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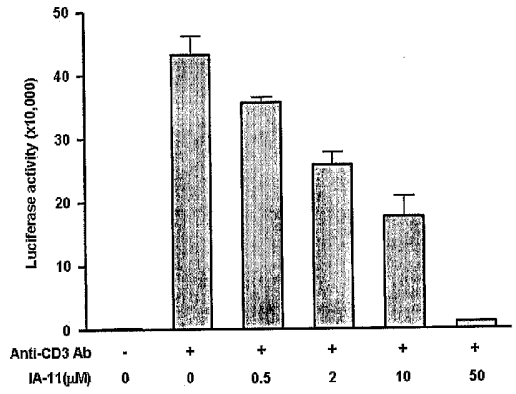
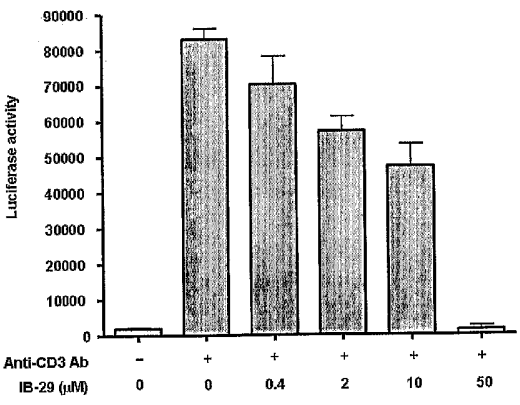
(54) Title: T-CELL INHIBITING COMPOUNDS AND THEIR USE FOR THE TREATMENT OF T-CELL-MEDIATED DISEASES





(57) Abstract: The present invention relates to compounds of formula IA or IB. The present invention also concerned to a method of treating immunologic diseases or pathological conditions in association with T cell involving an immunologic component using T-cell inhibitors, optionally in combination with one or more other drugs selected from steroids, DMARDs, NSAIDs, immunosuppressive, and biological modifiers, pharmaceutical compositions comprising said compounds of formula IA or IB together with said other drugs, and the use of T-cell inhibitors for the manufacture of a pharmaceutical composition for the treatment of immunologic diseases or pathological conditions involving an immunologic component.

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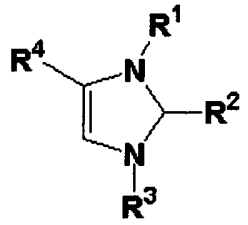
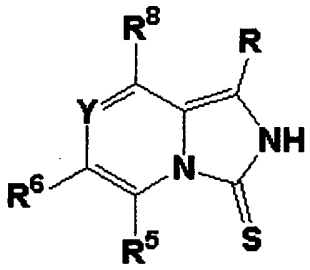
T-CELL INHIBITING COMPOUNDS AND THEIR USE FOR THE TREATMENT OF T-CELL-MEDIATED DISEASES

FIELD OF THE INVENTION

The present invention is concerned with the novel compounds of formula



IA



IB

or

wherein the substituents are defined hereinbelow.

The present invention relates to the compounds of formula IA or IB with T-cell inhibiting activities, a method of treating immunologic diseases or pathological conditions in association with T-cell activity by administering the compounds of formula IA or IB to a human being or an animal, a pharmaceutical composition comprising the compounds of formula IA or IB, and a use of said compounds for the manufacture of a pharmaceutical composition for the treatment of immunologic diseases or pathological conditions.

BACKGROUND OF THE INVENTION

T cells play cardinal roles in protective immune responses against neoplasia and microbial infection by actively participating in cell-mediated killing as well as by triggering activation of other immune cells. Uncontrolled T cell responses or recognition of auto- or allo-antigens as foreign antigens, however, provoke undesirable immune responses such as allergy, autoimmune disease and transplantation rejection.

Autoimmune diseases generally believed to be caused by uncontrolled T cell activation include inflammatory bowel disease, rheumatoid arthritis,

glomerulonephritis and lung fibrosis, psoriasis, hypersensitivity reactions of the skin, atherosclerosis, restenosis, allergic asthma, multiple sclerosis and type 1 diabetes (Hanke J H *et al.* (1995) *Inflamm. Res.* 357).

There are accumulating reports about the importance of T cells in the initiation as well as progression of autoimmune diseases. Multiple sclerosis (MS) is an autoimmune demyelinating disorder of the central nervous system (CNS), which is characterized by inflammatory lesions consisting of T cells, B cells and macrophages in the white matter of the CNS (Hafler, DA. (2004) *J. Clin. Invest.* 113:788-794). Although its etiology is not well-known, MS has been considered as a CD4 T cell-dependent disease (Hohlfeld. (2001) *Curr. Opin. Neurol.* 14:299-304). This notion is based on observation of the genetic linkage of MS susceptibility with MHC II genes (Zamvil SS *et al.* (1985) *J. Exp. Med.* 162(6):2107-24) and high frequency of activated, myelin-reactive T cells in the peripheral blood as well as cerebrospinal fluid of MS patients (Traugott U *et al.* (1983) *Science* 219(4582):308-10; Hauser SL *et al.* (1986) *Ann. Neurol.* 19(6):578-87). Early study demonstrated that transgenic mice expressing myelin-specific T-cell antigen receptor spontaneously developed demyelinating disease, suggesting that myelin-specific T cells might be one of the causative agents of multiple sclerosis and can initiate inflammatory disease process (Goverman et al. (1993) *Cell* 72:551-560). Moreover, experimental autoimmune encephalomyelitis (EAE), an animal model of MS, was induced by immunizing genetically susceptible animals with myelin peptides or myelin antigens including myelin basic protein (MBP), proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG) or by adoptively transferring myelin-reactive T cells (McRae B L *et al.* (1992) *J. Neuroimmunol.* 38:229-240; McRae B L *et al.* (1995) *J. Exp. Med.* 182:75-85).

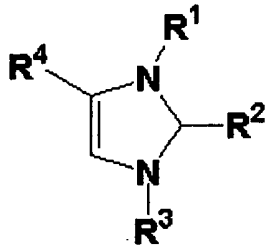
Transplantation rejections as well as Graft versus Host Disease (GvHD) after allogeneic bone marrow and stem cell transplantation are also mediated by T cells. Therefore, T-cell-targeted drugs would provide a strong therapeutic tool for

the treatment of said immunologic diseases or pathological conditions.

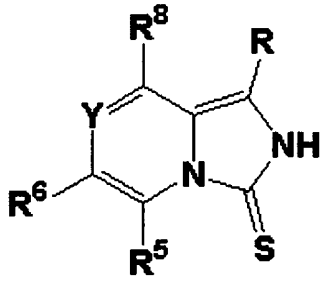
T-cell-specific inhibitor would fulfill unmet needs of current drugs and be effective for the treatment of those said immunologic diseases or pathological conditions, which include inflammatory bowel disease, rheumatoid arthritis, glomerulonephritis and lung fibrosis, psoriasis, hypersensitivity reactions of the skin, atherosclerosis, restenosis, multiple sclerosis and type 1 diabetes, allergic asthma, atopic disease, transplantation rejections and GvHD after allogeneic bone marrow and stem cell transplantation.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide the compounds of formula



IA



IB

or

wherein

R^1 is H or C_1-C_4 alkyl;

R^2 is =S, -SH, =O, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_1-C_4 alkoxymethylthio, C_1-C_4 alkoxybenzylthio or -S-$(CH_2)_n$-C(=O)-O-R^g;

R^3 is phenyl optionally substituted with one or more substituents selected from the group consisting of -OH, -NO_2, -NH_2, halo, -C_1-C_4 alkyl, –C_1-C_4 alkoxy, C_1-C_4 alkylcarbonylamino, -$(CH_2)_m$-C(=O)-O-R^g and -CH_2-C(=O)-O-R^g,

-$CH(CH_3)$-C(=O)-NR'R", wherein R' and R" together with N atom to which they are attached may form morpholine or piperazine optionally substituted with C_1-C_4 alkoxycarbonyl,

-$(CH_2)_n$-phenyl, phenyl being optionally substituted with one or more

substituents selected from the group consisting of halo, hydroxy, cyano and C_1-C_4 alkoxy,

-CH_2-pyridine,

-C_1-C_4 alkyl optionally substituted with hydroxy,

-(CH)(CH_3)-C(=O)-O-R^g,

-CH_2-C(=O)-NR^aR^b, wherein each of R^a and R^b is independently H, C_1-C_4 alkyl or benzyl substituted with halo, or R^a and R^b together with N atom to which they are attached may form a five or six-membered ring selected from the group consisting of morpholine, pyrrolidine, piperidine and piperazine, that optionally substituted with C_1-C_4 alkyl or C_1-C_4 alkoxycarbonyl,

-CH_2-C(=O)-O-R^g,

-$(CH_2)_2$-NR^cR^d, wherein each of R^c and R^d is C_1-C_4 alkyl, or R^c and R^d together with N atom to which they are attached may form morpholine, pyrrolidine, piperidine and piperazine optionally substituted with C_1-C_4 alkyl, or phenylcarbonyl, phenyl being optionally substituted with halo;

R^4 is phenyl optionally substituted with one or more substituents selected from the group consisting of cyano, -NO_2, -NH_2, hydroxy, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, phenyl, -C(=O)-O-R^g and CH_2-O-R^g,

-C(=O)-NR^eR^f, wherein each of R^e and R^f is independently H, C_1-C_4 alkyl or phenyl optionally substituted with C_1-C_4 alkoxy, or R^e and R^f together with N atom to which they are attached may form a five or six-membered ring selected from the group consisting of pyrrolidine, piperidine, piperazine and morpholine, that optionally substituted with C_1-C_4 alkyl or C_1-C_6 alkoxycarbonyl,

-(CH_2)-piperazine, piperazine being substituted with C_1-C_4 alkyl,

thienyl optionally substituted with halo or C_1-C_4 alkyl,

furyl optionally substituted with halo, C_1-C_4 alkyl or –C(=O)-O-R^g,

benzofuryl,

-CH_2-O-C(=O)-C_1-C_4 alkyl,

C_1-C_4 alkyl optionally substituted with hydroxy, or

C_1-C_4 alkoxycarbonyl;

R^g is hydrogen or C_1-C_4 alkyl;

n is 1 or 2;

m is 0 or 1;

R is C_1-C_6 alkyl,

C_1-C_6 alkenyl,

C_3-C_8 cycloalkyl,

pyridyl,

thienyl optionally substituted with halo,

-(CH_2)-pyridine,

furyl optionally substituted with C_1-C_4 alkyl or C_1-C_4 alkoxy,

isobenzofuryl,

naphthalenyl,

benzyl optionally substituted with C_1-C_4 alkoxy or hydroxy, or

phenyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkyl substituted with halo, C_1-C_4 alkoxy and C_1-C_4 alkoxycarbonylamino;

Y is N or CR^7, wherein R^7 is H or C_1-C_4 alkyl;

each of R^5 and R^8 is independently H or C_1-C_4 alkyl; and

R^6 is H, halo or C_1-C_4 alkyl; or

R^5 and R^6 together with the atoms to which they are attached may form a six membered aromatic ring, or

tautomers, stereoisomers or pharmaceutically acceptable salts thereof.

It is another object of the invention to provide a method of treating T-cell-mediated autoimmune diseases including, but are not intended to be limited to, multiple sclerosis, psoriasis, inflammatory bowl disease, rheumatoid arthritis, lupus and type 1 diabetes by employing the compounds of formula IA or IB.

It is a further object of the invention to provide a method of treating T cell-mediated diseases such as graft/tissue rejection and Graft versus Host Diseases.

It is an additional object of the invention to provide a use of the compound of formula IA or IB for the treatment and/or prophylaxis of T-cell mediated diseases.

BRIEF DESCRIPTION OF THE DRAWINGS

The above and other objects and features of the present invention will become apparent from the following description, when taken in conjunction with the accompanying drawings, in which:

FIG. 1A shows the dose-dependent inhibitory effect of 1,4-diphenyl -1,3-dihydro-imidazole-2-thione (IA-11)) and 1-(3-hydroxy-benzyl)-2H–imidazo [1,5-a]pyridine-3-thione (IB-29) on anti-CD3 antibody-induced NFAT activation.

FIG. 1B illustrates the dose-dependent inhibitory effect of 1, 4-diphenyl -1,3-dihydro-imidazole-2-thione (IA-11) derivatives (IA-109, 25, 111, 114) on anti-CD3 antibody-induced NFAT activation.

FIG. 1C depicts the dose-dependent inhibitory effect of 1,4-diphenyl-1,3-dihydro-imidazole-2-thione (IA-11) and [1,5-a]pyridine-3-thione (IB-29) of the subject invention on phorbol 12-myristate 13-acetate (PMA) and ionomycin (IM)-induced NFAT activation.

FIG. 2A shows the dose-dependent inhibitory effect of 1, 4-diphenyl -1,3-dihydro-imidazole-2-thione(IA-11) and derivatives thereof, i.e., [1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazol-4-yl]-pyrrolidin-1-yl-meth anone (IA-83) and 4-(4-amino-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione IA-21) on anti-CD3 antibody-induced splenocyte proliferation

FIG. 2B illustrates the dose-dependent inhibitory effect of 1,4-diphenyl-1,3-dihydro-imidazole-2-thione (IA-11) on mixed lymphocyte reaction.

FIG. 3 depicts a series of graphs depicting *in vivo* efficacy of 1,4-diphenyl-1,3-dihydro-imidazole-2-thione (IA-11) and 1-(3-hydroxy-benzyl)-2H-imidazo[1,5-a]pyridine-3-thione (IB-29) of the subject invention on anti-CD3 antibody-induced T cell activation and subsequent secretion of IL-2.

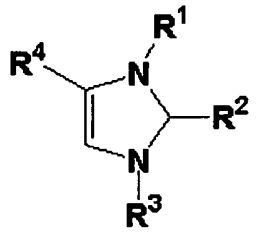
FIG. 4 shows *in vivo* inhibitory effect of 1, 4-diphenyl-1,3–dihydro -imidazole-2-thione (IA-11) on delayed type hypersensitivity.

FIG. 5 illustrates the dose-dependent inhibitory effect of 1, 4-diphenyl-1,3 -dihydro-imidazole-2-thione (IA-11) and 1-(3-Hydroxy-benzyl)-2H-imidazo[1,5-a] pyridine-3-thione (IB-29) on EAE.

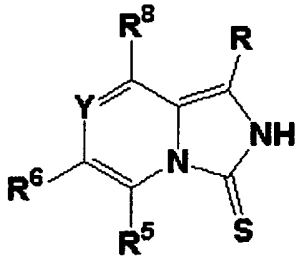
FIG. 6 depicts *in vitro* proliferation of splenocytes taken from mice after 10 days from the immunization with MOG emulsified with CFA in 1:1 ratio and given 1,4-diphenyl-1,3-dihydro-imidazole-2-thione (IA-11) or vehicle.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides the compounds of formula



IA



IB

or

wherein

R^1 is H or C_1-C_4 alkyl;

R^2 is =S, -SH, =O, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_1-C_4 alkoxymethylthio, C_1-C_4 alkoxybenzylthio or -S-$(CH_2)_n$-C(=O)-O-R^g;

R^3 is phenyl optionally substituted with one or more substituents selected from the group consisting of -OH, -NO_2, -NH_2, halo, -C_1-C_4 alkyl, –C_1-C_4 alkoxy, C_1-C_4 alkylcarbonylamino, -$(CH_2)_m$-C(=O)-O-R^g and -CH_2-C(=O)-O-R^g, -$CH(CH_3)$-C(=O)-NR'R", wherein R' and R" together with N atom to which

they are attached may form morpholine or piperazine optionally substituted with C_1-C_4 alkoxycarbonyl,

-$(CH_2)_n$-phenyl, phenyl being optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, cyano and C_1-C_4 alkoxy,

-CH_2-pyridine,

-C_1-C_4 alkyl optionally substituted with hydroxy,

-(CH)(CH_3)-C(=O)-O-R^g,

-CH_2-C(=O)-NR^aR^b, wherein each of R^a and R^b is independently H, C_1-C_4 alkyl or benzyl substituted with halo, or R^a and R^b together with N atom to which they are attached may form a five or six-membered ring selected from the group consisting of morpholine, pyrrolidine, piperidine and piperazine, that optionally substituted with C_1-C_4 alkyl or C_1-C_4 alkoxycarbonyl,

-CH_2-C(=O)-O-R^g,

-$(CH_2)_2$-NR^cR^d, wherein each of R^c and R^d is C_1-C_4 alkyl, or R^c and R^d together with N atom to which they are attached may form morpholine, pyrrolidine, piperidine or piperazine optionally substituted with C_1-C_4 alkyl, or phenylcarbonyl, phenyl being optionally substituted with halo;

R^4 is phenyl optionally substituted with one or more substituents selected from the group consisting of cyano, -NO_2, -NH_2, hydroxy, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, phenyl, -C(=O)-O-R^g and CH_2-O-R^g,

-C(=O)-NR^eR^f, wherein each of R^e and R^f is independently H, C_1-C_4 alkyl or phenyl optionally substituted with C_1-C_4 alkoxy, or R^e and R^f together with N atom to which they are attached may form a five or six-membered ring selected from the group consisting of pyrrolidine, piperidine, piperazine and morpholine, that optionally substituted with C_1-C_4 alkyl or tert-butoxycarbonyl,

-(CH_2)-piperazine, piperazine being substituted with C_1-C_4 alkyl,

thienyl optionally substituted with halo or C_1-C_4 alkyl,

furyl optionally substituted with halo, C_1-C_4 alkyl or –C(=O)-O-R^g,

benzofuryl,

$-CH_2-O-C(=O)-C_1-C_4$ alkyl,

C_1-C_4 alkyl optionally substituted with hydroxy, or

C_1-C_4 alkoxycarbonyl;

R^g is hydrogen or C_1-C_4 alkyl;

n is 1 or 2;

m is 0 or 1;

R is C_1-C_6 alkyl,

C_1-C_6 alkenyl,

C_3-C_8 cycloalkyl,

pyridyl,

thienyl optionally substituted with halo,

$-(CH_2)$-pyridine,

furyl optionally substituted with C_1-C_4 alkyl or C_1-C_4 alkoxy,

isobenzofuryl,

naphthalenyl,

benzyl optionally substituted with C_1-C_4 alkoxy or hydroxy, or

phenyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkyl substituted with halo, C_1-C_4 alkoxy and C_1-C_4 alkoxycarbonylamino;

Y is N or CR^7, wherein R^7 is H or C_1-C_4 alkyl;

each of R^5 and R^8 is independently H or C_1-C_4 alkyl; and

R^6 is H, halo or C_1-C_4 alkyl; or

R^5 and R^6 together with the atoms to which they are attached may form a six membered aromatic ring, or

the tautomers, stereoisomers or physiologically acceptable salts thereof.

