N. et al., Arthritis Rheum., 2004, 50; Gerald G. et al., N. Engl. J. Med., 2007, 356). This also confirms that the inhibition of STAT3 signal transduction is an effective therapeutic method for such diseases.

In contrast, while having intracellular response pathways of identical cytokines and growth factors to those of STAT3, STAT1 increases inflammation and congenital and acquired immunities to inhibit the proliferation of cancer cells or cause pro-apoptotic responses, unlike STAT3 (Valeria Poli *et al*., *Review, Landes Bioscience*, 2009).

In order to develop STAT3 inhibitors, the following methods can be considered: i) inhibition of the phosphorylation of STAT3 protein by IL-6/gp-130/JAK kinase, ii) inhibition of the dimerization of activated STAT3 proteins, and iii) inhibition of the binding of STAT3 dimer to nuclear DNA. Small molecular STAT3 inhibitors are currently under development. Specifically, OPB-31121 and OPB-51602 are under clinical studies on patients with solid cancers or blood cancers by Otsuka Pharmaceutical Co., Ltd. Further, S3I-201 (Siddiquee *et al*., *Proc. Natl. Acad. Sci.*, 2007, 104), S3I-M2001 (Siddiquee *et al*., *Chem. Biol*., 2007, 2), LLL-12 (Lin *et al*., *Neoplasia*, 2010, 12), Stattic (Schust *et al*., *Chem. Biol.* 2006, 13), STA-21 (Song *et al*., *Proc. Natl. Acad. Sci.,* 2005, 102), SF-1-066 (Zhang *et a*l., *Biochem. Pharm*., 2010, 79) and STX-0119 (Matsuno *et al*., *ACS Med. Chem. Lett.*, 2010, 1), etc. have been reported to be effective in a cancer cell growth inhibition experiment and in animal model (in vivo Xenograft model). Furthermore, although peptide compounds mimicking the sequence of amino acid of pY-705 (STAT3) adjacent to the binding site to SH2 domain or the amino acid sequence of gp-130 receptor in which JAK kinases bind were studied (Coleman *et al*., *J. Med. Chem.,* 2005, 48), the development of the peptide compounds has not been successful due to the problems such as solubility and membrane permeability.

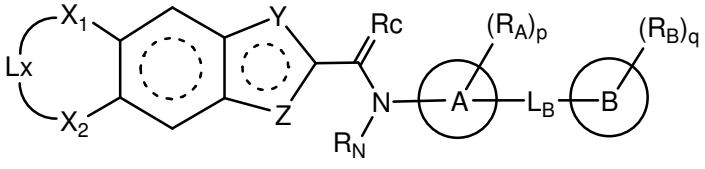
SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide novel heterocyclic derivatives for the inhibition of the activation of STAT3 protein.

It is another object of the present invention to provide uses of the heterocyclic derivatives for the prevention or treatment of diseases associated with the activation of STAT3 protein.

The invention is defined in the independent claims. Further embodiments of the invention are defined in the dependent claims.

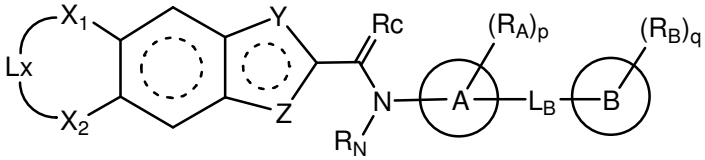
In accordance with one aspect of the present invention, there is provided a compound selected from the group consisting of a heterocyclic derivative represented by formula (I), and a pharmaceutically acceptable salt and a stereoisomer thereof:



(I)

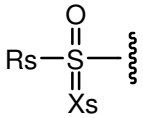
WHAT IS CLAIMED IS:

1. A compound selected from the group consisting of a heterocyclic derivative represented by formula (I), and a pharmaceutically acceptable salt and a stereoisomer thereof:



(I)

wherein one of X_1 and X_2 is -C(-Rx)(-Rx")-, -C(-Rx')(-Rx")-, -C(=O)-, -N(Rx)- or -N(-Rx')-, and the other is -C(-Rx")(-Rx")-, -N(-Rx")- or -O-;

Rx is  ;

Xs is =O or =NH;

Rs is C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, C_{2-7}alkenyl, amino, or aminoC_{1-6}alkyl;

