_2), heterocyclyl and phenyl, where the heterocyclyl is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably, heteroatoms selected from N, O and S).

[Claim 2] The heterocyclic compound, or a racemate, isomer or pharmaceutically acceptable salt thereof according to claim 1, wherein each of X_1, X_2 and X_3 is independently C or N, and X_4 is N.

[Claim 3] The heterocyclic compound, or a racemate, isomer or pharmaceutically acceptable salt thereof according to claim 1, wherein each of Y_1, Y_2, Y_3, Y_4 and Y_5 is independently C or a heteroatom (preferably a heteroatom independently selected from N, O and S), provided that at least three of Y_1, Y_2, Y_3, Y_4 and Y_5 are N.

[Claim 4] The heterocyclic compound, or a racemate, isomer or pharmaceutically acceptable salt thereof according to claim 1, wherein R_1 is a saturated or unsaturated 3-8 membered mono- or poly-heterocyclyl containing

1-3 heteroatoms (preferably heteroatoms selected from N, O and S), where R_1 is unsubstituted or substituted with 1-3 substituents selected from NR_6R_7, C_1-C_6alkyl-NR_6R_7 and R_8.

[Claim 5] The heterocyclic compound, or a racemate, isomer or pharmaceutically acceptable salt thereof according to claim 1, wherein R_3 is selected from -H; -C_1-C_6alkyl; -C_1-C_6haloalkyl; -C_1-C_6perhaloalkyl; -halogen (-F, Cl, -Br, -I); -CN; -C_1-C_6alkoxy; -C_1-C_6haloalkoxy; -C_1-C_6 perhaloalkoxy; -C_2-C_7alkenyl; -C_2-C_8alkynyl and -OH.

[Claim 6] The heterocyclic compound, or a racemate, isomer or pharmaceutically acceptable salt thereof according to claim 1, wherein

each of X_1, X_2, X_3 and X_4 is independently C or N, provided that at least one of X_1, X_2, X_3 and X_4 is N,

R_1 is a saturated or unsaturated 3-12 membered mono- or poly-heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S), where R_1 is unsubstituted or substituted with 1-3 substituents selected from -NR_6R_7, -C_1-C_6alkyl-NR_6R_7 and R_8; or R_1 is selected from -NR_6R_7 and R_8,

R_2, R_3, R_4 and R_5 may be the same or different; and each of them is independently selected from -H; -C_1-C_6alkyl; -C_1-C_6haloalkyl; -C_1-C_6 perhaloalkyl; -halogen (-F, -Cl, -Br, -I); -CN; -C1-C6alkoxy; -C_1-C_6 haloalkoxy; -C_1-C_6perhaloalkoxy; -C_2-C_7alkenyl; -C_2-C_8alkynyl; and -OH,

provided that when X_1 is N, R_2 does not exist; when X_2 is N, R_3 does not exist; when X_3 is N, R_4 does not exist; and when X_4 is N, R_5 does not exist,

each of Y_1, Y_2, Y_3, Y_4 and Y_5 is independently C or a heteroatom (preferably a heteroatom independently selected from N, O and S), provided that at least two of Y_1, Y_2, Y_3, Y_4 and Y_5 are heteroatoms independently selected from N, O and S,

each of Y_2 and Y_3 may be independently substituted with R_9,

Y_4 may be substituted with -H or -C_1-C_6alkyl,

each of R_6 and R_7 is independently selected from -H; -C_1-C_6alkyl; and -carboxyl (-COOH),

R_8 is selected from -C_1-C_6alkyl; and -C_3-C_8cycloalkyl, and

R_9 is selected from -H; -C_1-C_6alkyl; and -C_3-C_7cycloalkyl,

wherein each of the alkyl, cycloalkyl, heterocyclyl, alkoxy, alkenyl and alkynyl groups may be independently unsubstituted or substituted with one or more substituents selected from the group consisting of -C_1-C_4

alkyl, -OH and -C_1-C_4alkoxy, where the heterocyclyl is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S).

[Claim 7] The heterocyclic compound, or a racemate, isomer or pharmaceutically acceptable salt thereof according to claim 1, wherein

each of X_1, X_2, X_3 and X_4 is independently C or N, provided that at least one of X_1, X_2, X_3 and X_4 is N,

R_1 is a saturated or unsaturated 3-12 membered mono- or poly-heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S), where R_1 is unsubstituted or substituted with 1-3 substituents selected from -NR_6R_7 and R_8,