The object of the subject invention is to provide the compounds of formula IA or IB with T-cell inhibiting activities. These compounds suppress T-cell antigen

receptor-induced NFAT-promoter activation, IL-2 production, and subsequent T-cell proliferation. Intraperitoneal or oral administration of these compounds also inhibit T-cell activation *in vivo* as exemplified by IL-2 level measured after anti-CD3 antibody inoculation and this implicates that their T-cell inhibitory activities are functional *in vivo*. Further, disease models indicate that these compounds exhibit prophylactic and therapeutic effects in delayed type hypersensitivity (DTH), experimental autoimmune encephalomyelitis (EAE) and rheumatoid arthritis (RA).

Preferred compounds of formula IA of the present invention are compounds of formula IA wherein R^1 is H, R^2 is =S, R^3 is phenyl and R^4 is phenyl substituted with C_1-C_4 alkoxy or halo.

Examples of preferred compounds of formula IA are the following:

1,4-diphenyl-1H-imidazole-2-thiol,

4-(1-phenyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)-benzonitrile,

4-(2,4-dimethoxy-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-(4-fluoro-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-(2-methoxy-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-(4-methoxy-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-biphenyl-4-yl-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-(4-chloro-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

1-phenyl-4-p-tolyl-1,3-dihydro-imidazole-2-thione,

3-(1,4-diphenyl-1H-imidazol-2-ylsulfanyl)-propionic acid ethyl ester,

1,4-diphenyl-1,3-dihydro-imidazole-2-thione,

3-(1,4-diphenyl-1H-imidazol-2-ylsulfanyl)-propionic acid,

(1,4-diphenyl-1H-imidazol-2-ylsulfanyl)-acetic acid ethyl ester,

(1,4-diphenyl-1H-imidazol-2-ylsulfanyl)-acetic acid,

4-phenyl-1-o-tolyl-1,3-dihydro-imidazole-2-thione,

1,4-diphenyl-1,3-dihydro-imidazol-2-one,

2-methanesulfonyl-1,4-diphenyl-1H-imidazole,

2-methylsulfanyl-1,4-diphenyl-1H-imidazole,

4-(4-methoxy-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-(4-nitro-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-(4-amino-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-(4-hydroxy-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

1-(4-hydroxy-phenyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,

4-(1-phenyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)-benzoic acid methyl ester,

4-(1-phenyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)-benzoic acid,

3-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-benzoic acid ethyl ester,

3-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-benzoic acid,

4-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-benzoic acid ethyl ester,

4-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-benzoic acid,

1-(3-nitro-phenyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,

1-(3-amino-phenyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,

N-[4-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-phenyl]-acetamide,

1-(3-fluoro-benzyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,

1-benzyl-4-phenyl-1,3-dihydro-imidazole-2-thione,

1-(2-methoxy-benzyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,

1-(4-methoxy-benzyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,

1-(4-hydroxy-benzyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,

1-(2-hydroxy-benzyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,

4-[1-(4-fluoro-benzyl)-2-thioxo-2,3-dihydro-1H-imidazol-4-yl]-benzonitrile,

4-[1-(4-fluoro-benzyl)-2-thioxo-2,3-dihydro-1H-imidazol-4-yl]-benzoic acid,

1-(4-fluoro-benzyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,

4-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-ylmethyl)-benzonitrile,

1-(2-chloro-benzyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,

4-phenyl-1-pyridin-2-ylmethyl-1,3-dihydro-imidazole-2-thione,

2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-propionic acid methyl ester,

2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-propionic acid,

1-(2-hydroxy-1-methyl-ethyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,
1-morpholin-4-yl-2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-ethanone,
2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-1-piperidin-1-yl-ethanone,
1-(4-methyl-piperazin-1-yl)-2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-etha
none,
4-[2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-acetyl]-piperazine-1-carboxyli
c acid tert-butyl ester,
N,N-diethyl-2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-acetamide,
2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-1-pyrrolidin-1-yl-ethanone,
1-(2-morpholin-4-yl-ethyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,
4-phenyl-1-(2-piperidin-1-yl-ethyl)-1,3-dihydro-imidazole-2-thione,
4-phenyl-1-(2-pyrrolidin-1-yl-ethyl)-1,3-dihydro-imidazole-2-thione,
(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-acetic acid methyl ester,
(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-acetic acid,
1-methyl-4-phenyl-1,3-dihydro-imidazole-2-thione,
3-methyl-1,4-diphenyl-1,3-dihydro-imidazole-2-thione,
4-methyl-1-phenyl-1,3-dihydro-imidazole-2-thione,
1-(2-hydroxy-ethyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,
1-morpholin-4-yl-2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-propan-1-one,
4-[2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-propionyl]-piperazine-1-carbo
xylic acid tert-butyl ester,
1-[2-(4-methyl-piperazin-1-yl)-ethyl]-4-phenyl-1,3-dihydro-imidazole-2-thione,
N-(4-fluoro-benzyl)-2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-acetamide,
1-(2-diethylamino-ethyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,
1-isopropyl-4-phenyl-1,3-dihydro-imidazole-2-thione,
1-[2-(4-fluoro-phenyl)-ethyl]-4-phenyl-1,3-dihydro-imidazole-2-thione,
(4-fluoro-phenyl)-[2-(4-methoxy-benzylsulfanyl)-4-phenyl-imidazol-1-yl]-methan
one,
(4-fluoro-phenyl)-(2-methoxymethylsulfanyl-4-phenyl-imidazol-1-yl)-methanone,

(4-fluoro-phenyl)-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-methanone,
1-(2-chloro-benzyl)-2-methoxymethylsulfanyl-4-phenyl-1H-imidazole,
2-(2-methoxymethylsulfanyl-4-phenyl-imidazol-1-ylmethyl)-pyridine,
4-(2-methoxymethylsulfanyl-4-phenyl-imidazol-1-ylmethyl)-pyridine,
1-(2-fluoro-benzyl)-2-methoxymethylsulfanyl-4-phenyl-1H-imidazole,
2,2-dimethyl-propionic acid 1-(4-fluoro-benzyl)-2-thioxo-2,3-dihydro-1H –imidazol-4- yl-methyl ester,
1-(4-fluoro-benzyl)-4-hydroxymethyl-1,3-dihydro-imidazole-2-thione,
1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazole-4-carboxylic acid ethyl ester,
1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazol-4-yl]-(4-methyl-piperazin-1-yl)-methanone,
[1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazol-4-yl]-morpholin-4-yl-methanone,
[1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazol-4-yl]-piperidin-1-yl-methanon,
[1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazol-4-yl]-pyrrolidin-1-yl-methanone,
1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazole-4-carboxylic acid diethylamide,
4-[1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazole-4-carbonyl]-piperazine-1- carboxylic acid tert-butyl ester,
1-(4-methoxy-phenyl)-4-(4-methyl-piperazin-1-yl-methyl)-1,3-dihydro-imidazole-2-thione,
1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazole-4-carboxylic acid phenylamide,
1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazole-4-carboxylic acid (4-methoxy-phenyl)-amide,
1-phenyl-4-thiophen-2-yl-1,3-dihydro-imidazole-2-thione,

1-phenyl-4-thiophen-3-yl-1,3-dihydro-imidazole-2-thione,
4-(5-bromo-thiophen-2-yl)-1-(4-methoxy-phenyl)-1,3-dihydro-imidazole-2-thione,
4-(3-methyl-thiophen-2-yl)-1-phenyl-1,3-dihydro-imidazole-2-thione,
3-[4-(5-bromo-thiophen-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-benzoic acid,
3-[4-(5-bromo-thiophen-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-benzoic acid ethyl ester,
4-(5-bromo-thiophen-2-yl)-1-phenyl-1,3-dihydro-imidazole-2-thione,
4-(5-chloro-thiophen-2-yl)-1-phenyl-1,3-dihydro-imidazole-2-thione,
4-(2,5-dimethyl-thiophen-3-yl)-1-phenyl-1,3-dihydro-imidazole-2-thione,
4-furan-2-yl-1-phenyl-1,3-dihydro-imidazole-2-thione,
4-(5-methyl-furan-2-yl)-1-phenyl-1,3-dihydro-imidazole-2-thione,
4-(5-bromo-furan-2-yl)-1-phenyl-1,3-dihydro-imidazole-2-thione,
4-benzofuran-2-yl-1-phenyl-1,3-dihydro-imidazole-2-thione,
3-[4-(5-bromo-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-benzoic acid ethyl ester,
3-[4-(5-bromo-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-benzoic acid,
1-(4-methoxy-phenyl)-4-(5-methyl-furan-2-yl)-1,3-dihydro-imidazole-2-thione,
N-{3-[4-(5-methyl-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-phenyl}-acetamide,
N-{4-[4-(5-methyl-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-phenyl}-acetamide,
N-{3-[4-(5-bromo-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-phenyl}-acetamide,
5-(1-phenyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)-furan-2-carboxylic acid methyl ester,
N-{4-[4-(5-bromo-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-phenyl}-acetamide,
5-(1-phenyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)-furan-2-carboxylic acid,

{4-[4-(5-methyl-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-phenoxy}-acetic acid ethyl ester,

{4-[4-(5-methyl-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-phenoxy}-acetic acid,

{4-[4-(5-methyl-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-phenyl}-acetic acid methyl ester,

3-[4-(5-methyl-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-benzoic acid ethyl ester,

3-[4-(5-methyl-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-benzoic acid,

5-[1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazol-4-yl]-furan-2-carboxylic acid methyl ester and

{4-[4-(5-methyl-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-phenyl}-acetic acid.

Preferred compounds of formula IB of the present invention are compounds of formula IB wherein Y is CH and R is phenyl optionally substituted with halo, C_1-C_4 alkyl optionally substituted with halo or C_1-C_4 alkoxy.

Examples of preferred compounds of formula IB are the following:

1-(2-methoxy-phenyl)-2H-imidazo[1,5-a]pyridine-3-thione,

1-(3-methoxy-phenyl)-2H-imidazo[1,5-a]pyridine-3-thione,

1-(4-methoxy-phenyl)-2H-imidazo[1,5-a]pyridine-3-thione,

1-(4-hydroxy-phenyl)-2H-imidazo[1,5-a]pyridine-3-thione,

1-(4-fluoro-phenyl)-2H-imidazo[1,5-a]pyridine-3-thione,

1-(4-chloro-phenyl)-2H-imidazo[1,5-a]pyridine-3-thione,

1-(4-trifluoromethyl-phenyl)-2H-imidazo[1,5-a]pyridine-3-thione,

1-(4-bromo-phenyl)-2H-imidazo[1,5-a]pyridine-3-thione,

1-p-tolyl-2H-imidazo[1,5-a]pyridine-3-thione,

6-chloro-1-phenyl-2H-imidazo[1,5-a]pyridine-3-thione,

1-phenyl-2H-imidazo[1,5-a]pyridine-3-thione,

1-pyridin-4-yl-2H-imidazo[1,5-a]pyridine-3-thione,

[4-(3-thioxo-2,3-dihydro-imidazo[1,5-a]pyridin-1-yl)-phenyl]-carbamic acid tert-butyl ester,

1-naphthalen-1-yl-2H-imidazo[1,5-a]pyridine-3-thione,

1-naphthalen-2-yl-2H-imidazo[1,5-a]pyridine-3-thione,

6-chloro-1-phenyl-2H-imidazo[1,5-a]pyridine-3-thione,

1-(4-methoxy-phenyl)-8-methyl-2H-imidazo[1,5-a]pyridine-3-thione,

1-(4-methoxy-phenyl)-7-methyl-2H-imidazo[1,5-a]pyridine-3-thione,

1-(4-methoxy-phenyl)-6-methyl-2H-imidazo[1,5-a]pyridine-3-thione,

1-(4-methoxy-phenyl)-5-methyl-2H-imidazo[1,5-a]pyridine-3-thione,

3-p-tolyl-2H-imidazo[1,5-a]quinoline-1-thione,

1-phenyl-2H-imidazo[1,5-a]pyrazine-3-thione,

1-benzyl-2H-imidazo[1,5-a]pyridine-3-thione,

1-(2-methoxy-benzyl)-2H-imidazo[1,5-a]pyridine-3-thione,

1-(3-methoxy-benzyl)-2H-imidazo[1,5-a]pyridine-3-thione,

1-(4-methoxy-benzyl)-2H-imidazo[1,5-a]pyridine-3-thione,

1-(2-hydroxy-benzyl)-2H-imidazo[1,5-a]pyridine-3-thione,

1-(3-hydroxy-benzyl)-2H-imidazo[1,5-a]pyridine-3-thione,

1-(4-hydroxy-benzyl)-2H-imidazo[1,5-a]pyridine-3-thione,

1-pyridin-4-ylmethyl-2H-imidazo[1,5-a]pyridin-3-one,

4-(3-thioxo-2,3-dihydro-imidazo[1,5-a]pyridin-1-ylmethyl)-pyridinium chloride,

1-methyl-2H-imidazo[1,5-a]pyridine-3-thione,

1-ethyl-2H-imidazo[1,5-a]pyridine-3-thione,

1-isopropyl-2H-imidazo[1,5-a]pyridine-3-thione,

1-tert-butyl-2H-imidazo[1,5-a]pyridine-3-thione,

1-allyl-2H-imidazo[1,5-a]pyridine-3-thione,

1-butyl-2H-imidazo[1,5-a]pyridine-3-thione,

1-(3-methyl-butyl)-2H-imidazo[1,5-a]pyridine-3-thione,

1-cyclohexyl-2H-imidazo[1,5-a]pyridine-3-thione,

1-thiophen-2-yl-2H-imidazo[1,5-a]pyridine-3-thione,
1-thiophen-3-yl-2H-imidazo[1,5-a]pyridine-3-thione,
1-(5-bromo-thiophen-2-yl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-furan-2-yl-2H-imidazo[1,5-a]pyridine-3-thione,
1-(5-methyl-furan-2-yl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-(5-methoxy-furan-2-yl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-furan-3-yl-2H-imidazo[1,5-a]pyridine-3-thione,
1-benzofuran-2-yl-2H-imidazo[1,5-a]pyridine-3-thione.

Compounds of formulae IA and IB may form acid addition salts. The acids may be hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, salicylate, sulphate, pyruvate, citrate, lactate, mandelate, tartarate and methansulphonate.

Compounds of formula IA or IB can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates. The optically active forms can be obtained, e.g., by resolution of the racemates, asymmetric synthesis or asymmetric chromatograph (chromatography with a chiral adsorbents or eluants). All of these forms are included in the scope of the subject invention.

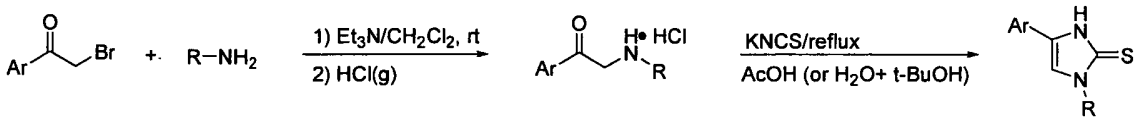
Compounds of the present invention can be made by various methods depicted in the illustrative synthetic reaction schemes shown below.

The starting materials and reagents used in preparing these compounds generally are either available from commercial suppliers or are prepared by methods known to those skilled in the art. The skills required for carrying out the reaction and purification of the resulting products are known to those in the art (For reaction conditions for LAH reduction, *see* for example: Micovič, V.M.;

Mihailovič, M.L. *J. Org. Chem.* 1953, 18, 1190; for amide coupling, *see* for example: *JACS* 107, 1421, 4342 (1985) and for ester hydrolysis, *see* for example J.M. Khurana and A. Sehgal, *Org. Prep. Proced. Int.*, 26, 580 (1994)).