Rx' is haloC_{1-6}alkyl, C_{1-4}alkoxycarbonyl, cyano, nitro, azido, amino, or a 3-6 membered heterocyclyl unsubstituted or substituted with Rx";

Rx" is each independently hydrogen, halogen, nitro, amino, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, carbamoylC_{1-6}alkyl, C_{1-6}alkylamino-C_{1-6}alkyl, or diC_{1-6}alkylamino-C_{1-6}alkyl;

one of Y and Z is -S- or -NH-, and the other is -CH= or -N=;

Lx is a saturated or unsaturated C_{1-4} hydrocarbon chain not containing or containing 1 to 3 heterogroups selected from the group consisting of -O-, -NH-, -N=, -S-, -S(=O)- and -S(=O)$_2$- in the chain, and unsubstituted or substituted with at least one Rx" moiety;

A and B are each independently a monocyclic- or bicyclic-saturated or unsaturated C_{3-10}carbocycle or 5- to 12-membered heterocycle;

Rc is =O, =NH, =N(-C_{1-6}alkyl), or =N(-OH);

R_N is hydrogen or C_{1-6}alkyl;

L_B is -[C(-R_L)(-R_L')]$_m$-, -[C(-R_L)(-R_L')]$_n$-O-, -O-, -NH-, -N(C_{1-6}alkyl)-, -S(=O)$_2$-, -C(=O)-, or -C(=CH_2)-, wherein m is an integer of 0 to 3, n is an integer of 1 to 3, R_L and R_L' are each independently hydrogen, hydroxy, halogen or C_{1-6}alkyl, or R_L and R_L' are linked together to form C_{1-6}alkylene;

R_A is hydrogen, halogen, cyano, C_{1-6}alkyl, haloC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, C_{1-6}alkylamino, diC_{1-}

dihydro-2*H*-thieno[3,2-*g*]chromene-7-carboxamide;

53) *N*-(2-chloro-6-(4-chlorophenoxy)pyridin-4-yl)-4-(2-oxopyrrolidin-1-yl)-3,4-dihydro-2*H*-thieno[3,2-*g*]chromene-7-carboxamide;

54) *N*-(2-chloro-6-(4-chlorophenoxy)pyridin-4-yl)-4-cyano-3,4-dihydro-2*H*-thieno[3,2-*g*]chromene-7-carboxamide;

55) 4-azido-*N*-(2-chloro-6-(4-chlorophenoxy)pyridin-4-yl)-3,4-dihydro-2*H*-thieno[3,2-*g*]chromene-7-carboxamide; and

56) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-1-(methylsulfonyl)-2,3-dihydro-1*H*-thieno[3',2':4,5]benzo[1,2-*b*][1,4]oxazine-7-carboxamide.

13. A pharmaceutical composition for preventing or treating diseases associated with the activation of STAT3 protein, comprising the compound as defined in any one of claims 1 to 12 as an active ingredient.

14. The pharmaceutical composition according to claim 13, wherein the diseases associated with the activation of STAT3 protein is selected from the group consisting of solid cancers, hematological or blood cancers, radio- or chemo-resistant cancers, metastatic cancers, inflammatory diseases, immunological diseases, diabetes, macular degeneration, human papillomavirus infection and tuberculosis.

15. The pharmaceutical composition according to claim 13, wherein the diseases associated with the activation of STAT3 protein are selected from the group consisting of breast cancer, lung cancer, stomach cancer, prostate cancer, uterine cancer, ovarian cancer, kidney cancer, pancreatic cancer, liver cancer, colon cancer, skin cancer, head and neck cancer, thyroid cancer, osteosarcoma, acute or chronic leukemia, multiple myeloma, B- or T-cell lymphoma, non-Hodgkin's lymphoma, auto-immune diseases comprising rheumatoid arthritis, psoriasis, hepatitis, inflammatory bowel disease, Crohn's disease, diabetes, macular degeneration, human papillomavirus infection, and tuberculosis.

16. A use of the compound as defined in any one of claims 1 to 12 for the manufacture of a medicament for preventing or treating diseases associated with the activation of STAT3 protein, wherein the diseases associated with the activation of STAT3 protein is selected from the group consisting of solid cancers, hematological or blood cancers, radio- or chemo- resistant cancers, metastatic cancers, inflammatory diseases, immunological diseases, diabetes, macular degeneration, human papillomavirus infection and tuberculosis.