R_2, R_3, R_4 and R_5 may be the same or different; and each of them is independently selected from -H; -C_1-C_6alkyl; -C_1-C_6haloalkyl; -halogen (-F, -Cl, -Br, -I); -CN; -C_1-C_6alkoxy; -C_1-C_6haloalkoxy; -C_2-C_7alkenyl; and -C_2-C_8alkynyl,

provided that when X_1 is N, R_2 does not exist; when X_2 is N, R_3 does not exist; when X_3 is N, R_4 does not exist; and when X_4 is N, R_5 does not exist,

each of Y_1, Y_2, Y_3, Y_4 and Y_5 is independently selected from C, N and O, provided that at least two of Y_1, Y_2, Y_3, Y_4 and Y_5 are N or O,

each of Y_2 and Y_3 may be independently substituted with R_9,

each of R_6 and R_7 is independently selected from -H and -C_1-C_6alkyl,

R_8 is selected from -C_1-C_6alkyl, and

R_9 is selected from -H, -C_1-C_6alkyl and -C_3-C_7cycloalkyl,

wherein each of the alkyl, cycloalkyl, heterocyclyl, alkoxy, alkenyl and alkynyl groups may be independently unsubstituted or substituted with one or more substituents selected from the group consisting of -C_1-C_4 alkyl, -OH and -C_1-C_4alkoxy, where the heterocyclyl is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S).

[Claim 8] The heterocyclic compound, or a racemate, isomer or pharmaceutically acceptable salt thereof according to claim 1, wherein

each of X_1, X_2, X_3 and X_4 is independently C or N, provided that at least one of X_1, X_2, X_3 and X_4 is N,

R_1 is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S), where R_1 is unsubstituted or substituted with -NR_6R_7,

R_2, R_3, R_4 and R_5 may be the same or different; and each of them is in-

dependently selected from -H; -C_1-C_6alkyl; -C_1-C_6haloalkyl; -halogen (-F, Cl, -Br, -I); -CN; -C_1-C_6alkoxy; -C_1-C_6haloalkoxy; -C_2-C_7alkenyl; and -C_2-C_8alkynyl,

provided that when X_1 is N, R_2 does not exist; when X_2 is N, R_3 does not exist; when X_3 is N, R_4 does not exist; and when X_4 is N, R_5 does not exist,

each of Y_1, Y_2, Y_3, Y_4 and Y_5 is independently selected from C, N and O, provided that at least two of Y_1, Y_2, Y_3, Y_4 and Y_5 are N,

each of Y_2 and Y_3 may be independently substituted with R_9,

each of R_6 and R_7 is independently selected from -H and -C_1-C_6alkyl, and

R_9 is selected from -H, -C_1-C_6alkyl and -C_3-C_7cycloalkyl,

wherein each of the alkyl, cycloalkyl, heterocyclyl, alkoxy, alkenyl and alkynyl groups may be independently unsubstituted or substituted with one or more substituents selected from the group consisting of -C_1-C_4 alkyl, -OH and -C_1-C_4alkoxy, where the heterocyclyl is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S).

[Claim 9] The heterocyclic compound, or a racemate, isomer or pharmaceutically acceptable salt thereof according to claim 1, wherein

each of X_1, X_2, X_3 and X_4 is independently C or N, provided that at least one of X_1, X_2, X_3 and X_4 is N,

R_1 is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S), where R_1 is unsubstituted or substituted with -NR_6R_7,

R_2, R_3, R_4 and R_5 may be the same or different; and each of them is independently selected from -H; -C_1-C_6alkyl; -C_1-C_6haloalkyl; and -halogen (-F, -Cl, -Br, -I),

provided that when X_1 is N, R_2 does not exist; when X_2 is N, R_3 does not exist; when X_3 is N, R_4 does not exist; and when X_4 is N, R_5 does not exist,

each of Y_1, Y_2, Y_3, Y_4 and Y_5 is independently selected from C, N and O, provided that at least two of Y_1, Y_2, Y_3, Y_4 and Y_5 are N,

each of Y_2 and Y_3 may be independently substituted with R_9,

each of R_6 and R_7 is independently selected from -H and -C_1-C_6alkyl, and

R_9 is selected from -H and -C_1-C_6alkyl,

wherein each of the alkyl and heterocyclyl groups may be inde-

pendently unsubstituted or substituted with one or more substituents selected from the group consisting of -C_1-C_4alkyl, -OH and -C_1-C_4 alkoxy, where the heterocyclyl is a saturated or unsaturated 3-6 membered heterocyclyl containing 1-3 heteroatoms (preferably heteroatoms selected from N, O and S.

[Claim 10] The heterocyclic compound, or a racemate, isomer or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound is selected from the group consisting of:

3-Methyl-6-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine (compound 1);

8-Methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 2);

4-(4-Methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 3);

8-Chloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 4);

3-Chloro-6-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine (compound 5);

6-(4-Methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazine (compound 6);

8-Chloro-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 7);

1-(8-Chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine (compound 8);

(R)-1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*,*N*-dimethylpyrrolidin-3-amine (compound 9);

(R)-1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylpyrrolidin-3-amine (compound 10);

(R)-1-(3-chloropyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazin-6-yl)-*N*-methylpyrrolidin-3-amine (compound 11);

8-Bromo-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 12);

4-(4-Methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-carbonitrile (compound 13);

8-Chloro-1-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 14);

8-Chloro-1-methyl-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 15);