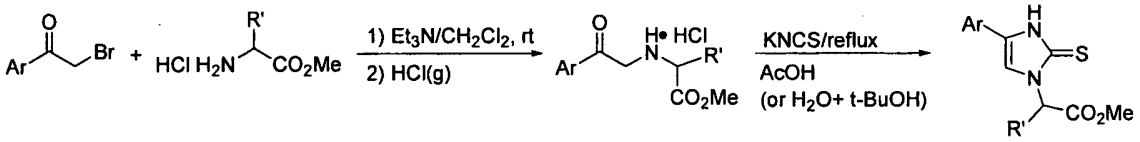
The compound of formula IA can be prepared according to schemes 1 to 3 as follows:

Scheme 1



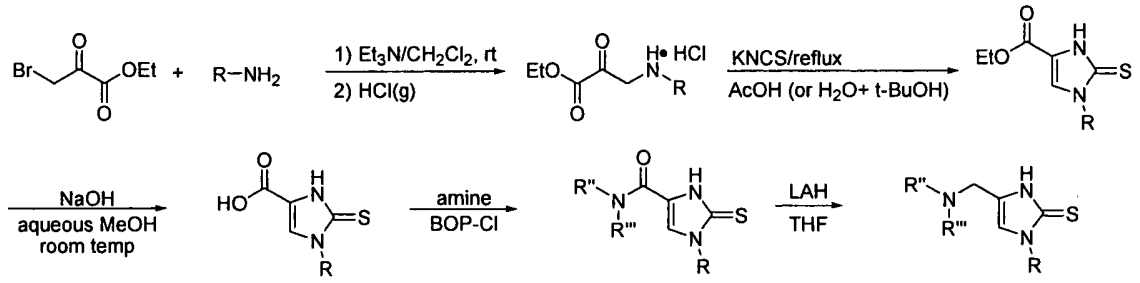
Ar: substituted phenyl; R: substituted phenyl

Scheme 2



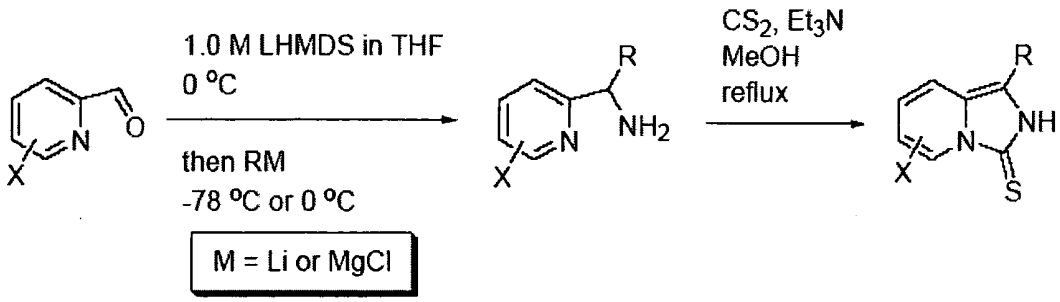
Ar: substituted phenyl, R': H, CH_3

Scheme 3



Compounds of general formula IB can be prepared according to scheme 4 as follows:

Scheme 4



Further, the inventive compounds are effective inhibitors of T-cell activation demonstrated by *in vitro* cell-based assays, and therefore, the subject invention provides a method of treating immunologic diseases or pathological conditions associated with T-cell activity.

As described above, the compounds of formula IA or IB of the present invention can be used as medicaments for the prophylactic and/or therapeutic treatment of T-cell mediated disease including graft rejection, Graft versus Host Disease, asthma, atopic diseases and autoimmune diseases such as multiple sclerosis, psoriasis, inflammatory bowl disease, rheumatoid arthritis, lupus and type I diabetes.

Furthermore, the invention provides a pharmaceutical composition comprising the compound of formula IA or IB and a pharmaceutically acceptable carrier.

The compounds of formula IA or IB and their pharmaceutically acceptable salts possess valuable pharmacological properties. Specifically, these compounds exhibit inhibitory activity on T-cell antigen receptor induced NFAT (one of major transcription factors important for the activation and expression of interleukin-2) activation, IL-2 production and subsequent T-cell proliferation.

In a specific embodiment, the pharmacological activities of the subject compounds have been tested by measuring the level of TCR- or PMA/IM-induced NFAT activation (Example 10) and by the mixed lymphocyte reaction (MLR) (Example 11), which is a known method for determining the transplantation

compatibility between the donor (graft) and the recipient (Park and Good, p71, in Tissue typing and organ transplantation, 1973, Academic Press Inc., N.Y.).

Further, in order to determine if the inventive compounds are delivered to the blood stream and stable enough to exert their activity, T cell activation status *in vivo* was monitored, after T cell activation by administering anti-CD3 antibody to mice (Example12).

In accordance with an embodiment of the present invention, these compounds have prophylactic and therapeutic effects on delayed type hypersensitivity and autoimmune encephalomyelitis in disease models (Examples 13 to 15).

The compounds of the present invention have IC_{50} values within the range of about 0.4 μM to 50 μM, preferably less than 20μM, more preferably less than 5μM. Tables 1 and 2 show measured IC_{50} value ranges for the preferred compounds of the present invention.

The compounds of formula IA or IB and their pharmaceutically acceptable salts can be used as medicaments, e.g., in the form of pharmaceutical preparation for enteral, parenteral or topical administration. They can be administered, for example, orally, in the form of tablets, coated tablets, dragees, hard and soft gelatine capsules, solutions, emulsions or suspensions; rectally, in the form of suppositories; parenterally, in the form of injection solutions or infusion solutions; or topically, in the form of ointments, creams or oils. The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula IA or IB and their pharmaceutically acceptable, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets,

coated tablets, dragees and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers are, however, required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi- synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency- improving agents, flavor-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

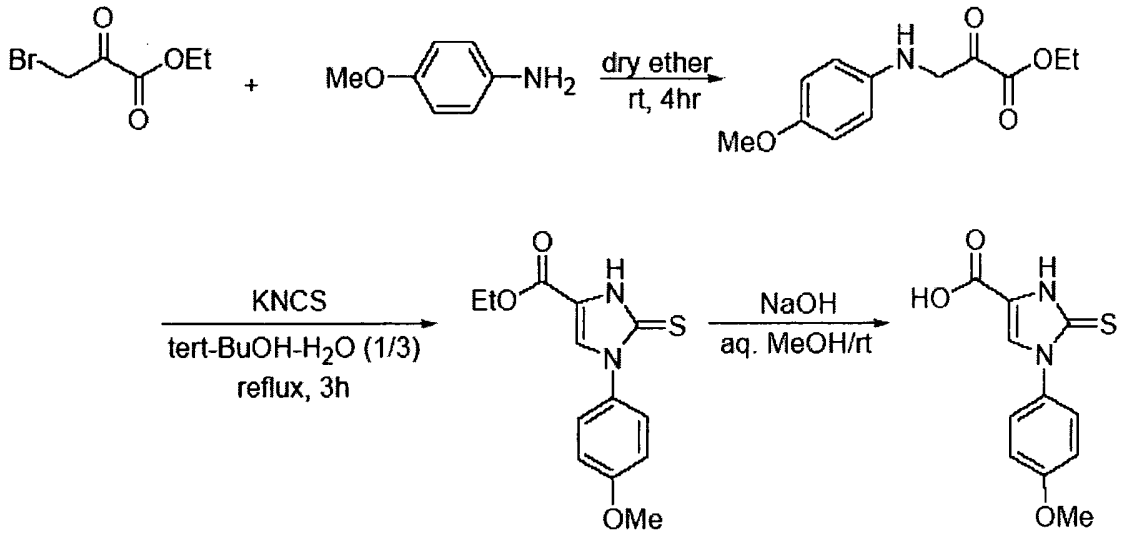
The dosage of the compounds of formula IA or IB can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 0.01 mg to about 1000 mg, especially about 0.1 mg to about 500 mg, comes into consideration. Depending on the dosage it is convenient to administer the daily dosage in several dosage units.

The pharmaceutical preparations conveniently contain about 500 mg, preferably 50 mg, of the compound of formula IA or IB.

The following examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Examples

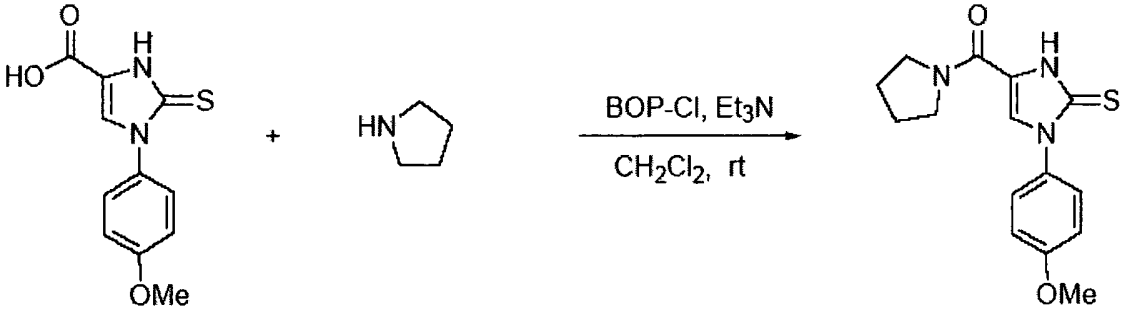
Example 1: Preparation of 1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H -imidazole-4-carboxylic acid



Ethyl bromopyruvate(7.15g, 36mmol) and *p*-anisidine(7.40g, 60mmol) in 100ml of dry ether were charged to 250ml round bottomed flask, and they were stirred for 4 hrs at room temperature. Then, the solution was filtered to remove the insoluble salt. The filtrate was concentrated to obtain brown liquid composition. Without further purification procedure, said composition was taken up in 100ml of water/t-BuOH (v/v=1/3). Subsequently KNCS(0.1mol) was added to the solution and heated to reflux for 3hrs. The reaction mixture was cooled to room temperature, extracted with ethyl acetate/H_2O, dried over $MgSO_4$ and evaporated under reduced pressure. The resulting concentrates were purified by the column chromatography (hexane:ethyl acetate: 3:1, v/v) to yield 3.19g (11.46mmol) of the desired compounds as brown solid. The obtained solid was charged to 100ml round bottomed flask and a solution of NaOH (1.5g) in MeOH/H_2O (5/1, v/v) was added. On completion of the reaction, the solution was evaporated under reduced pressure to remove MeOH. Light greenish yellow

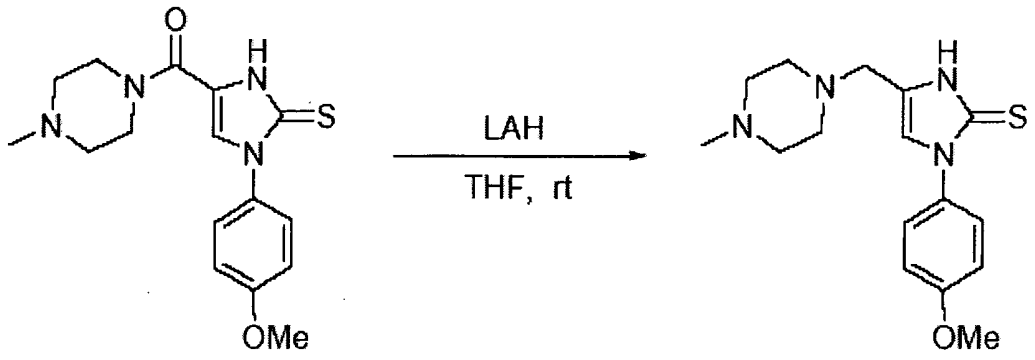
solids were formed in the aqueous solution. 2N HCl was added to acidify the solution to pH 3 and a light yellow solid was formed. The solid was filtered, washed with water and dried to yield 1.77g (7.07mmol, 94%) of the desired yellow solid.

Example 2: Preparation of [1-(4-Methoxy-phenyl)-2-thioxo-2,3-dihydro -1H-imidazol-4-yl]-piperidin-1-yl-methanone



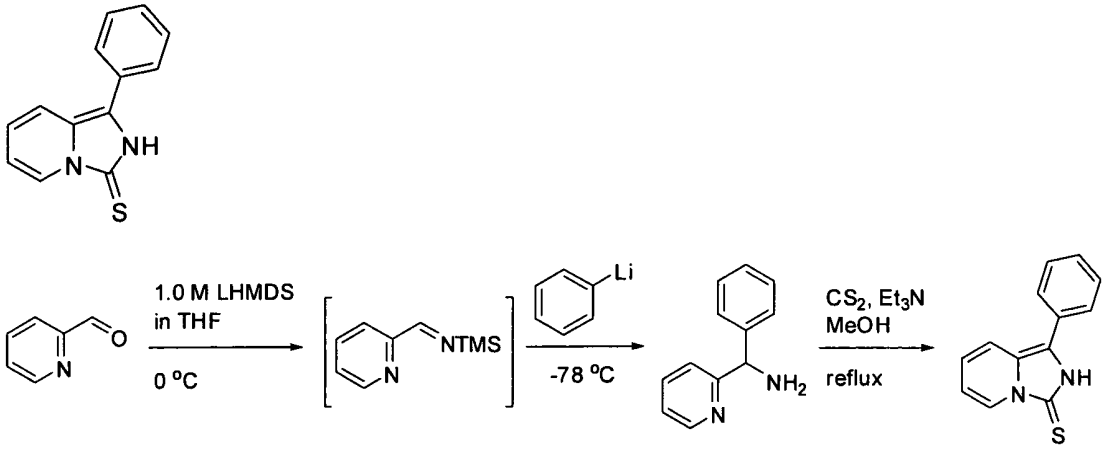
To the obtained solid (75mg, 0.299mmol) in 25ml round bottomed flask, dry CH_2Cl_2 was added. The solution was cooled with ice-bath and stirred with BOP-Cl (94.38mg, 0.36mmol). Triethylamine(92.9 $\mu\ell$) was added. The reaction mixture was stirred for further 30 minutes, and pyrrolidine(44.3 $\mu\ell$, 0.45mmol) was added. After the completion of the reaction, the solution was acidified and extracted with ethyl acetate. The combined organic solution was washed with $NaHCO_3$, dried over $MgSO_4$, filtered, concentrated and purified by column chromatography (dimethylchloride:methanol = 10:1, v/v) to obtain the title compound as light brown solid. ^1H NMR (200 MHz, $CDCl_3$) 8.00 (s, 1H, NH), 7.12 (m, 5H), 3.82 (s, 3H), 3.71(m, 4H), 1.59 (m, 6H).

Example 3: Preparation of 1-(4-methoxy-phenyl)-4-(4-methyl-piperazin-1-yl -methyl)-1,3-dihydro-imidazole-2-thione



To the solution of amide(14mg, 0.042mmol) obtained by the above procedure in THF, lithium aluminum hydride (LAH) (1.2mg, 0.032mmol) was added and stirred at room temperature. On completion of the reaction, water and ether were added and stirred. And, then, the solution was acidified, extracted with ether and purified via column chromatography (dimethylchloride: methanol = 10:1) to obtain the title compound. ^{1}H NMR (200 MHz, $CDCl_3$) 7.75 (s, 1H, NH), 7.29 (d, J = 7.0Hz, 2H), 7.25 (s, 1H), 6.90 (d, J = 7.4Hz, 2H), 3.81 (m, 7H), 2.37 (m, 7H).

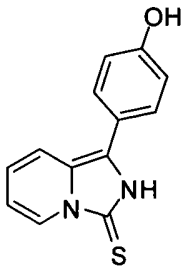
Example 4: Preparation of 1-phenylimidazo[1,5-a]pyridine-3(2H)-thione :

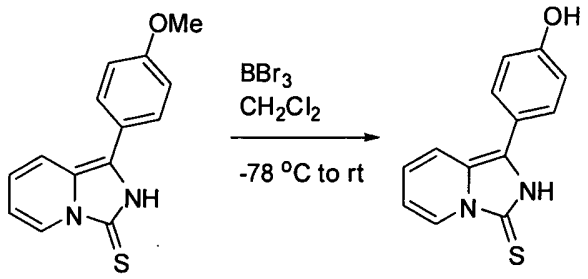


To a solution of 2-pyridinecarboxaldehyde (1 g, 9.34 mmol) in THF (10 mL), LHMDS solution (1.0 M in THF, 11 mL, 1.2 eq.) was slowly added at 0 °C. To an another flask containing iodobenzene (2.1 mL, 2 equiv) in THF (15 mL), n-BuLi (1.6 M in hexanes, 10.5 mL, 1.8 eq.) was slowly added at -78 °C. After 20 minutes, the *N*-TMS aldimine solution was slowly added to the phenyl lithium

solution at -78 °C. After 30 min, the reaction mixture was quenched with H_2O. The mixture was diluted with ethyl acetate and washed with water and brine. The water layer was extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The resulting residue was further purified by silica gel column chromatography (hexane:ethyl acetate = 1:1 to ethyl acetate only to dichloromethane: methanol = 10:1) to give C-phenyl-C-pyridin-2-ylmethyl amine (1.65 g, 96%). This amine (1.65 g, 8.97 mmol) was dissolved in MeOH (30 mL), and CS_2 (3.9 mL, 7.2 equiv) and Et_3N (2.5 mL, 2.0 equiv) were added at room temperature. The reaction mixture was heated to reflux overnight. After being cooled to room temperature, the mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane and washed with water. The water layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was suspended in a small amount of ethyl acetate and filtered. The solid was washed with small amount of ethyl acetate and dried to yield 1-phenylimidazo[1,5-a]pyridine-3(*2H*)-thione (1.75 g, 93%). 300 MHz ^{1}H NMR (DMSO-d_6) 13.8 (1H, br s), 8.16 (1H, dt, J = 7.4, 1.0 Hz), 7.73~7.66 (3H, m), 7.47 (2H, t, J = 8.0 Hz), 7.32 (1H, t, J = 7.4 Hz), 6.89 (1H, ddd, J = 9.4, 6.3, 0.9 Hz), 6.72 (1H, ddd, J = 7.3, 6.5, 1.0 Hz).

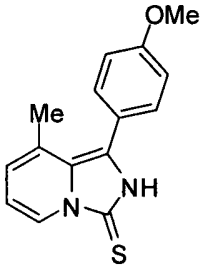
Example 5: Preparation of 1-(4-hydroxyphenyl)imidazo[1,5-a]pyridine-3(2H) -thione :

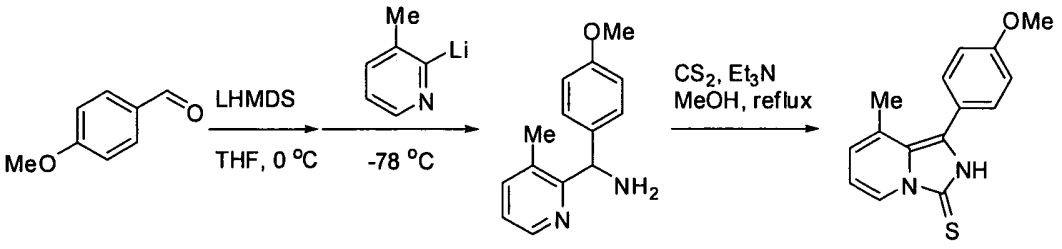




To a solution of 1-(4-methoxyphenyl)imidazo[1,5-a]pyridine-3(*2H*)-thione (150 mg, 0.62 mmol) in CH_2Cl_2 (2 mL) was added BBr_3 (1M in CH_2Cl_2, 3.1 mL, 5 equiv) at -78 °C. After being stirred at -78 °C for 1 h, the reaction mixture was stirred at room temperature for additional 2 hrs. The mixture was quenched with cold H_2O at 0 °C. The organic layer was separated from the mixture and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give 1-(4-hydroxyphenyl)imidazo[1,5-a]pyridine-3(*2H*)-thione. (200 MHz ^1H NMR ($CDCl_3$) 8.19 (1H, d),7.43-7.58 (6H, m), 6.77 (1H, d), 6.47 (1H, t).

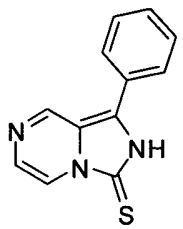
Example 6: Prepration of 1-(4-methoxyphenyl)-8-methylimidazo[1,5-a]pyridine -3(2H)-thione :

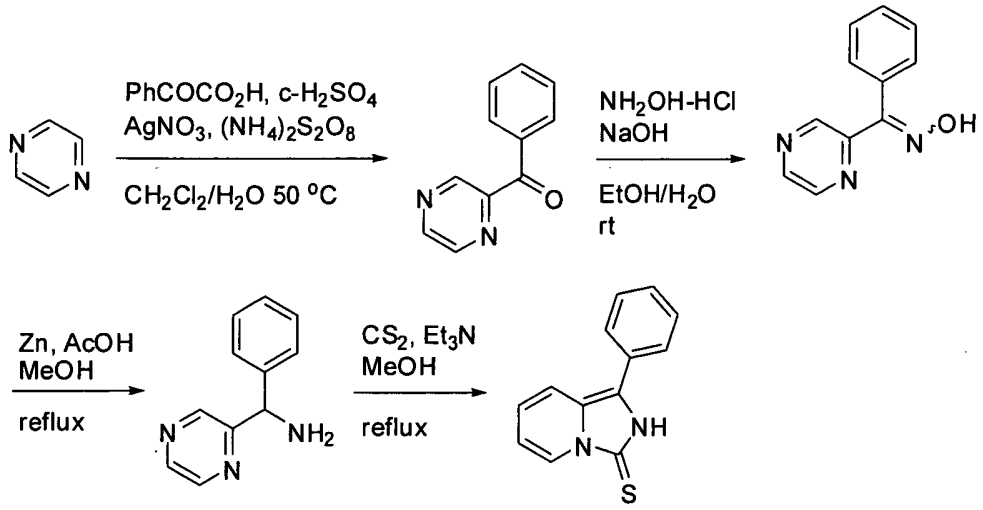




To a solution of *p*-anisaldehyde (1.271 g, 9.336 mmol) in THF (10 mL) was added LHMDS solution (1.0 M in THF, 11 mL, 1.2 equiv) at 0 °C. To an another flask containing 2-bromo-3-methylpyridine (2.1 mL, 2 equiv) in THF (15 mL) was slowly added n-BuLi (1.6 M in hexanes, 10.5 mL, 1.8 equiv) at -78 °C. After 20 min, the *N*-TMS aldimine solution was slowly added to the pyridinyl lithium solution at -78 °C. After 30 min, the reaction mixture was quenched with H_2O. The mixture was diluted with ethyl acetate and washed with water and brine. The water layer was extracted with ethyl acetate one more. The combined organic layer was dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The resulting residue was further purified by silica gel column chromatography (hexane:ethyl acetate = 1:1 to ethyl acetate only to dichloromethane: methanol = 10:1) to give amine (1.73 g, 81%). This amine (1.73 g, 7.59 mmol) was dissolved in MeOH (38 mL), and CS_2 (3.3 mL, 7.2 equiv) and Et_3N (2.1 mL, 2.0 equiv) were added at room temperature. The reaction mixture was heated to reflux overnight. After being cooled to room temperature, the mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane and washed with water. The water layer was extracted with dichloromethane one more time. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was suspended in a small amount of MeOH and filtered. The solid was washed with small amount of MeOH and dried to yield 1-(4-methoxyphenyl)-8 -methylimidazo[1,5-a]pyridine-3(*2H*)-thione (1.54 g, 75%). 200 MHz ^{1}H NMR (DMSO-d_6) 13.5 (1H, br s), 8.04 (1H, d, J = 7.0 Hz), 7.43 (2H, d, J = 8.6 Hz), 7.02 (2H, d, J= 8.6 Hz), 6.70~6.40 (2H, m), 3.82 (3H, s), 1.98 (3H, s).

Example 7: Preparation of 1-phenylimidazo[1,5-a]pyrazine-3(2H)-thione:

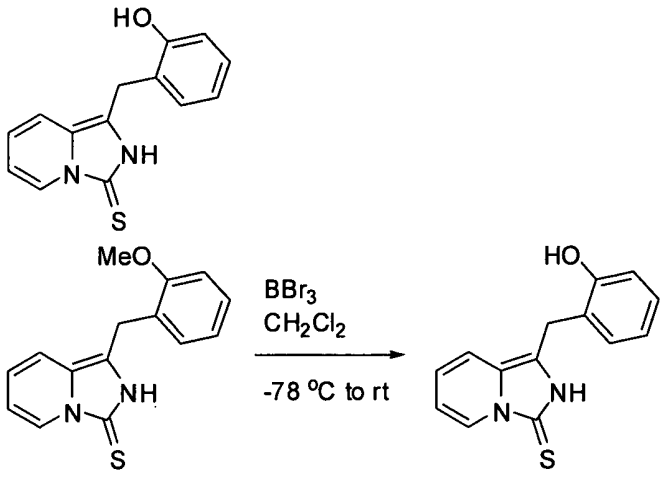




To a mixture of pyrazine (610 mg, 7.62 mmol), phenylglyoxylic acid (3.429 g, 3 equiv), c-H_2SO_4 (0.4 mL, 1 equiv), $AgNO_3$ (129 mg, 0.1 equiv), $(NH_4)_2S_2O_8$ (5.22 g, 3 equiv) in CH_2Cl_2/H_2O (=1/1, 60 mL) was stirred at 50 °C for 2 h. The reaction mixture was diluted with CH_2Cl_2 and washed with aqueous $NaHCO_3$. The water layer was extracted with CH_2Cl_2 one more time. The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate:dichloromethane = 5:1:2) to give ketone (1.27 g, 91%). This ketone (801 mg, 4.35 mmol) in $EtOH/H_2O$ (=10:1, 10 mL) were added hydroxylamine hydrochloride (393 mg, 1.3 equiv) and NaOH (226 mg, 1.3 equiv) at rt. After being stirred at rt overnight, the mixture was concentrated in vacuo. The residue was diluted with CH_2Cl_2 and washed with water. The water layer was extracted with CH_2Cl_2 one more time. The combined organic layers were dired over $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude oxime, which was used for the next step without further purification. To this oxime in MeOH (15 mL) were added Zn powder (853mg, 3 equiv) and AcOH (0.25 mL, 1 equiv) at rt. After being heated to reflux for 2 h, the mixture was cooled to rt. The reaction mixture was filtered through a pad of Celite and the filtrate was evaporated *in vacuo*. The residue was diluted with CH_2Cl_2 and washed with aqueous $NaHCO_3$. The insoluble salt was filtered out. The organic layer was dried over $MgSO_4$,

filtered, and evaporated to give a crude mixture which was further purified by silica gel column chromatography (hexanes:ethyl acetate = 1:1 to ethyl acetate only to dichloromethane:methanol = 10:1) to afford amine (330 mg, 41%). To a solution of amine (255 mg, 1.378mmol) in MeOH (7 mL) were added CS_2 (0.6 mL, 7.2 equiv) and Et_3N (0.4 mL, 2 equiv) at rt. After being heated to reflux overnight, the mixture was cooled to rt. The reaction mixture was concentrated in vacuo and the residue was suspended in CH_2Cl_2/H_2O. The solid was filtered and dried to give 1-phenylimidazo[1,5-a]pyrazine-3(*2H*)-thione (250 mg, 80%). 300 MHz ^{1}H NMR (DMSO-d_6) 9.10 (1H, d, J = 1.5 Hz), 7.94 (1H, dd, J = 5.1, 1.5 Hz), 7.83 (2H, d, J = 6.9 Hz), 7.60~7.35 (4H, m).

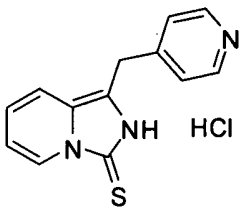
Example 8: Preparation of 1-(2-hydroxybenzyl)imidazo[1,5-a]pyridine-3(2H) -thione



To a solution of 1-(2-methoxybenzyl)imidazo[1,5-a]pyridine-3(*2H*)-thione (590 mg, 2.185 mmol) in CH_2Cl_2 (20 mL) was added BBr_3 (1M in CH_2Cl_2, 11 mL, 5 equiv) at -78 °C. After being stirred at -78 °C for 1 h, the reaction mixture was stirred at rt for additional 2 h. The mixture was quenched with cold H_2O at 0 °C. The precipitated solid was filtered and washed with dichloromethane. The solid was dried to give 1-(2-hydroxybenzyl)imidazo[1,5-a]pyridine-3(*2H*)-thione (484 mg, 87%). 200 MHz ^{1}H NMR (DMSO-d_6) 7.96 (1H, d, J = 7.0 Hz), 7.20 (1H, d,

J = 9.4 Hz), 7.14~6.98 (2H, m), 6.76 (2H, t, J = 8.2 Hz), 6.70~6.48 (2H, m), 3.99 (3H, s).

Example 9: Preparation of 4-(3-thioxo-2,3-dihydroimidazo[1,5-a]pyridin-1-ylmethyl)pyridinium chloride:

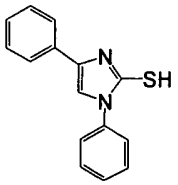


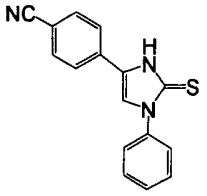
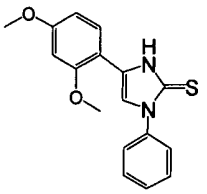
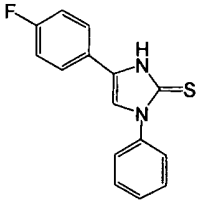
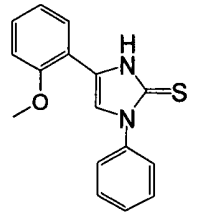
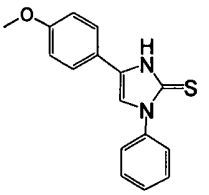
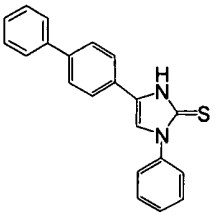
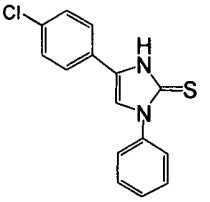
To a solution of 1-(pyridin-4-ylmethyl)imidazo[1,5-a]pyridin-3(*2H*)-one (50 mg, 0.207 mmol) in CH_2Cl_2/MeOH (=10:1, 2 mL) was added ether solution saturated with HCl at 0 oC. Then, the mixture was concentrated in vacuo to give 4-(3-thioxo-2,3-dihydroimidazo[1,5-a]pyridin-1-ylmethyl)pyridinium chloride (57.6 mg, 100%). 200 MHz ^{1}H NMR (DMSO-d_6) 13.5 (1H, br s), 8.80 (2H, d, J = 5.2 Hz), 8.02 (1H, dd, J = 7.2, 0.8 Hz), 7.87 (2H, d, J= 5.8 Hz), 7.60 (1H, dd, J = 9.4, 1.2 Hz), 6.79 (1H, dd, J = 9.2, 6.4 Hz), 6.63 (1H, dd, J = 7.4, 6.6 Hz), 4.45 (2H, s).

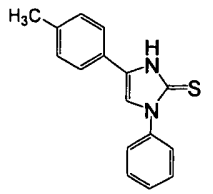
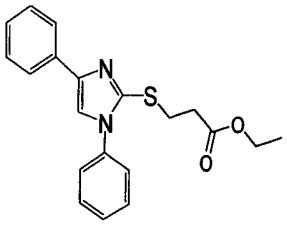
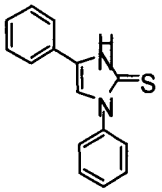
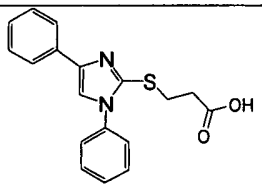
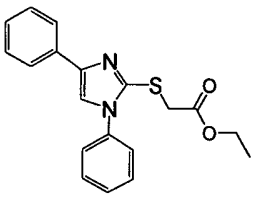
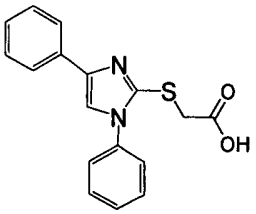
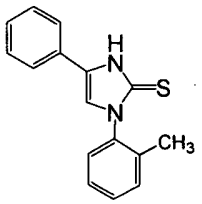
According to the procedures described for the synthesis of Example 4, further compounds of formula IB have been synthesized.

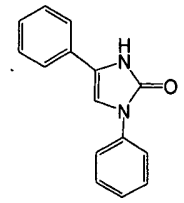
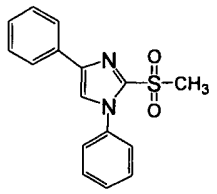
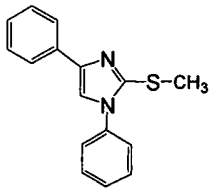
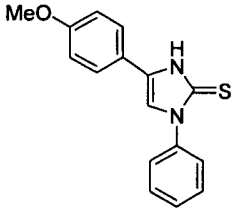
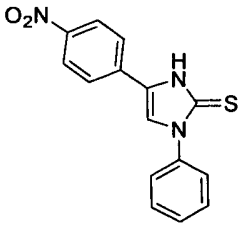
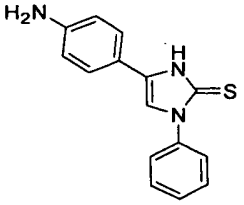
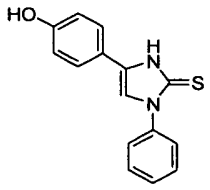
The results are shown in Tables 1 and 2 below.

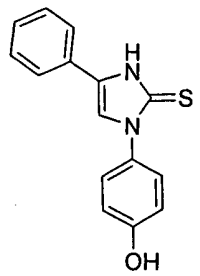
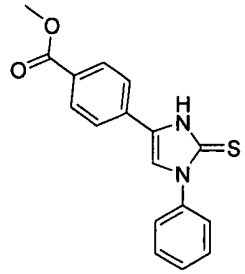
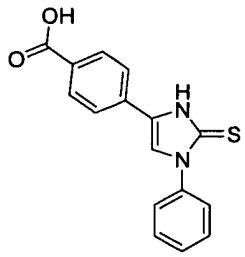
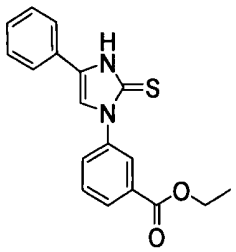
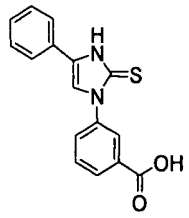
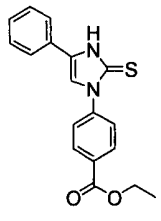
Table 1: formula IA series

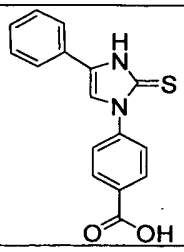
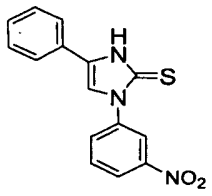
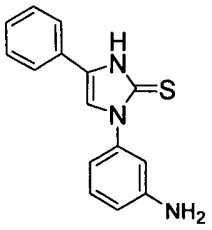
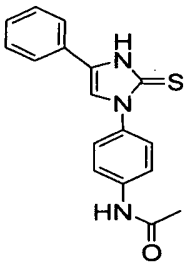
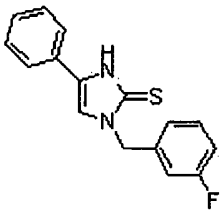
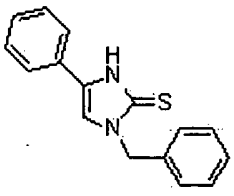
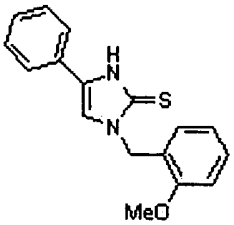
No	Structure	NMR data	Activity
1		200 MHz DMSO-d_6 + D_2O δ 7.78-7.58(*m*, Ar, 5H), 7.58-7.22(*m*, Ar, C=CH, 6H).	+

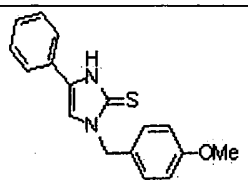
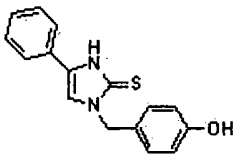
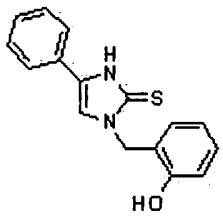
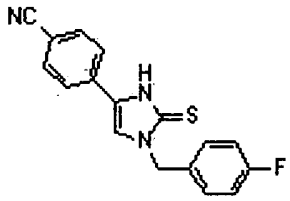
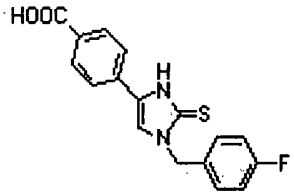
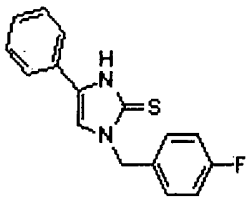
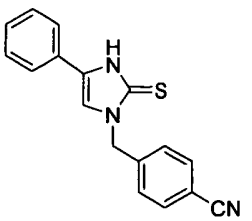
2		200 MHz DMSO-d_6 δ 13.2(*br*, *s*, NH, 1H), 8.13-7.40(*m*, Ar, C=CH, 10H).	++
3		300 MHz DMSO-d_6 δ 7.29-6.59(*m*, Ar, C=CH, 9H), 3.87(*s*, 3H), 3.80(*s*, 3H).	+++
4		300 MHz DMSO-d_6 δ 12.96(*br*, *s*, NH, 1H), 7.45-7.26(*m*, Ar, C=CH, 10H).	+++
5		300 MHz DMSO-d_6 δ 12.72(*br*, *s*, NH, 1H), 8.0-7.02(*m*, Ar, C=CH, 10H), 3.90(*s*, 3H).	+++
6		300 MHz DMSO-d_6 δ 12.84(*br*, *s*, NH, 1H), 8.57-6.50(*m*, Ar, C=CH, 10H). 3.79(*s*, 3H).	++
7		300 MHz DMSO-d_6 δ 13.01(*br*, *s*, NH, 1H), 7.94-7.38(*m*, Ar, C=CH, 15H).	+
8		300 MHz DMSO-d_6 δ 13.00(*br*, *s*, NH, 1H), 7.93.7.44(*m*, Ar, C=CH, 10H).	+++