8-Bromo-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 16);
7,8-Dichloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 17);
1-(8-Chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 18);
(S)-8-chloro-4-(3-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 19);
(S)-8-chloro-4-(3,4-dimethylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 20);
8-Chloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-7-carbonitrile (compound 21);
8-Chloro-4-(3,4,5-trimethylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 22);
8-Chloro-7-ethoxy-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 23);
1-(8-Bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 24);
4-(3-(Methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-carbonitrile (compound 25);
4-(Piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-carbonitrile (compound 26);
1-(7,8-Dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (compound 27);
8-Chloro-4-(3-(methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-7-carbonitrile (compound 28);
8-Chloro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 29);
(R)-1-(8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)pyrrolidin-3-amine (compound 30);
9-Chloro-2-methyl-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (compound 31);
9-Chloro-2-methyl-5-(piperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (compound 32);
1-(9-Chloro-2-methylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-yl)-*N*-methylazetidin-3-amine (compound 33);
9-Chloro-2-cyclopropyl-*N*,*N*-diethylpyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amine (compound 34);

9-Chloro-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (compound 35);

1-(9-Chloropyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-5-yl)-*N*-methylazetidin-3-amine (compound 36);

9-Chloro-5-(piperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (compound 37);

9-Chloro-2-cyclopropyl-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (compound 38);

9-Chloro-2-cyclopropyl-5-(piperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (compound 39);

9-Chloro-2-(methoxymethyl)-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (compound 40);

9-Chloro-2-ethyl-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (compound 41);

9-Chloro-5-(4-methylpiperazin-1-yl)pyrido[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (compound 42);

8-Chloro-2-methyl-4-(4-methylpiperazin-1-yl)-2H-pyrazolo[3,4-c][1,8]naphthylidine (compound 43);

1-(8-Chloro-2-methyl-2H-pyrazolo[3,4-c][1,8]naphthylidine-4-yl)-*N*-methylazetidin-3-amine (compound 44);

8-Chloro-2-methyl-4-(piperazin-1-yl)-2H-pyrazolo[3,4-c][1,8]naphthylidine (compound 45);

8-Chloro-4-(4-methylpiperazin-1-yl)imidazo[1,2-a]pyrido[2,3-e]pyrazine (compound 46);

8-Chloro-4-(piperazin-1-yl)imidazo[1,2-a]pyrido[2,3-e]pyrazine (compound 47).

1-(8-Iodopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 48);

8-Iodo-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 49);

N-Methyl-1-(8-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine (compound 50);

1-(8-(Difluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 51);

N-Methyl-1-(8-(trifluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine (compound 52);

4-(4-Methylpiperazin-1-yl)-8-(trifluoromethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 53);

1-(8-Ethynylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 54);
N-Methyl-1-(8-vinylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine (compound 55);
1-(8-Ethylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 56);
4-(3-(Methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-ol(compound 57);
1-(8-Methoxypyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 58);
1-(8-(Difluoromethoxy)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 59);
8-Chloro-7-methoxy-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 60);
8-Chloro-7-methoxy-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 61);
7,8-Dichloro-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 62);
8-Chloro-7-ethoxy-4-(piperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 63);
8-Chloro-4-(4-methylpiperazin-1-yl)-7-(2,2,2-trifluoroethoxy)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 64);
1-(8-Bromo-9-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 65);
8-Bromo-9-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 66);
1-(8,9-Dichloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 67);
1-(8-Bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine hydrochloride (compound 68);
1-(8-Bromopyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine hydrochloride (compound 69);
8-Chloro-4-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 70);
8-Bromo-4-(5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 71);
1-(8-Bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-3-methylazetidin-3-amine (compound 72);

1-(8-Bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*,3-dimethylazetidin-3-amine (compound 73);
8-Bromo-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 74);
4-(Hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-8-iodopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 75);
8-Chloro-4-(4-cyclopropylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 76);
4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-8-chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 77);
8-Chloro-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 78);
8-Chloro-4-(1,4-diazepan-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 79);
8-Chloro-4-(4-methyl-1,4-diazepan-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 80);
(R)-1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylpyrrolidin-3-amine (compound 81);
8-Chloro-4-(hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 82);
8-Chloro-4-(1-methylhexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 83);
1-(8-Chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*,*N*-dimethylazetidin-3-amine (compound 84);
1-(8-Bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*,*N*-dimethylazetidin-3-amine (compound 85);
(1-(8-Bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)(methyl)carbamic acid (compound 86);
2-((8-Chloropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)amino)ethanol (compound 87);
1-(8-Chloroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-N-methylazetidin-3-amine (compound 88);
1-(8-Bromoimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 89);
tert-Butyl
(1-(8-chloro-2-methyloxazolo[4,5-c][1,8]naphthylidine-4-yl)azetidin-3-yl)(methyl)carbamate (compound 90);
1-(8-Chloro-2-methyloxazolo[4,5-c][1,8]naphthylidine-4-yl)-*N*-methyl