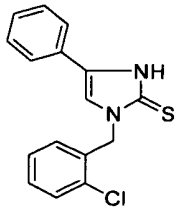
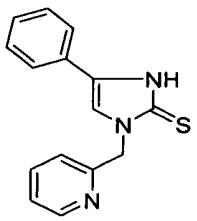
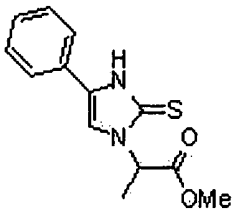
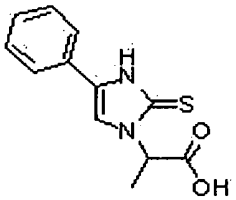
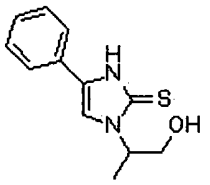
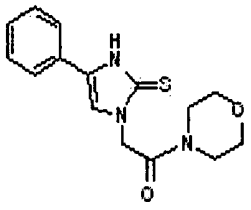
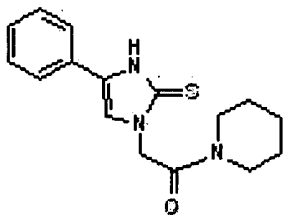
9		300 MHz DMSO-d_6 δ 12.88(*br*, *s*, NH, 1H), 7.80-7.22(*m*, Ar, C=CH, 10H). 2.32(*s*, 3H).	++
10		200 MHz $CDCl_3$ δ 7.82-7.18(*m*, Ar, C=CH, 11H), 4.08(*q*, *J* = 7.3 Hz, *J* = 7.12 Hz, 2H), 3.38(*t*, *J* = 7.0 Hz, 2H), 2.82, (*t*, *J* = 7.0 Hz, 2H), 1.19 (*t*, *J* =7.12 Hz, 3H).	+
11		1H NMR (200 MHz, CDCl3) δ 12.41 (br s, 1H, NH), 7.20-7.70 (m, aromatic, 10H), 7.08 (s, 1H, =CH)	++
12		200 MHz $CDCl_3$ δ 7.80-7.26(*m*, Ar, C=CH, 11H), 3.37(*t*, *J* = 7.12 Hz, 2H), 2.96, (*t*, *J* = 6.8 Hz, 2H).	+
13		200 MHz $CDCl_3$ δ 7.82-7.26*m*, Ar, C=CH, 11H), 4.18(*q*, *J* = 1.0 Hz, *J* = 6.1 Hz, 2H), 4.03(*s*, 2H), 1.25 (*t*, *J* = 8.0 Hz, 3H).	+
14		200 MHz $CDCl_3$ δ 7.70-7.25(*m*, Ar, C=CH, 11H), 3.76(*s*, 2H).	+
15		200 MHz $CDCl_3$ δ 7.754-6.95(*m*, Ar, C=CH, 10H), 2.27(*s*, 2H).	+

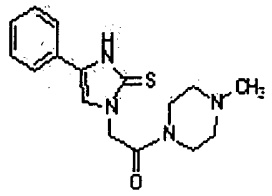
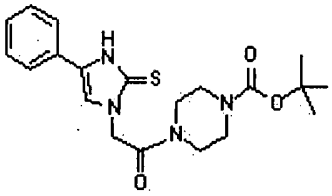
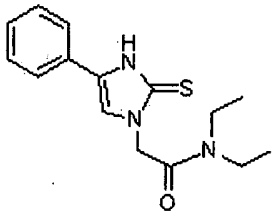
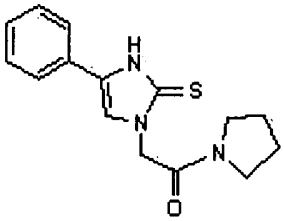
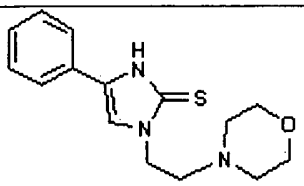
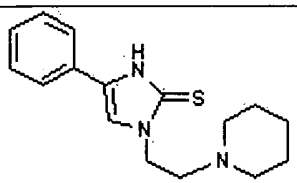
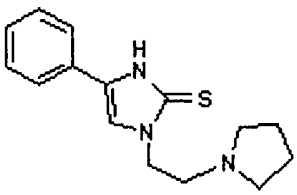
16		200 MHz DMSO-d_6 δ 11.2(*br*, *s*, NH, 1H), 7.89-7.05(*m*, Ar, C=CH, 11H).	+
17		200 MHz DMSO-d_6 δ 8.21(s, C=CH, 1H), 7.85-7.23(*m*, Ar, 10H).	+
18		200 MHz DMSO-d_6 δ 7.99(s, C=CH, 1H), 7.85-7.20(*m*, Ar, 10H), 2.6(*s*, 3H).	+
19		1H NMR (300 MHz, $CDCl_3$) δ 766 (m, Ar, 7H), 7.35 (m, 3H), 3.84(s, 3H)	+
20		1H NMR (300 MHz, DMSO-d_6) δ 10.51 (s, NH, 1H), 8.31 (d, J = 9.0Hz, 2H), 8.12 (d, J = 9.0Hz, 2H), 7.71 (d, J = 8.7Hz, 2H), 7.32 (d, J = 8.3Hz, 2H), 7.08 (s, 1H).	+
21		1H NMR (300 MHz, Methanol d_4) δ 7.64 (d, J = 9.1Hz, 2H), 7.39 (m, Ar, 5H), 6.74 (d, J = 8.7Hz, 2H).	++
22		1H NMR (300 MHz, Methanol d_4) δ 7.58 (d, J = 7.2Hz, 2H), 7.39 (m, Ar, 5H), 6.84 (d, J = 8.0Hz, 2H).	++

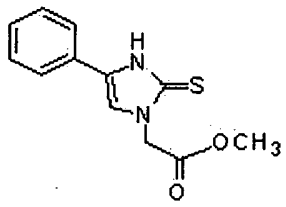
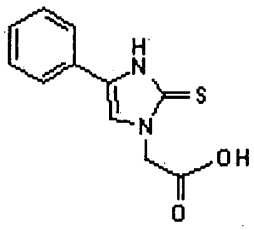
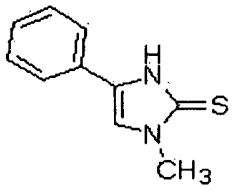
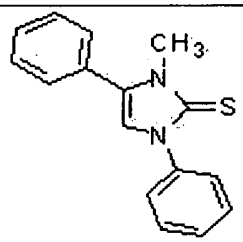
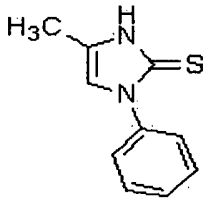
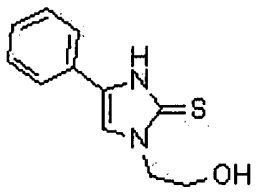
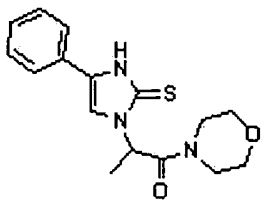
23		1H NMR (300 MHz, Methanol d_4) δ 7.23 (m, Ar, 10H).	+
24		1H NMR (300 MHz, $CDCl_3$) δ 11.63(s, 1H, NH), 8.21 (s, 1H), 8.20 (s, 1H), 7.82 (m, 3H), 7.51 (m, 4H), 7.20 (s, 1H), 3.91 (s, 3H).	+
25		1H NMR (300 MHz, DMSO-d_6) δ 13.1(s, 1H, NH), 8.17 (s, 1H), 7.70 (m, 4H), 7.61(s, 1H), 7.51 (m, 4H), 7.48 (d, J = 8.1Hz, 2H), 7.34 (s, 1H), 7.23(s, 1H).	++
26		200 MHz $CDCl_3$ δ 12.28(*br*, *s*, NH, 1H), 8.24-7.26(*m*, 9H), 7.12(*s*, C=CH, 1H), 4.42(*q*, J = 7.12 Hz, J = 7.12 Hz, 2H), 1.41(*t*, J = 7.12 Hz, 3H).	+
27		200 MHz $CDCl_3$ δ 12.13(*br*, *s*, NH, 1H), 8.27-7.26(*m*, 9H), 7.14(*s*, C=CH, 1H).	+
28		200 MHz $CDCl_3$ δ 12.13(*br*, *s*, NH, 1H), 8.23-7.26(*m*, 9H), 7.12(*s*, C=CH, 1H), 4.42(*q*, J = 7.12 Hz, J = 7.12 Hz, 2H), 1.42(*t*, J = 7.12 Hz, 3H).	++

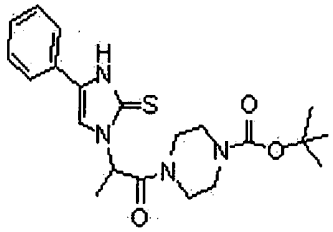
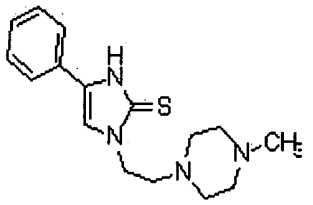
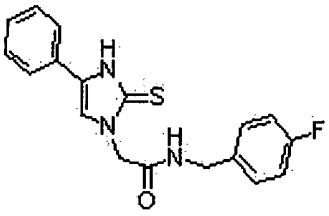
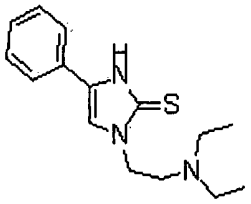
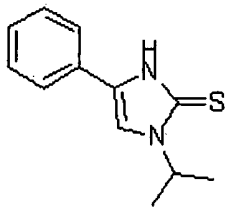
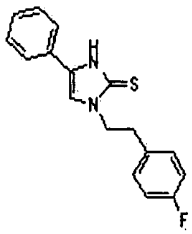
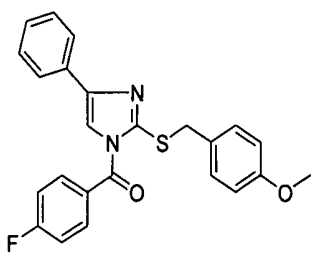
29		200 MHz $CDCl_3$ + CD_3OD δ 8.18-7.30(*m*, 9H), 7.13(*s*, C=CH, 1H).	+
30		200 MHz DMSO-d_6 δ 13.20(*br*, *s*, NH, 1H), 8.75-7.30(*m*, aroma, C=CH, 10H).	++
31		200 MHz CD_3OD δ 7.68-6.76(*m*, aroma, C=CH, 10H).	++
32		300 MHz DMSO-d_6 δ 12.92(*br*, *s*, NH, 1H), 10.14(*br*, *s*, NH, 1H), 7.82-7.28(m,aroma, C=CH, 10H), 2.08(*s*, 3H).	++
33		1H NMR (200 MHz, $CDCl_3$) 11.69(s, NH) 7.26-7.51(m, aromatic, 9H) 6.79(s, 1H) 5.29(s, 2H)	+
34		1H NMR (200 MHz, $CDCl_3$+DMSO) 12.73(s, NH) 6.99-7.60(m, aromatic, 11H) 5.28(s, 2H)	+
35		1H NMR (200 MHz, $CDCl_3$) 11.42(s, NH) 7.24-7.45(m, aromatic, 8H) 6.86-6.93(m, 2H) 5.28(s, 2H) 3.87(s, 3H)	+

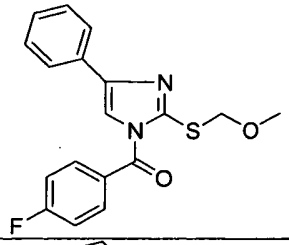
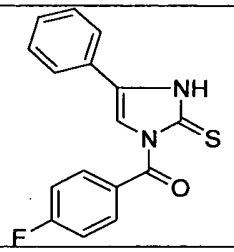
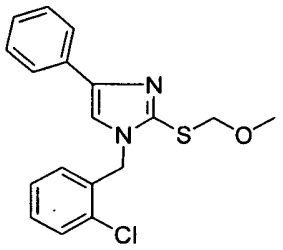
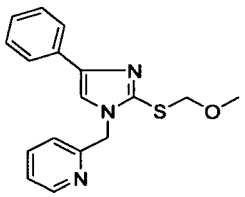
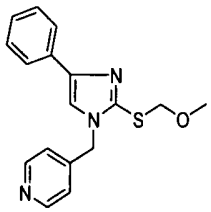
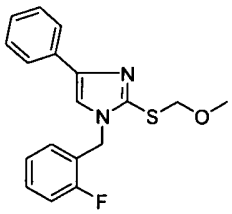
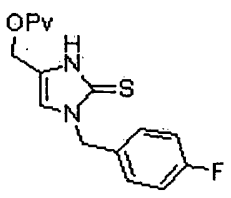
36		1H NMR (200 MHz, $CDCl_3$) 11.91(s, NH) 7.26-7.52(m, aromatic, 7H) 6.86(d, J=8.5Hz, 2H) 6.25(s, 1H) 5.21(s, 2H) 3.79(s, 3H)	+
37		1H NMR (200 MHz, $CDCl_3$) 8.90(br s, NH) 7.10-7.60(m, aromatic& OH, 6H) 6.85(s, 1H) 5.14(s, 2H)	+
38			+
39		1H NMR (200 MHz, $CDCl_3$) 12.10(s, NH) 7.03-7.86(m, aromatic, 8H) 6.92(s, 1H) 5.28(s, 2H)	+
40		1H NMR (200 MHz, $CDCl_3$+MeOD) 8.02(d, J=6.9, 2H) 7.59(d, J=7.2, 2H) 7.41(t, J=6.9, 2H) 7.13(s, 1H) 7.06(t, J=7.2Hz, 2H) 5.26(s, 2H)	+
41		1H NMR (200 MHz, $CDCl_3$) 11.90(s, NH) 7.25-7.52(m, aromatic, 9H) 6.79(s, 1H) 5.29(s, 2H)	+
42		1H NMR (200 MHz, $CDCl_3$) δ 7.27 (m, Ar, 1H), 6.84 (s, 1H), 5.36(s, 2H).	+

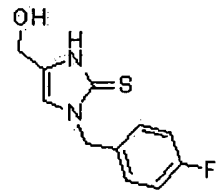
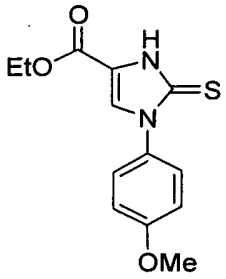
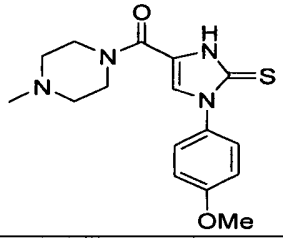
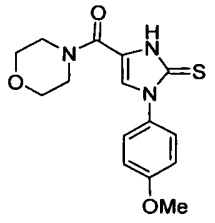
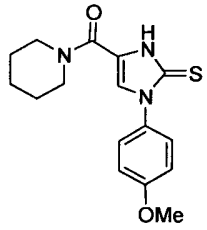
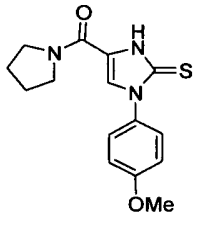
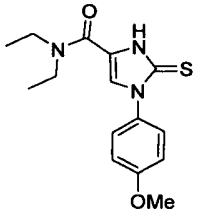
43		200 MHz $CDCl_3$ δ 11.8(*br*, *s*, NH, 1H), 7.47-6.87(*m*, 10H), 5.43(*s*, 2H).	+
44		200 MHz $CDCl_3$ δ 8.53-7.01(*m*, 11H), 5.26(*s*, 2H).	+
45		1H NMR (200 MHz, $CDCl_3$) 11.24(s, NH) 7.26-7.48(m, aromatic, 5H) 7.08(s, 1H) 5.69-5.92(m, 1H) 3.80(s, 3H) 1.69(d, J=7.3Hz, 3H)	+
46		1H NMR (200 MHz, $CDCl_3$) 7.19-7.55(m, aromatic, 5H) 7.03(s, 1H) 5.63-5.82(m, 1H) 1.75(d, J=7.4Hz, 3H)	+
47		1H NMR (200 MHz, $CDCl_3$) 11.87(s, NH) 7.12-7.40(m, aromatic, 5H) 6.96(s, 1H) 5.01-5.08(m, 1H) 3.65-3.89(m, 2H) 3.00(s, OH) 1.33(d, 3H)	+
48		1H NMR (200 MHz, $CDCl_3$) 7.22-7.60(m, aromatic& NH, 6H) 7.12(s, 1H) 4.95(s, 2H) 3.60-3.90(m, 8H)	+
49		1H NMR (200 MHz, $CDCl_3$) 7.25-7.55(m, aromatic, 5H) 7.12(s, 1H) 4.95(s, 2H) 3.45-3.65(m, 4H) 1.50-2.00(m, 6H)	+