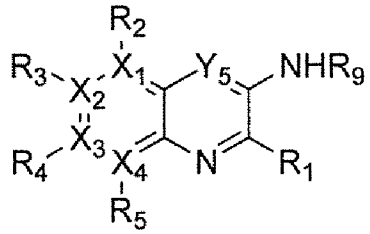
azetidin-3-amine (compound 91);
8-Chloro-2-methyl-4-(4-methylpiperazin-1-yl)oxazolo[4,5-c][1,8]naphthylidine (compound 92);
1-(8-Chloropyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 93);
8-Chloro-4-(4-methylpiperazin-1-yl)pyrido[2,3-e]tetrazolo[1,5-a]pyrazine (compound 94);
1-(8-Bromopyrido[2,3-e]tetrazolo[1,5-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 95);
8-Bromo-4-(4-methylpiperazin-1-yl)pyrido[2,3-e]tetrazolo[1,5-a]pyrazine (compound 96);
1-(8-Chloro-2-methylpyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 97);
8-Chloro-2-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[1,5-a]pyrazine (compound 98);
1-(8-bromo-7-methylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 99);
8-bromo-7-methyl-4-(4-methylpiperazin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (compound 100);
8-chloro-4-(3-(methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-7-ol HCl salt (compound 101);
N-(1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-yl)-*N*-methylhydroxylamine (compound 102);
1-(2-bromopyrido[3,2-e]pyrrolo[1,2-c]pyrimidin-6-yl)-*N*-methylazetidin-3-amine (compound 103);
1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-*N*-methylazetidin-3-amine 2,2,2-trifluoroacetate (compound 104);
(S)-1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-N-methylazetidin-3-amine (compound 105);
(R)-1-(8-bromo-2-methyl-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-N-methylazetidin-3-amine (compound 106);
1-(8-bromo-1,2-dihydroimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 107);
1-(8-bromo-2-methylimidazo[1,2-a]pyrido[2,3-e]pyrazin-4-yl)-*N*-methylazetidin-3-amine (compound 108);
1-(9-bromo-2-methylpyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-yl)-*N*-methylazetidin-3-amine (compound 109);
1-(9-bromopyrazolo[1,5-c]pyrido[3,2-e]pyrimidin-5-yl)-*N*-methylazetid

in-3-amine (compound 110);
N-methyl-1-(8-nitropyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine (compound 111);
4-(3-(methylamino)azetidin-1-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-8-amine (compound 112);
N-methyl-1-(8-phenylpyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)azetidin-3-amine (compound 113);
1-(8-(furan-2-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (compound 114);
1-(2-bromopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6-yl)-*N*-methylazetidin-3-amine (compound 115);
1-(2-chloropyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrazin-6-yl)-N-methylazetidin-3-amine (compound 116);
1-(8-chloropyrido[3,4-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (compound 117);
1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine methanesulfonic acid salt (compound 118);
1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine maleic acid salt (compound 119);
1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine 2-hydroxypropane-1,2,3-tricarboxylic acid salt (compound 120);
1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine nitric acid salt (compound 121);
1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine hydroiodic acid salt (compound 122);
1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine phosphoric acid salt (compound 123);
1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine 4,4'-methylenebis(3-hydroxy-2-naphthoic acid) salt (compound 124);
1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine hydrobromic acid salt (compound 125);
1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine sulfuric acid salt (compound 126);
1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (2R,3R)-2,3-dihydroxysuccinic acid salt (compound 127);

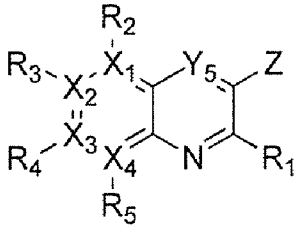
1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (1S)-(+)-10-Camphorsulfonic acid salt (compound 128);
8-bromo-N-(1-methylpyrrolidin-3-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-amine (compound 129);
1-(8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-yl)-N-methylazetidin-3-amine (S)-2-hydroxypropanoic acid salt (compound 130);
N-(azetidin-3-ylmethyl)-8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-4-amine trifluoroacetic acid salt (compound 131); and
4-(azetidin-3-ylmethoxy)-8-bromopyrido[2,3-e][1,2,4]triazolo[4,3-a]pyrazine hydrochloric acid salt (compound 132).

[Claim 11] A method for preparing a heterocyclic compound having a structure of formula 1 as defined in Claim 1, or a racemate, isomer or pharmaceutically acceptable salt thereof, the method comprising the steps of:
(a) preparing a compound of formula 3 via arylation of a compound of formula 4 with a compound of formula R_1-H (except that R_1 is -H);
(b) preparing a compound of formula 2 via arylation of the prepared compound of formula 3; and
(c) cyclizing the prepared compound of formula 2 (or, a step of deprotecting R_1 may be comprised):

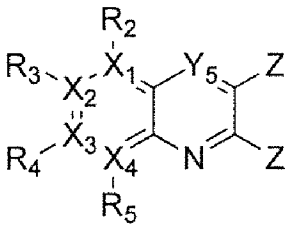
[Formula 2]



[Formula 3]



[Formula 4]



wherein, in formulas 2 to 4, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5, R_9 and Y_5 are the same as defined in formula 1; and Z represents a reactive leaving group.