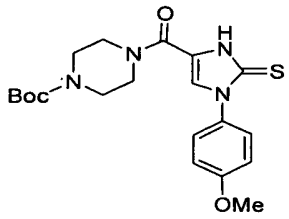
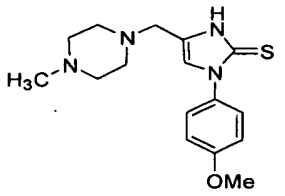
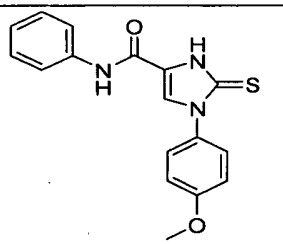
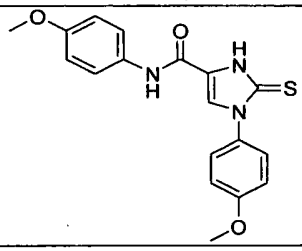
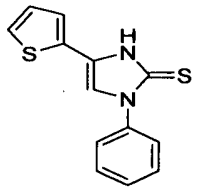
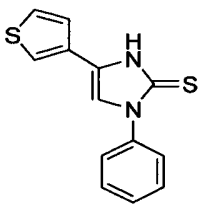
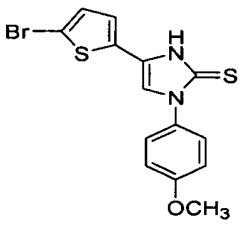
50		1H NMR (200 MHz, $CDCl_3$) 7.25-7.60(m, aromatic, 5H) 7.10(s, 1H) 4.93(s, 2H) 3.60-4.00(m, 4H) 2.60-3.00(m, 4H) 2.51(s, 3H)	+
51		1H NMR (200 MHz, $CDCl_3$) 7.21-7.55(m, aromatic, 5H) 7.12(s, 1H) 4.96(s, 2H) 3.40-3.75(m, 8H) 1.47(s, 9H)	+
52		1H NMR (200 MHz, $CDCl_3$) 11.05(s, NH) 7.26-7.65(m, aromatic, 5H) 7.20(s, 1H) 4.96(s, 2H) 3.41-3.55(m, 4H) 1.29(t, J=6.9Hz, 3H) 1.15(t, J=6.9Hz, 3H)	+
53		1H NMR (200 MHz, $CDCl_3$) 7.29-7.49(m, aromatic, 5H) 7.17(s, 1H) 4.88(s, 2H) 3.67(t, J=6.9Hz, 2H) 3.52(t, J=6.9Hz, 2H) 1.90-2.07(m, 4H)	+
54		1H NMR (200 MHz, $CDCl_3$) 11.62(br s, NH) 7.25-7.60(m, aromatic, 5H) 7.05(s, 1H) 4.20(t, J=6.3Hz, 2H) 3.65-3.75(m, 4H) 2.75(t, J=6.3Hz, 2H) 2.70-2.82(m, 4H)	+
55		1H NMR (200 MHz, $CDCl_3$) 7.10-7.60(m, aromatic, 5H) 7.11(s, 1H) 4.18(t, J=6.5Hz, 2H) 2.71(t, J=6.5Hz, 2H) 2.40-2.60(m, 4H) 1.00-1.75(m, 6H)	+
56		1H NMR (200 MHz, $CDCl_3$) 7.20-7.60(m, aromatic, 5H) 7.07(s, 1H) 4.21(t, J=6.5Hz, 2H) 2.91(t, J=6.5Hz, 2H) 2.45-2.75(m, 4H) 1.60-1.95(m, 4H)	+

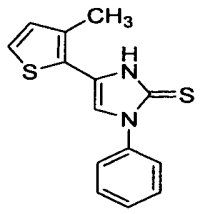
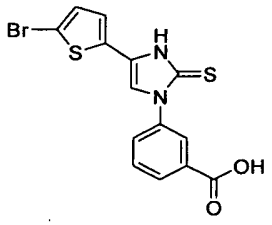
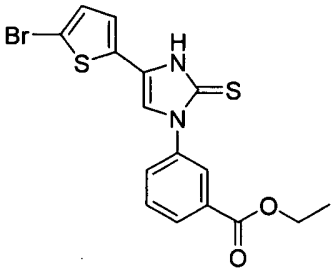
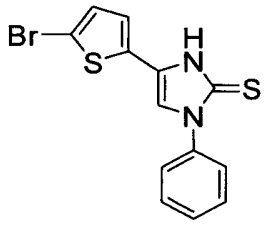
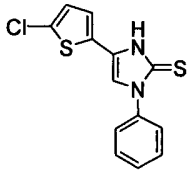
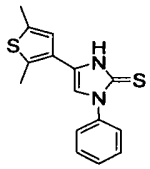
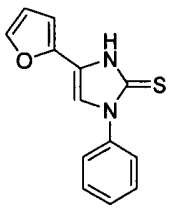
57		1H NMR (200 MHz, $CDCl_3$) 11.8(s, NH) 7.23-7.52(m, aromatic, 5H) 6.97(s, 1H) 4.91(s, 2H) 3.80(s, 3H)	+
58		1H NMR (200 MHz, $CDCl_3$+DMSO) 12.4(s, NH) 7.33-7.58(m, aromatic, 5H) 7.03(s, 1H) 4.87(s, 2H)	+
59		1H NMR (200 MHz, $CDCl_3$) 11.28(s, NH) 7.25-7.50(m, aromatic, 5H) 6.89(s, 1H) 3.66(s, 3H)	+
60		1H NMR (200 MHz, $CDCl_3$) 7.44-7.65(m, aromatic, 10H) 6.90(s, 1H) 3.71(s, 3H)	+
61		1H NMR (200 MHz, $CDCl_3$) 12.59(s, 1H) 7.32-7.61(m, aromatic, 5H) 6.54(s, 1H) 2.16(s, 3H)	+
62		1H NMR (200 MHz, $CDCl_3$) 7.31-7.51(m, aromatic, 5H) 7.12(s, 1H) 4.20(t, J=4.9Hz, 2H) 3.94(t, J=5.3Hz, 2H)	+
63		1H NMR (200 MHz, $CDCl_3$) 11.35(s, NH) 7.21-7.53(m, aromatic, 5H) 7.20(s, 1H) 5.95(q, J=7.0Hz, 1H) 3.50-3.79(m, 8H) 1.59(d, J=6.9Hz, 3H)	+

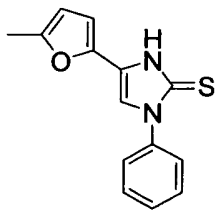
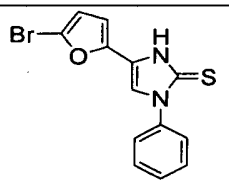
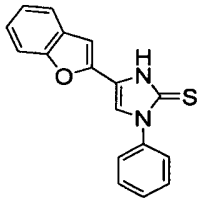
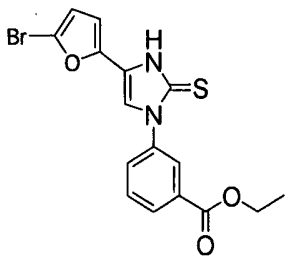
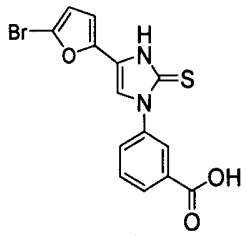
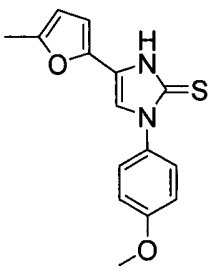
64		1H NMR (200 MHz, $CDCl_3$) 10.72(br s, NH) 7.02-7.60(m, aromatic, 5H) 7.26(s, 1H) 5.97(q, J=6.9Hz, 1H) 3.10-3.90(m, 8H) 1.61(q, J=6.9Hz, 3H) 1.45(s, 9H)	+
65		1H NMR (200 MHz, $CDCl_3$) 7.20-7.50(m, aromatic, 5H) 7.06(s, 1H) 4.18(t, J=6.5Hz, 2H) 2.77(t, J=6.5Hz, 2H) 2.30-2.70(m, 8H) 2.29(s, 3H)	+
66		1H NMR (200 MHz, $CDCl_3$) 7.90(br s, NH) 6.90-7.60(m, aromatic& NH, 11H) 4.75(s, 2H) 4.42(s, 2H)	+
67		1H NMR (200 MHz, $CDCl_3$) 7.25-7.55(m, aromatic, 5H) 7.07(s, 1H) 4.12(t, J=6.3Hz, 2H) 2.83(t, J=6.5Hz, 2H) 2.59(q, J=7.1Hz, 4H) 1.02(t, J=7.1Hz, 6H)	+
68		1H NMR (200 MHz, $CDCl_3$) 11.90(br s, NH) 7.25-7.70(m, aromatic, 5H) 6.96(s, 1H) 5.11(m, 1H) 1.43(d, J=6.9Hz, 6H)	+
69		1H NMR (200 MHz, $CDCl_3$) 7.00-7.60(m, aromatic, 6H) 6.60(br s, NH) 4.27(t, J=6.5Hz, 2H) 3.12(t, J=6.5Hz, 2H)	+
70		200 MHz $CDCl_3$ δ 7.84-6.82(*m*, 14H), 4.53(*s*, 2H), 3.77(*s*, 3H).	+

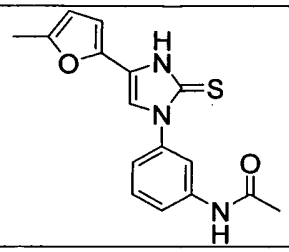
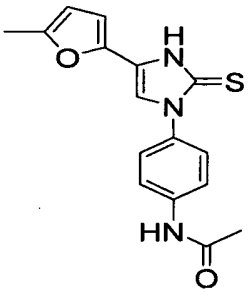
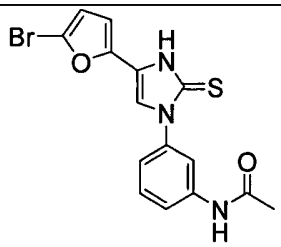
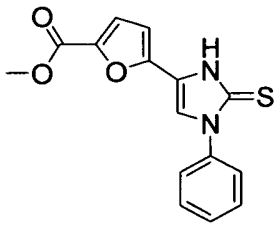
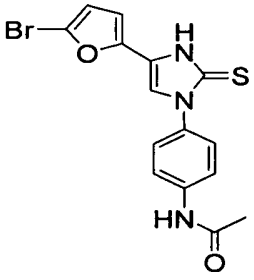
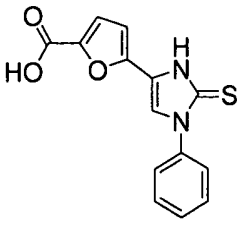
71		200 MHz $CDCl_3$ δ 7.87-7.16(*m*, 10H), 5.51(*s*, 2H), 3.48(*s*, 3H).	+
72		200 MHz $CDCl_3$ δ 11.2(*br*, *s*, NH, 1H), 7.99-7.12(*m*, 10H).	+
73		200 MHz $CDCl_3$ δ 7.79-6.90(*m*, 10H), 5.35(*s*, 2H), 5.15(*s*, 2H), 3.37(*s*, 3H).	+
74		200 MHz $CDCl_3$ δ 8.60-6.99(*m*, 10H), 5.38(*s*, 2H), 5.21(*s*, 2H), 3.36(*s*, 3H).	+
75		200 MHz $CDCl_3$ δ 8.58-7.02(*m*, 10H), 5.22(*s*, 2H), 5.13(*s*, 2H), 3.32(*s*, 3H).	+
76		200 MHz $CDCl_3$ δ 7.78-6.93(*m*, 10H), 5.34(*s*, 2H), 5.27(*s*, 2H), 3.39(*s*, 3H).	+
77		1H NMR (200 MHz, $CDCl_3$) 6.98-7.41(m, aromatic, 4H) 6.54(s, 1H) 5.19(s, 2H) 4.81(s, 2H) 1.18(s, 9H)	+

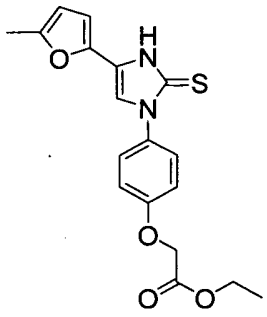
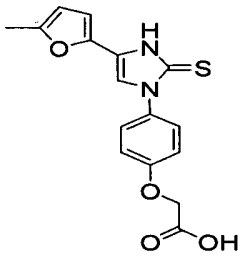
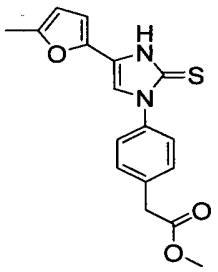
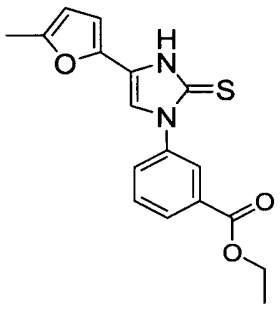
78		1H NMR (200 MHz, $CDCl_3$+MeOD) 6.95-7.38(m, aromatic, 4H) 6.42(s, 1H) 5.14(s, 2H) 4.37(s, 2H)	+
79		1H NMR (200 MHz, $CDCl_3$) δ 7.68 (s, 1H, NH), 7.44 (s, 1H), 7.43 (d, J = 1.4Hz, 2H), 7.25 (d, J = 1.4Hz, 2H), 6.94 (d, J = 1.0Hz, 2H), 6.9 (d, J = 1.0Hz, 2H), 4.33 (q, J = 7.1Hz, 2H), 3.82 (s, 3H), 1.35 (m, 3H).	+
80		1H NMR (200 MHz, $CDCl_3$) δ 7.75 (s, 1H, NH), 7.29 (d, J = 7.0Hz, 2H), 7.25 (s, 1H), 6.90 (d, J = 7.4Hz, 2H), 3.81 (m, 7H), 2.37 (m, 7H).	+
81		1H NMR (300 MHz, $CDCl_3$) δ 8.89 (s, 1H, NH), 7.11 (m, 5H), 3.75 (m, 11H).	+
82		1H NMR (200 MHz, $CDCl_3$) δ 8.00 (s, 1H, NH), 7.12 (m, 5H), 3.82 (s, 3H), 3.71(m, 4H), 1.59 (m, 6H).	+
83		1H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.31 (d, J =8.4Hz, 2H), 6.96 (d, J =8.4Hz, 2H), 3.84 (s, 3H), 3.28 (m, 4H), 2.28 (m, 4H).	++
84		1H NMR (300 MHz, $CDCl_3$) δ 8.20 (br s, 1H, NH), 7.04 (m, 5H), 3.82 (s, 3H), 3.35 (m, 2H), 1.10 (m, 8H).	+

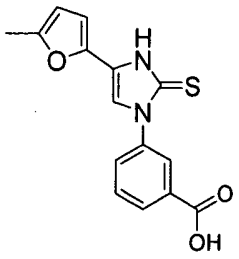
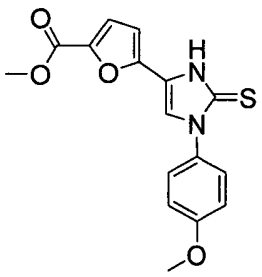
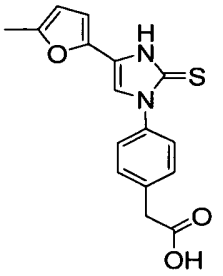
85		1H NMR (300 MHz, $CDCl_3$) δ 8.20 (br s, 1H, NH), 7.11 (m, 5H), 3.84 (s, 3H), 3.46(m, 8H), 1.51 (m, 9H).	+
86		1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 9.0Hz, 2H), 6.89 (d, J = 9.0Hz, 2H), 6.37 (s, 1H), 4.58 (s, 2H), 3.81(s, 3H), 2.8 (br s, 8H), 1.25 (s, 3H).	+
87		1H NMR (300 MHz,) δ 9.45(s, 1H, NH), 7.88 (d, J = 9.0Hz, 2H), 7.68 (s, 1H), 7.35 (m, 4H), 7.2(s,1H), 7.06 (d, J = 9.0Hz, 2H), 3.87 (s, 3H).	+
88		1H NMR (300 MHz, DMSO-d_6) δ 7.69 (d, J = 9.0Hz, 2H), 7.57 (d, J = 8.7Hz, 2H), 7.47 (s, 1H), 6.86 (d, J = 3.9Hz, 2H), 6.84 (d, J = 3.6Hz, 2H), 3.66 (s, 3H), 3.65 (s, 3H).	+
89		1H NMR (200 MHz, $CDCl_3$) δ 12.36(br s, NH, 1H), 7.26 (m, Ar, 9H).	+
90		1H NMR (300 MHz, $CDCl_3$) δ 12.56 (br s, NH, 1H), 7.03 (m, Ar, 9H).	+
91		1H NMR (200 MHz, $CDCl_3$ + CD_3OD) δ 7.50 (s, 1H), 7.45 (s, 1H), 7.35 (s, 1H), 7.01 (m, Ar, 4H), 3.86(s, 3H).	++

92		1H NMR (200 MHz, $CDCl_3$) δ 11.8(s, 1H, NH), 7.68(s, 1H), 7.65(d, J = 4.0Hz, 2H), 7.50(s, 1H), 7.39(s, 1H), 7.23(s, 1H), 6.95(d, J = 3.6Hz, 2H), 2.33(s, 3H).	+
93		1H NMR (200 MHz, DMSO-d_6) δ11.5(s, 1H, OH), 7.00~8.22(m, Ar, 7H), 3.96(s, 1H, NH).	++
94		1H NMR (200 MHz, $CDCl_3$) δ 7.00~8.20(m, aromatic, 7H), 4.42(s, 2H), 2.0(s, 1H, NH), 1.56(s, 3H).	+
95		200 MHz $CDCl_3$ δ 7.63-7.35(m, aroma, C=CH, 6H), 7.10(d, J = 4.10 Hz, thiophene, 1H), 7.05(d, J = 4.10 Hz, thiophene, 1H).	+
96		200 MHz $CDCl_3$ δ 7.63-7.38(m, aroma, C=CH, 6H), 7.16(d, J = 3.7 Hz, thiophene, 1H), 76.96(d, J = 4.10 Hz, thiophene, 1H).	++
97		200 MHz $CDCl_3$ δ 7.67-7.388(m, aroma, 5H), 6.87(s, C=CH, 1H), 6.80(s, thiophene, 1H), 2.44(s, 3H), 2.39(s, 3H).	+
98		1H NMR (300 MHz, $CDCl_3$) δ 12.45 (br s, NH, 1H), 7.44 (m, Ar, 8H), 7.00 (s, 1H).	+