[Claim 12] A method for preparing a heterocyclic compound having a structure of formula 5 which is formula 1 as defined in Claim 1 wherein Y_1, Y_2 and Y_4 are N, or a racemate, isomer or pharmaceutically acceptable salt thereof, the method comprising the steps of:

(a) preparing a compound of formula 9 via halogenation of a compound of formula 10;

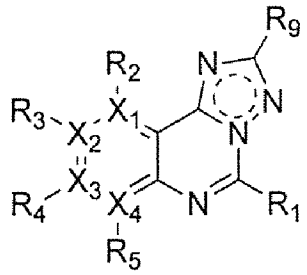
(b) preparing a compound of formula 8 via cyanation of the prepared compound of formula 9;

(c) preparing a compound of formula 7 via acylation of the prepared compound of formula 8;

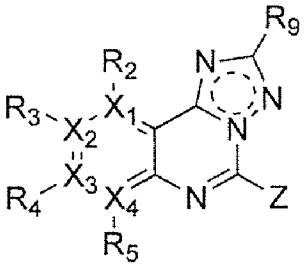
(d) preparing a compound of formula 6 via cyclization of the prepared compound of formula 7 followed by halogenation; and

(e) conducting arylation of the prepared compound of formula 6 with a compound of formula R_1-H (except that R_1 is -H) (or, a step of de-protecting R_1 may be comprised):

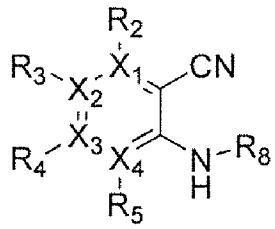
[Formula 5]



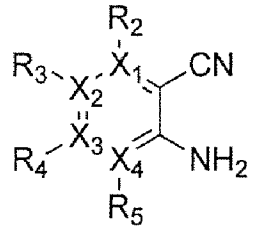
[Formula 6]



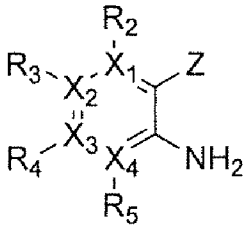
[Formula 7]



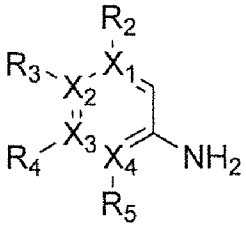
[Formula 8]



[Formula 9]



[Formula 10]



wherein, in formulas 5 to 10, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5, R_8 and R_9 are the same as defined in formula 1; and Z represents a reactive leaving group.

[Claim 13] A method for preparing a heterocyclic compound having a structure of formula 11 which is formula 1 as defined in Claim 1 wherein Y_2, Y_4 and Y_5 are N, or a racemate, isomer or pharmaceutically acceptable salt thereof, the method comprising the steps of:

(a) preparing a compound of formula 16 via arylation of a compound of formula 17;

(b) preparing a compound of formula 15 via imidation of the prepared compound of formula 16;

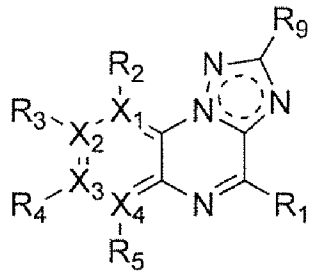
(c) preparing a compound of formula 14 via acylation of the prepared compound of formula 15;

(d) preparing a compound of formula 13 via cyclization of the prepared compound of formula 14;

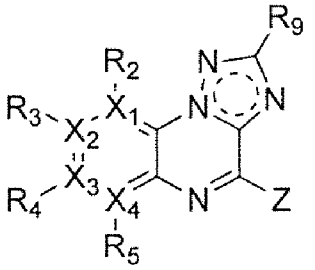
(e) preparing a compound of formula 12 via reduction of the prepared compound of formula 13 followed by halogenation; and

(f) conducting arylation of the prepared compound of formula 12 with a compound of formula R_1-H (except that R_1 is -H) (or, a step of de-protecting R_1 may be comprised):

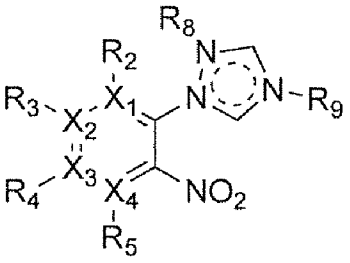
[Formula 11]



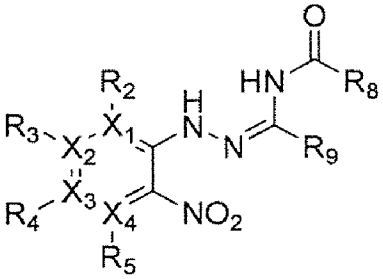
[Formula 12]



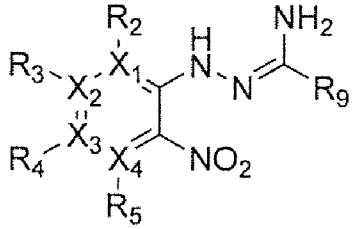
[Formula 13]