99		200 MHz $CDCl_3$ δ 11.63(*br*, *s*, NH, 1H), 7.67-7.27(*m*, aroma, 5H), 7.00(*s*, C=CH, 1H), 6.53(*d*, *J* = 3.3 Hz, furan, 1H), 6.02(*d*, *J* =2.80 Hz, furan, 1H), 2.32(*s*, 3H).	+
100		200 MHz $CDCl_3$ δ 7.66-7.26(*m*, aroma, 5H), 7.10(*s*, C=CH, 1H), 6.68(*d*, *J* = 3.5 Hz, furan, 1H), 6.34(*d*, *J* =3.5 Hz, furan, 1H).	++
101		200 MHz $CDCl_3$ δ 7.71-7.20(*m*, 10H), 7.06(*s*, C=CH, 1H).	++
102		200 MHz $CDCl_3$ δ 12.25(*br*, *s*, NH, 1H), 8.22(s, aroma, 1H), 8.14(*d*, *J* = 7.50 Hz, aroma, 1H), 7.62(*t*, *J* = 7.9 Hz, aroma, 1H), 7.14(*s*, C=CH, 1H), 6.67(*d*, *J* = 3.5 Hz, furan, 1H), 6.36(*d*, *J* =3.5 Hz, furan, 1H), 4.42(*q*, *J* = 7.12 Hz, *J* = 7.12 Hz, 2H), 1.41(*t*, *J* = 7.3 Hz, 3H).	++
103		200 MHz CD_3OD δ 8.30-7.60(*m*, aroma, 4H), 7.49(*s*, C=CH, 1H), 6.73(*d*, *J* = 3.5 Hz, furan, 1H), 6.54(*d*, *J* =3.5 Hz, furan, 1H).	+
104		200 MHz $CDCl_3$ δ 11.30(*br*, *s*, NH, 1H), 7.39(*d*, *J* = 5.50 Hz, aroma, 2H), 7.03(*s*, C=CH, 1H), 6.96(*d*, *J* = 5.50 Hz, aroma, 2H), 6.50(*d*, *J* = 3.3 Hz, furan, 1H), 6.03-6.01(*m*, furan, 1H), 3.86(*s*, 3H), 2.32(*s*, 3H).	++

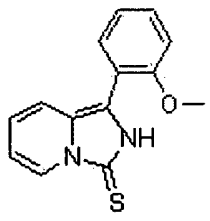
105		300 MHz $CDCl_3$ δ 11.42(*br*, *s*, NH, 1H), 8.14-7.29(*m*, 4H), 6.97(*s*, C=CH, 1H), 6.49(*d*, *J* = 3.3 Hz, furan, 1H), 6.00-5.99(*m*, furan, 1H), 2.29(*s*, 3H), 2.12(*s*, 3H).	+
106		300 MHz $CDCl_3$ δ 11.52(*br*, *s*, NH, 1H), 7.64(*d*, *J* = 8.7 Hz, aroma, 2H), 7.51(*d*, *J* = 8.7 Hz, aroma, 2H), 6.97(*s*, C=CH, 1H), 6.52(*d*, *J* = 3.00 Hz, furan, 1H), 6.04-6.03(*m*, furan, 1H), 2.32(*s*, 3H), 2.14(*s*, 3H).	++
107		300 MHz CD_3OD δ 8.16(*d*, *J* = 1.20 Hz, aroma, 1H), 7.95(*s*, aroma, 1H), 7.79(*d*, *J* = 1.2 Hz, aroma, 1H), 7.48(*s*, C=CH, 1H), 7.47-7.45(*m*, aroma, 1H), 6.67(*d*, *J* = 3.3 Hz, furan, 1H), 6.47(*d*, *J* =3.3 Hz, furan, 1H), 2.16(*s*, 3H).	+
108		300 MHz $CDCl_3$ δ 11.29(*br*, *s*, NH, 1H), 7.65-7.45(*m*, aroma, 5H), 7.31(*s*, C=CH, 1H), 7.19(*d*, *J* = 3.60 Hz, furan, 1H), 6.75(*d*, *J* = 3.60 Hz, furan, 1H), 3.90(*s*, 3H).	+
109		300 MHz $CDCl_3$ δ 7.61(*s*, C=CH, 1H), 7.60(*d*, *J* = 8.70 Hz aroma, 2H), 7.18(*d*, *J* = 8.70 Hz aroma, 2H), 6.69(*d*, *J* = 3.30 Hz, furan, 1H), 6.50(*d*, *J* = 3.30 Hz, furan, 1H), 2.15(*s*, 3H).	++
110		300 MHz CD_3OD δ 7.66-7.46(m, aroma, C=CH, 6H), 7.28(*d*, *J* = 3.60 Hz, furan, 1H), 6.84(*d*, *J* = 3.30 Hz, furan, 1H).	++

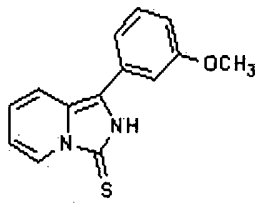
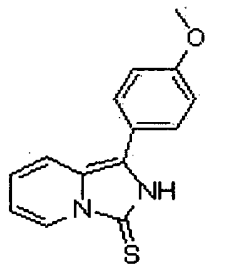
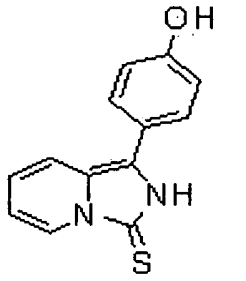
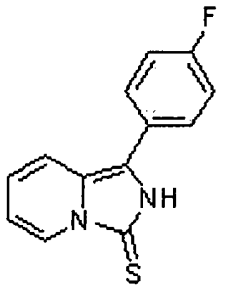
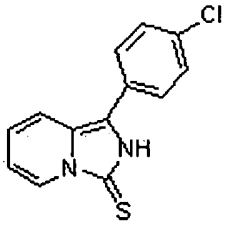
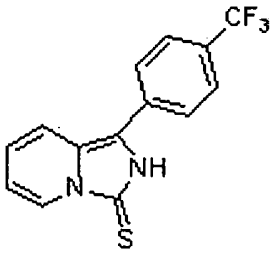
111		300 MHz $CDCl_3$ δ 12.15(*br*, *s*, NH, 1H), 7.54(*d*, *J* = 6.9 Hz aroma, 2H), 7.03(*d*, *J* = 6.9 Hz aroma, 2H), 6.96(*s*, C=CH, 1H), 6.56(*d*, *J* = 3.30 Hz, furan, 1H), 6.02-6.00(*m*, furan, 1H), 4.67(*s*, 2H), 4.30(*q*, *J* = 7.2 Hz, *J* = 6.9 Hz, 2H), 2.30(*s*, 3H), 1.34(*t*, *J* = 3.3 Hz, 3H).	+
112		300 MHz CD_3OD δ 7.52(*d*, *J* = 9.0 Hz aroma, 2H), 7.06(*d*, *J* = 9.0 Hz aroma, 2H), 7.24(*s*, C=CH, 1H), 6.57(*d*, *J* = 3.3 Hz, furan, 1H), 6.11(*q*, *J* = 3.2 Hz, *J* = 2.1 Hz, furan, 1H), 4.73(*s*, 2H), 2.32(*s*, 3H).	++
113		300 MHz $CDCl_3$ δ 12.19(*br*, *s*, NH, 1H), 7.62(*d*, *J* = 8.2 Hz aroma, 2H), 7.43(*d*, *J* = 8.4 Hz aroma, 2H), 6.99(*s*, C=CH, 1H), 6.57(*d*, *J* = 3.2 Hz, furan, 1H), 6.00(*d*, *J* = 3.2 Hz, furan, 1H), 3.73(*s*, 3H), 3.70(*s*, 2H), 2.31(*s*, 3H).	++
114		300 MHz $CDCl_3$ δ 11.37(*br*, *s*, NH, 1H), 8.32(*s*, aroma, 1H), 8.14-8.11(*m*, aroma, 1H), 8.01-7.98(*m*, aroma, 1H), 7.61(*t*, *J* = 7.8 Hz, aroma, 1H), 7.04(*s*, C=CH, 1H), 6.52(*d*, *J* = 3.00 Hz, furan, 1H), 6.30(*d*, *J* = 3.00 Hz, furan, 1H), 4.41(*q*, *J* = 6.9 Hz, *J* = 7.2 Hz, 2H), 2.32(*s*, 3H), 1.41(*t*, *J* = 6.6 Hz, 3H).	++

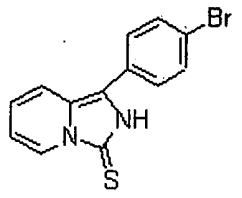
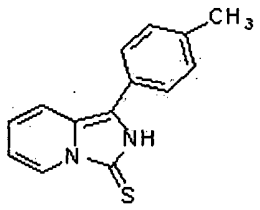
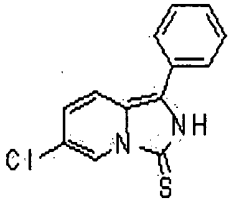
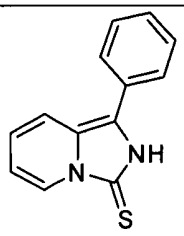
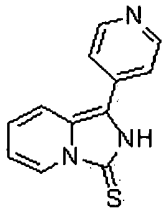
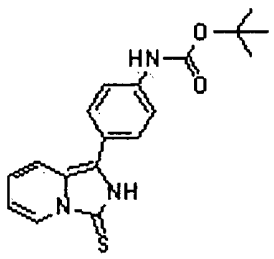
115		300 MHz CD_3OD δ 8.28(*s*, aroma, 1H), 8.09(*d*, *J* = 7.8 Hz, aroma, 1H), 7.90(*d*, *J* = 7.9 Hz, aroma, 1H), 7.62(*t*, *J* = 7.9 Hz, aroma, 1H), 7.36(*s*, C=CH, 1H), 6.60(*d*, *J* = 3.2 Hz, furan, 1H), 6.13(*dd*, *J* = 1.2 Hz, *J* = 1.2 Hz, furan, 1H), 2.34(*s*, 3H).	++
116		300 MHz $CDCl_3$ δ 7.61(*s*, C=CH, 1H), 7.51(*d*, *J* = 9.0 Hz aroma, 2H), 7.03(*d*, *J* = 8.7 Hz aroma, 2H), 7.19(*d*, *J* = 3.6 Hz, furan, 1H), 6.70(*d*, *J* = 3.36 Hz, furan, 1H), 3.90(*s*, 3H), 387(*s*, 3H).	++
117		300 MHz CD_3OD δ 7.60*d*, *J* = 8.2 Hz aroma, 2H), 7.45*d*, *J* = 8.4 Hz aroma, 2H), 7.29(=CH, 1H), 6.58(*d*, *J* = 3.3 Hz, furan, 1H), 6.11(*d*, *J* = 3.0 Hz, furan, 1H), 369(*s*, 2H), 2.33(*s*, 3H).	++

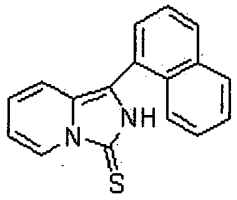
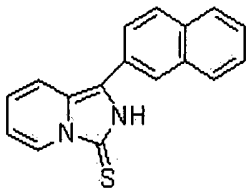
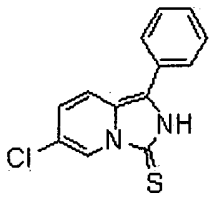
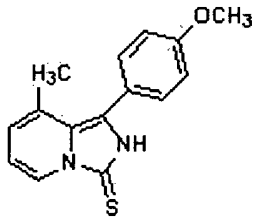
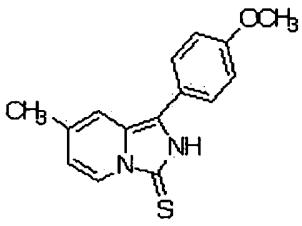
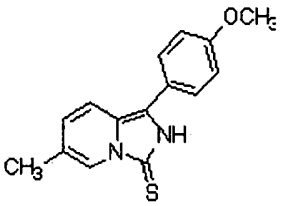
Activities are based on IC_{50} values in cell-based assay, i.e., NFAT-promoter assays: +, >20uM; ++, 5~20uM; +++, <5uM.

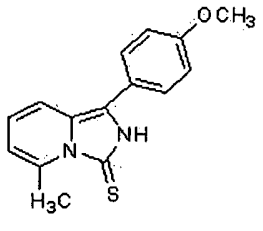
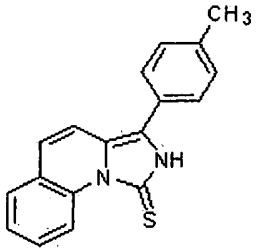
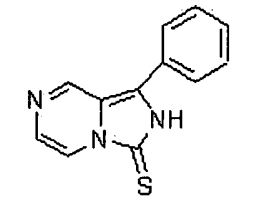
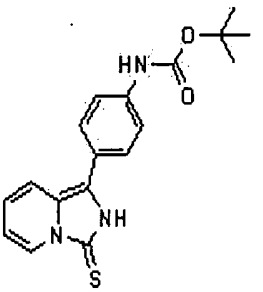
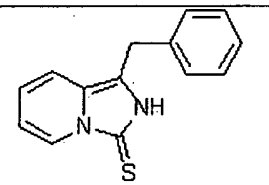
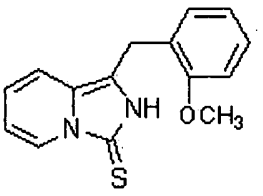
Table 2: formula IB series

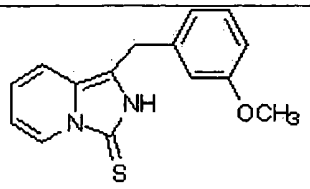
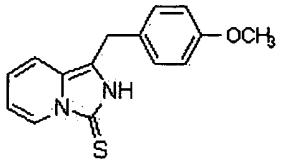
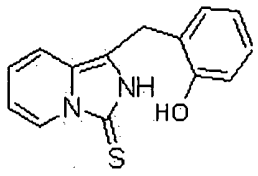
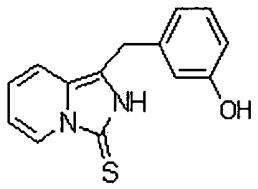
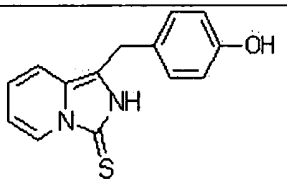
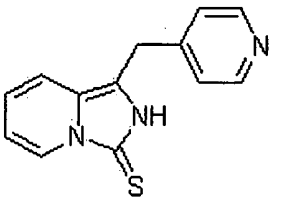
#	Structure	NMR data	Activity
1		(200 MHz, $CDCl_3$) δ 11.0 (br, NH), 8.26 (d, 1H), 7.51 (dd, 3H), 7.30 (t, 1H), 7.02 (m, 3H), 6.75 (dd, 1H), 6.56 (t, 1H), 3.94 (s, OCH3)	++

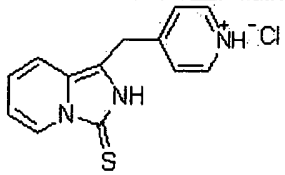
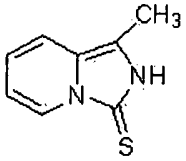
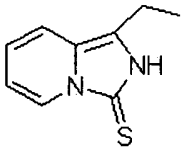
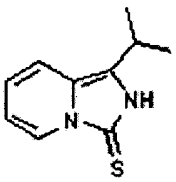
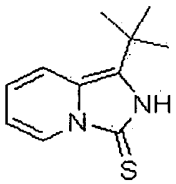
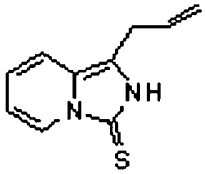
2		200 MHz 1H NMR (DMSO-d_6) δ 13.8 (1H, br s), 8.18 (1H, d, J = 7.4 Hz), 7.72 (1H, d, J = 9.4 Hz), 7.50~7.20 (3H, m), 7.00~6.80 (2H, m), 6.74 (1H, t, J = 6.8 Hz), 3.84 (3H, s)	++
3		300 MHz 1H NMR (DMSO-d_6) δ 13.7 (1H, br s), 8.11 (1H, dt, J = 7.4, 1.0 Hz), 7.62 (2H, d, J = 8.9 Hz), 7.62~7.56 (1H, m), 7.03 (2H, d, J = 8.9 Hz), 6.82 (1H, ddd, J = 9.4, 6.3, 1.0 Hz), 6.67 (1H, ddd, J = 7.3, 6.4, 1.0 Hz), 3.79 (3H, s)	+
4		(200 MHz, $CDCl_3$) δ 8.19 (d, 1H),7.43-7.58 (m, 6H), 6.77 (d, 1H), 6.47 (t, 1H)	+
5		200 MHz 1H NMR (DMSO-d_6) δ 13.8 (1H, br s), 8.17 (1H, dd, J = 7.4, 1.2 Hz), 7.85~7.60 (3H, m), 7.32 (2H, t, J = 9.0 Hz), 6.91 (1H, dd, J = 6.4, 5.2 Hz), 6.72 (1H, t, J = 7.2 Hz)	++
6		200 MHz 1H NMR (DMSO-d_6) δ 13.9 (1H, br s), 8.19 (1H, dd, J = 7.2, 0.8 Hz), 7.85~7.60 (3H, m), 7.51 (2H, d, J = 9.0 Hz), 6.94 (1H, dd, J= 9.4, 6.6 Hz), 6.74 (1H, dd, J = 7.2, 6.4 Hz)	++
7		200 MHz 1H NMR (DMSO-d_6) δ 14.0 (1H, br s), 8.25 (1H, d, J = 7.4 Hz), 7.94 (2H, d, J = 8.6 Hz), 7.88~7.70 (3H, m), 7.04 (1H, dd, J = 6.2, 5.4 Hz), 6.80 (1H, t, J = 7.4 Hz)	++