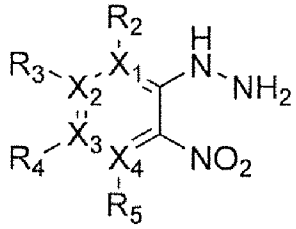
[Formula 14]



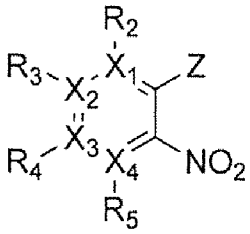
[Formula 15]



[Formula 16]



[Formula 17]



wherein, in formulas 11 to 17, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5, R_8 and R_9 are the same as defined in formula 1; and Z represents a reactive leaving group.

[Claim 14] A method for preparing a heterocyclic compound having a structure of formula 18 which is formula 1 as defined in Claim 1 wherein Y_2 and Y_3 are N, or a racemate, isomer or pharmaceutically acceptable salt thereof, the method comprising the steps of:

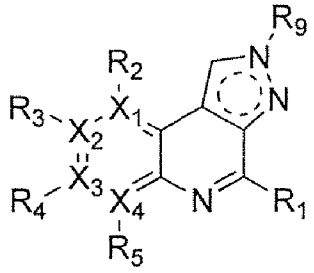
(a) preparing a compound of formula 21 via Friedel-Craft reaction of a compound of formula 23 with a compound of formula 22;

(b) preparing a compound of formula 20 via cyclization of the prepared compound of formula 21;

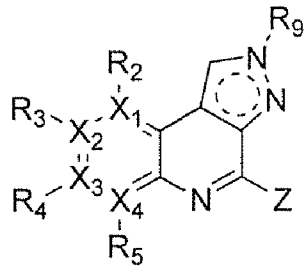
(c) preparing a compound of formula 19 via halogenation of the prepared compound of formula 20; and

(d) conducting arylation of the prepared compound of formula 19 with a compound of formula R_1-H (except that R_1 is -H) (or, a step of de-protecting R_1 may be comprised):

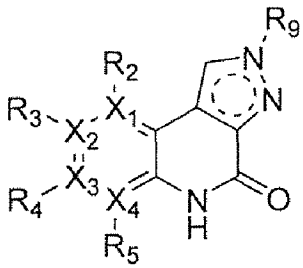
[Formula 18]



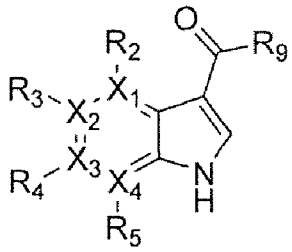
[Formula 19]



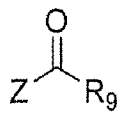
[Formula 20]



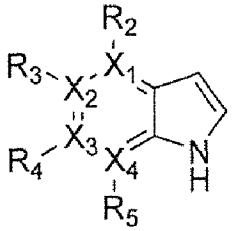
[Formula 21]



[Formula 22]



[Formula 23]



wherein, in formulas 18 to 23, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5 and R_9 are the same as defined in formula 1; and Z represents a reactive leaving group.

[Claim 15] A method for preparing a heterocyclic compound having a structure of formula 24 which is formula 1 as defined in Claim 1 wherein Y_1, Y_3 and Y_4 are N, or a racemate, isomer or pharmaceutically acceptable salt thereof, the method comprising the steps of:

(a) preparing a compound of formula 28 via cyclization of a compound of formula 29;

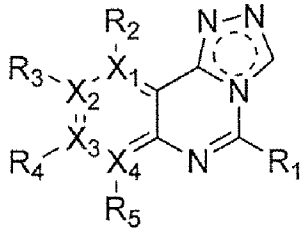
(b) preparing a compound of formula 27 via halogenation of the prepared compound of formula 28 followed by hydroxylation;

(c) preparing a compound of formula 26 via arylation of the prepared compound of formula 27 with a compound of formula R_1-H (except that R_1 is -H) followed by halogenation;

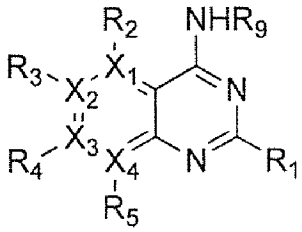
(d) preparing a compound of formula 25 via arylation of the prepared compound of formula 26; and

(e) cyclizing the prepared compound of formula 25 (or, a step of de-protecting R_1 may be comprised):

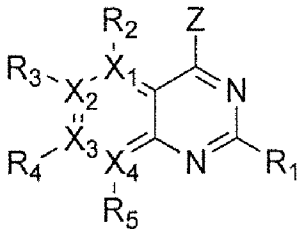
[Formula 24]



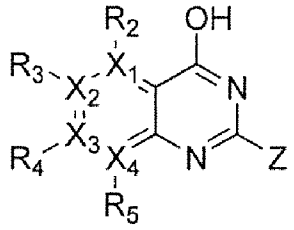
[Formula 25]



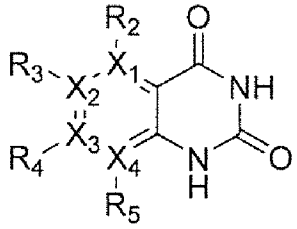
[Formula 26]



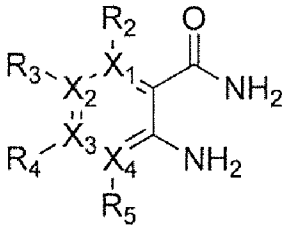
[Formula 27]



[Formula 28]



[Formula 29]



wherein, in formulas 24 to 29, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5 and R_9 are the same as defined in formula 1; and Z represents a reactive leaving group.

[Claim 16] A method for preparing a heterocyclic compound having a structure of formula 30 which is formula 1 as defined in Claim 1 wherein Y_2 is N and Y_4 is O, or a racemate, isomer or pharmaceutically acceptable salt thereof, the method comprising the steps of:

(a) preparing a compound of formula 36 via esterification of a compound of formula 37;

(b) preparing a compound of formula 35 via arylation of the prepared compound of formula 36;

(c) preparing a compound of formula 34 via cyclization of the prepared compound of formula 35;

(d) preparing a compound of formula 33 via enolate addition reaction of the prepared compound of formula 34;

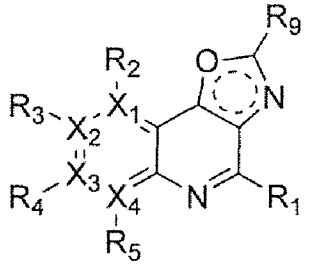
(e) preparing a compound of formula 32 via cyclization of the prepared compound of formula 33;

(f) preparing a compound of formula 31 via halogenation of the prepared compound of formula 32; and

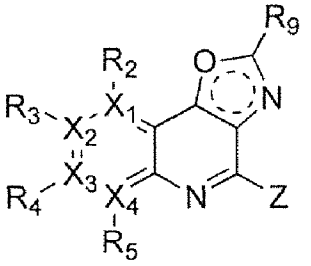
(g) conducting arylation of the prepared compound of formula 31 with

a compound of formula R_1-H (except that R_1 is -H) (or, a step of de-protecting R_1 may be comprised):

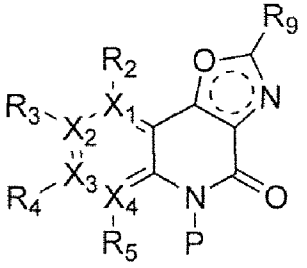
[Formula 30]



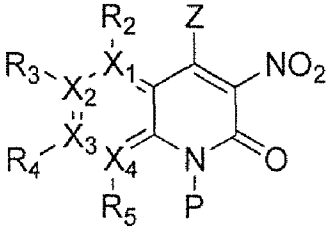
[Formula 31]



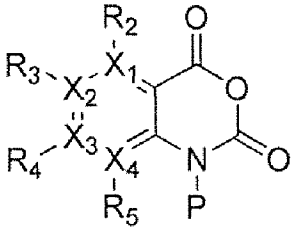
[Formula 32]



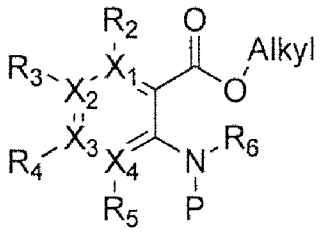
[Formula 33]



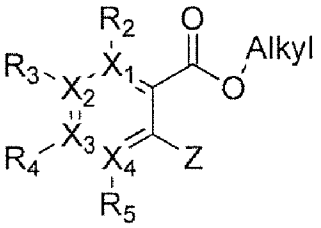
[Formula 34]



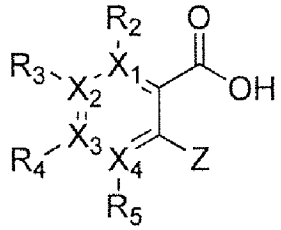
[Formula 35]



[Formula 36]



[Formula 37]



wherein, in formulas 30 to 37, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4, R_5, R_6 and R_9 are the same as defined in formula 1; P represents a protecting group; and Z represents a reactive leaving group.

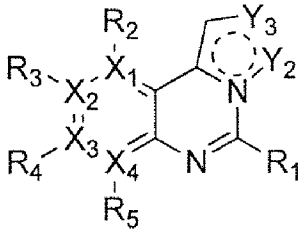
[Claim 17] A method for preparing a heterocyclic compound having a structure of formula 38 which is formula 1 as defined in Claim 1 wherein Y_1 is N and each of Y_2 and Y_3 is independently C or N, or a racemate, isomer or pharmaceutically acceptable salt thereof, the method comprising the steps of:

(a) preparing a compound of formula 40 via the Suzuki coupling reaction of a compound of formula 42 with a compound of formula 41;

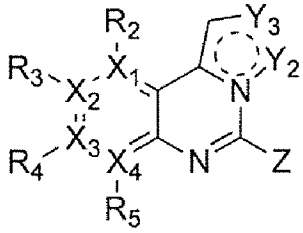
(b) preparing a compound of formula 39 via halogenation of the prepared compound of formula 40; and

(c) conducting arylation of the prepared compound of formula 39 with a compound of formula R_1-H (except that R_1 is -H) (or, a step of de-protecting R_1 may be comprised):

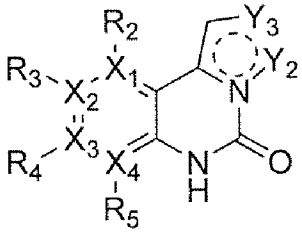
[Formula 38]



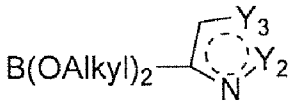
[Formula 39]



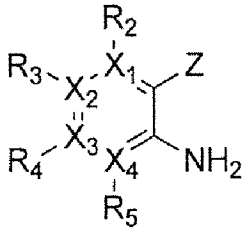
[Formula 40]



[Formula 41]



[Formula 42]



wherein, in formulas 38 to 42, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4 and R_5 are the same as defined in formula 1; and Z represents a reactive leaving group.

[Claim 18] A method for preparing a heterocyclic compound having a structure of formula 43 which is formula 1 as defined in Claim 1 wherein Y_5 is N, or a racemate, isomer or pharmaceutically acceptable salt thereof, the method comprising the steps of:

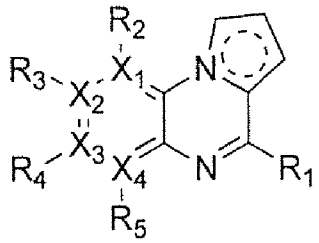
(a) preparing a compound of formula 46 via pyrrolation of a compound of formula 47;

(b) preparing a compound of formula 45 via cyclization of the prepared compound of formula 46;

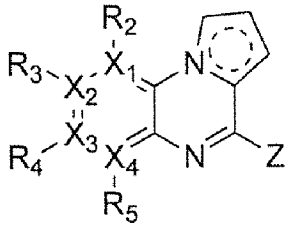
(c) preparing a compound of formula 44 via halogenation of the prepared compound of formula 45; and

(d) conducting arylation of the prepared compound of formula 44 with a compound of formula R_1-H (except that R_1 is -H) (or, a step of de-protecting R_1 may be comprised):

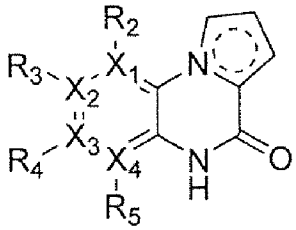
[Formula 43]



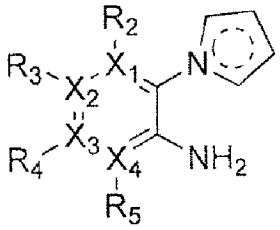
[Formula 44]



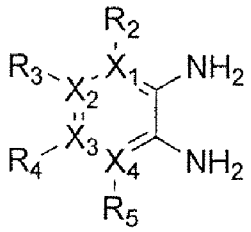
[Formula 45]



[Formula 46]



[Formula 47]



wherein, in formulas 43 to 47, X_1, X_2, X_3, X_4, R_1, R_2, R_3, R_4 and R_5 are the same as defined in formula 1; and Z represents a reactive leaving group.

[Claim 19] A pharmaceutical composition comprising an effective amount of a compound as defined in any one of Claims 1 to 10, or a racemate, isomer or pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

[Claim 20] The pharmaceutical composition according to Claim 19, wherein the composition exhibits a human histamine 4 receptor (hH4R) inhibition activity.

[Claim 21] The pharmaceutical composition according to Claim 19, wherein the composition is for treatment or prevention of a disease selected from the group consisting of inflammatory diseases, autoimmune diseases, allergic diseases, ocular diseases, skin diseases, respiratory diseases, pain diseases, cardiac diseases, and human histamine 4 receptor (hH4R)-related diseases.

[Claim 22] The pharmaceutical composition according to Claim 21, wherein the composition is for treatment or prevention of a disease selected from the group consisting of nasal polyps, allergic rhinitis, non-allergic rhinitis, viral rhinitis, nasal itch, sinusitis, nasal congestion, asthma, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, atopic dermatitis, psoriasis, eczema, pruritus, itchy skin, urticaria, idiopathic chronic urticaria, scleroderma, conjunctivitis, keratoconjunctivitis, ocular inflammation, dry eye, cardiac dysfunction, arrhythmia, atherosclerosis, multiple sclerosis, inflammatory bowel disease (including colitis, Crohn's disease, ulcerative colitis), inflammatory pain, neuropathic pain, osteoarthritic pain, autoimmune thyroid disease, immune-mediated (also known as type I) diabetes, lupus, post-operative adhesions, cancer and vestibular disorders.