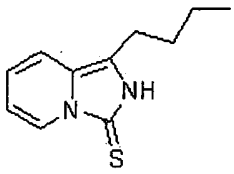
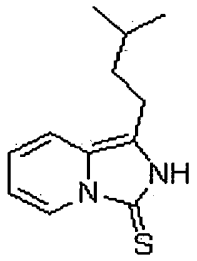
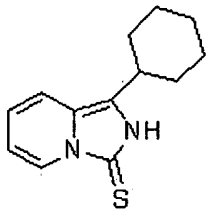
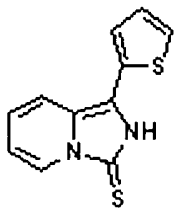
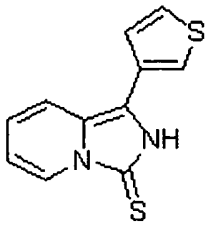
8		200 MHz ^{1}H NMR (DMSO-d_6) δ 13.9 (1H, br s), 8.20 (1H, d, J = 7.2 Hz), 7.80~7.60 (5H, m), 6.94 (1H, dd, J = 9.4, 6.4 Hz), 6.74 (1H, dd, J = 7.4, 6.6 Hz)	+
9		300MHz 1NMR (DMSO-d_6) δ 13.7 (1H, br s), 8.13 (1H, d, J = 7.5 Hz), 7.65 (1H, d, J = 9.6 Hz), 7.58 (2H, d, J= 8.1 Hz), 7.27 (2H, d, J = 7.8 Hz), 6.85 (1H, dd, J = 9.3,6.3 Hz), 6.69 (1H, t, J = 7.2 Hz), 2.33 (3H, s)	++
10		(200 MHz, $CDCl_3$) δ 8.60 (d, 1H), 8.10 (d, 1H), 7.81 (d, 2H), 7.60 (d, 2H), 6.98 (t, 1H), 6.62 (t, 1H)	+
11		300 MHz ^{1}H NMR (DMSO-d_6) δ 13.8 (1H, br s), 8.16 (1H, dt, J = 7.4, 1.0 Hz), 7.73~7.66 (3H, m), 7.47 (2H, t, J = 8.0 Hz), 7.32 (1H, t, J = 7.4 Hz), 6.89 (1H, ddd, J = 9.4, 6.3, 0.9 Hz), 6.72 (1H, ddd, J = 7.3, 6.5, 1.0 Hz)	++
12		(200 MHz, $CDCl_3$) δ 8.52 (d, 2H), 8.09(d, 1H), 7.47 (d, 2H), 7.50 (d, 1H), 6.73 (t, 1H), 6.55 (t, 1H)	+
13		(200 MHz, $CDCl_3$) δ 8.13 (d, 1H), 7.81 (dd, 3H), 7.45 (d, 2H), 6.90 (t, 1H), 6.83 (t, 1H), 6.55 (s, NH), 1.55 (s, 9H)	+

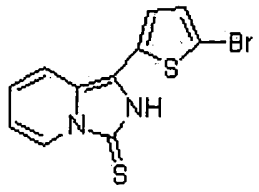
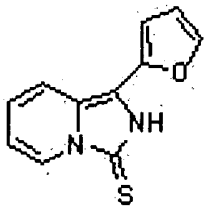
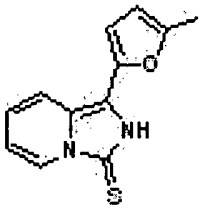
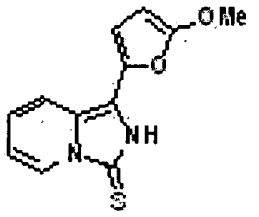
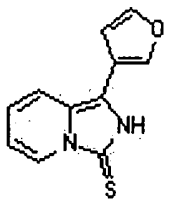
14		200 MHz 1H NMR (DMSO-d_6) δ 13.9 (1H, br s), 8.21 (1H, dt, J= 7.4, 1.8 Hz), 8.10~8.00 (2H, m), 7.84~7.74 (1H, m), 7.68~7.50 (4H, m), 7.08 (1H, d, J = 9.0 Hz), 6.88~6.68 (2H, m)	++
15		200 MHz 1H NMR (DMSO-d_6) δ 14.0 (1H, br s), 8.27 (1H, s), 8.22 (1H, d, J= 7.4 Hz), 8.06~7.82 (5H, m), 7.62~7.46 (2H, m), 6.97 (1H, ddd, J = 9.4, 6.2, 1.0 Hz), 6.77 (1H, t, J = 7.4 Hz)	++
16		(200 MHz, $CDCl_3$) δ 8.60 (d, 1H), 8.10 (d, 1H), 7.81 (d, 2H), 7.60 (d, 2H), 6.98 (t, 1H), 6.62 (t, 1H)	+
17		200 MHz 1H NMR (DMSO-d_6) δ 13.5 (1H, br s), 8.04 (1H, d, J = 7.0 Hz), 7.43 (2H, d, J = 8.6 Hz), 7.02 (2H, d, J= 8.6 Hz), 6.70~6.40 (2H, m), 3.82 (3H, s), 1.98 (3H, s)	+
18		200 MHz 1H NMR (DMSO-d_6) δ 13.6 (1H, br s), 8.06 (1H, d, J = 7.4 Hz), 7.63 (2H, d, J = 9.0 Hz), 7.40 (1H, d, J = 1.2 Hz), 7.04 (2H, d, J = 8.8 Hz), 6.53 (1H, dd, J = 7.8, 1.6 Hz), 3.80 (3H, s), 2.23 (3H, s)	++
19		300 MHz ^{1}H NMR (DMSO-d_6) δ 13.6 (1H, br s), 7.92 (1H, s), 7.62 (2H, d, *J* = 8.9 Hz), 7.56 (1H, d, *J* = 9.5 Hz), 7.02 (2H, d, *J* = 8.9 Hz), 6.70 (1H, d, *J* = 9.6 Hz), 3.78 (3H, s), 2.17 (3H, s)	++

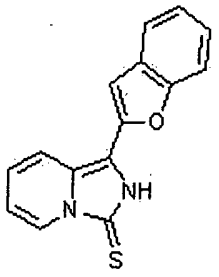
20		200 MHz 1H NMR (DMSO-d_6) δ 13.4 (1H, br s), 7.54 (2H, d, J = 9.0 Hz), 7.30 (1H, d, J = 9.5 Hz), 7.03 (2H, d, J = 8.8 Hz), 6.15 (1H, dd, J = 6.2, 5.4 Hz), 6.12 (1H, t, J = 7.4 Hz), 3.80 (3H, s), 3.16 (3H, s)	++
21		200 MHz 1H NMR (DMSO-d_6) δ 13.6 (1H, br s), 10.9 (1H, d, J = 8.6 Hz), 7.66 (1H, dd, J = 7.4, 2.0 Hz), 7.58 (2H, d, J = 8.2 Hz), 7.57~7.34 (3H, m), 7.32 (2H, d, J = 8.0 Hz), 7.13 (1H, d, J = 9.4 Hz), 2.37 (3H, s)	++
22		300 MHz 1H NMR (DMSO-d_6) δ 9.10 (1H, d, J = 1.5 Hz), 7.94 (1H, dd, J = 5.1, 1.5 Hz), 7.83 (2H, d, J = 6.9 Hz), 7.60~7.35 (4H, m)	+
23		(200 MHz, $CDCl_3$) δ 8.13 (d, 1H), 7.81 (dd, 3H), 7.45 (d, 2H), 6.90 (t, 1H), 6.83 (t, 1H), 6.55 (s, NH), 1.55 (s, 9H)	+
24		200 MHz 1H NMR (DMSO-d_6) δ 13.4 (1H, br s), 7.96 (1H, dt, J = 7.2, 1.2 Hz), 7.42 (1H, dt, J = 9.4, 1.6 Hz), 7.40~7.08 (5H, m), 6.68 (1H, ddd, J = 9.4, 6.6, 1.4 Hz), 6.56 (1H, ddd, J = 7.6, 6.4, 1.6 Hz), 4.10 (2H, s)	++
25		300 MHz 1H NMR (DMSO-d_6) δ 13.4 (1H, br s), 7.99 (1H, dd, J = 7.2, 0.9 Hz), 7.30~7.10 (2H, m), 6.99 (1H, d, J = 8.1 Hz), 6.91 (1H, t, J = 7.5 Hz), 6.68 (1H, t, J = 6.3 Hz), 6.58 (1H, t, J = 7.2 Hz), 4.05 (2H, s), 3.81 (3H, s)	++

26		200 MHz 1H NMR (DMSO-d_6) δ 13.4 (1H, br s), 7.96 (1H, dd, J = 6.0, 1.2 Hz), 7.45 (1H, dd, J = 9.4, 1.4 Hz), 7.21 (1H, t, J = 7.8 Hz), 6.94~6.48 (5H, m), 4.06 (2H, s), 3.72 (3H, s)	++
27		200 MHz 1H NMR ($CDCl_3$) δ 12.0 (1H, br s), 8.11 (1H, d, J = 7.4 Hz), 7.13 (2H, d, J = 8.6 Hz), 7.00 (1H, d, J= 9.4 Hz), 6.84 (2H, d, J = 8.6 Hz), 6.61 (1H, dd, J = 9.4, 5.6 Hz), 6.49 (1H, t, J = 6.4 Hz), 4.08 (2H, s), 3.78 (3H, s)	++
28		200 MHz 1H NMR (DMSO-d_6) δ 7.96 (1H, d, J = 7.0 Hz), 7.20 (1H, d, J = 9.4 Hz), 7.14~6.98 (2H, m), 6.76 (2H, t, J = 8.2 Hz), 6.70~6.48 (2H, m), 3.99 (3H, s)	++
29		200 MHz 1H NMR (DMSO-d_6) δ 13.4 (1H, br s), 9.32 (1H, s), 7.97 (1H, d, J = 7.2 Hz), 7.40 (1H, d, J = 9.4 Hz), 7.08 (1H, t, J= 7.6 Hz), 6.78~6.45 (5H, m), 4.01 (2H, s)	++
30		200 MHz 1H NMR (DMSO-d_6) δ 13.4 (1H, br s), 9.26 (1H, s), 7.94 (1H, dd, J= 7.4, 1.2 Hz), 7.37 (1H, d, J = 9.0 Hz), 7.05 (2H, d, J = 8.6 Hz), 6.65 (2H, d, J = 8.6 Hz), 6.65 (2H, d, J = 8.6 Hz), 6.64~6.50 (2H, m), 3.96 (2H, s)	++
31		300 MHz ^{1}H NMR (DMSO-d_6) δ 13.5 (1H, br s), 8.48 (2H, d, *J* = 6.0 Hz), 7.99 (1H, dd, *J* = 7.2, 0.9 Hz), 7.50 (1H, dd, *J* = 9.6, 1.2 Hz), 7.27 (2H, d, *J* = 5.7 Hz), 6.72 (1H, dd, *J*= 9.3, 6.3 Hz), 6.59 (1H, dd, *J* = 6.9, 6.3 Hz), 4.15 (2H, s)	++

32		200 MHz 1H NMR (DMSO-d_6) δ 13.5 (1H, br s), 8.80 (2H, d, J = 5.2 Hz), 8.02 (1H, dd, J = 7.2, 0.8 Hz), 7.87 (2H, d, J= 5.8 Hz), 7.60 (1H, dd, J = 9.4, 1.2 Hz), 6.79 (1H, dd, J = 9.2, 6.4 Hz), 6.63 (1H, dd, J = 7.4, 6.6 Hz), 4.45 (2H, s)	+
33		200 MHz 1H NMR ($CDCl_3$) δ 8.11 (1H, dd, J = 7.4, 0.8 Hz), 7.11 (1H, dd, J = 9.4, 1.2 Hz), 6.63 (1H, t, J = 6.0 Hz), 6.49 (1H, t, J = 6.0 Hz), 2.46 (3H, s)	++
34		300 MHz 1H NMR ($CDCl_3$) δ 8.31 (1H, d, J = 7.4 Hz), 7.14 (1H, d, J = 9.3 Hz), 7.00 (1H, s), 6.74 (1H, dd, J = 9.3, 6.4 Hz), 6.53 (1H, dd, J = 7.4, 6.4 Hz), 4.37 (2H, q, J = 7.3 Hz), 1.49 (3H, t, J = 7.3 Hz)	+
35		200 MHz 1H NMR ($CDCl_3$) δ 8.13 (1H, d, J = 7.2 Hz), 7.18 (1H, dd, J = 9.4, 1.2 Hz), 6.60 (1H, t, J = 6.4 Hz), 6.49 (1H, t, J = 6.4 Hz), 3.27 (1H, septet, J = 7.4 Hz), 1.40 (6H, d, J = 7.4 Hz)	++
36		(200 MHz, $CDCl_3$) δ 7.62 (d, 1H), 7.50 (d, 1H), 6.83 (t, 1H), 6.37 (t, 1H), 1.52 (s, 9H)	+
37		200 MHz 1H NMR ($CDCl_3$) δ 12.6 (1H, br s), 8.16 (1H, d, J = 7.4 Hz), 7.17 (1H, d, J = 9.0 Hz), 6.80~6.40 (2H, m), 6.05~5.80 (1H, m), 5.40~5.05 (2H, m), 3.60 (2H, dd, J = 6.4, 1.2 Hz)	++

38		300 MHz 1H NMR ($CDCl_3$) δ 13.0 (1H, br s), 8.11 (1H, d, J = 7.2 Hz), 7.12 (1H, d, J = 9.3 Hz), 6.61 (1H, t, J= 6.3 Hz), 6.49 (1H, t, J = 6.9 Hz), 2.82 (2H, t, J = 7.5 Hz), 1.71 (2H, pentet, J = 7.5 Hz), 1.34 (2H, sixtet, J = 7.2 Hz), 0.90 (3H, t, J = 7.2 Hz)	++
39		(200 MHz, $CDCl_3$) δ 8.03 (d, 1H),7.50 (d, 1H), 6.83 (t, 1H), 6.71 (t, 1H), 1.96 (dd, 2H), 1.83 (m, 1H), 1.29 (m, 2H), 1.01(d, 6H)	+
40		300 MHz 1H NMR (DMSO-d_6) δ 13.9 (1H, br s), 8.13 (1H, dt, J = 7.4, 1.1 Hz), 7.62~7.53 (3H, m), 7.15 (1H, dd, J = 5.0, 3.7 Hz), 6.94 (1H, ddd, J = 9.4, 6.4, 1.0 Hz), 6.72 (1H, ddd, J = 7.4, 6.4, 1.1 Hz)	++
41		300 MHz 1H NMR (DMSO-d_6) δ 13.9 (1H, br s), 8.13 (1H, dt, J = 7.4, 1.1 Hz), 7.62~7.53 (3H, m), 7.15 (1H, dd, J = 5.0, 3.7 Hz), 6.94 (1H, ddd, J = 9.4, 6.4, 1.0 Hz), 6.72 (1H, ddd, J = 7.4, 6.4, 1.1 Hz)	++
42		300 MHz 1H NMR (DMSO-d_6) δ 13.8 (1H, br s), 8.12 (1H, d, J = 7.3 Hz), 7.91 (1H, dd, J = 2.8, 1.3 Hz), 7.78~7.68 (2H, m), 7.64 (1H, dd, J = 5.1, 1.2 Hz), 6.87 (1H, ddd, J = 9.5, 6.3, 0.6 Hz), 6.69 (1H, t, J = 6.5 Hz)	++

43		200 MHz 1H NMR (DMSO-d_6) δ 14.0 (1H, br s), 8.16 (1H, d, J = 7.4 Hz), 7.57 (1H, d, J = 9.4 Hz), 7.36 (1H, d, J= 4.2 Hz), 7.30 (1H, d, J = 3.8 Hz), 6.98 (1H, ddd, J = 9.4, 6.2, 0.8 Hz), 6.75 (1H, ddd, J = 7.4, 6.6, 1.2 Hz)	+
44		200 MHz 1H NMR (DMSO-d_6) δ 13.9 (1H, br s), 8.11 (1H, dt, J = 7.4, 0.8 Hz), 7.78 (1H, dd, J = 2.0, 0.8 Hz), 7.68 (1H, dt, J= 9.4, 1.4 Hz), 6.98~6.84 (2H, m), 6.72 (1H, ddd, J = 7.2, 6.0, 0.8 Hz), 6.63 (1H, dd, J = 3.6, 2.0 Hz)	++
45		300 MHz 1H NMR (DMSO-d_6) δ 13.8 (1H, br s), 8.06 (1H, d, J = 7.4 Hz), 7.65 (1H, dt, J = 9.4, 1.1 Hz), 6.86 (1H, dd, J= 9.4, 6.0 Hz), 6.76 (1H, d, J = 3.3 Hz), 6.68 (1H, t, J = 7.2 Hz), 6.22 (1H, dd, J = 3.3, 1.0 Hz), 2.35 (3H, s)	++
46		300 MHz 1H NMR (DMSO-d_6) δ 13.8 (1H, br s), 8.02 (1H, d, J= 7.4 Hz), 7.52 (1H, dt, J = 9.4, 1.0 Hz), 6.81 (1H, ddd, J = 9.4, 6.3, 0.7 Hz), 6.76 (1H, d, J = 3.5 Hz), 6.65 (1H, t, J = 6.3 Hz), 5.50 (1H, d, J= 3.5 Hz), 3.88 (3H, s)	++
47		300 MHz 1H NMR (DMSO-d_6) δ 13.7 (1H, br s), 8.25 (1H, s), 8.06 (1H, d, J = 7.4 Hz), 7.80 (1H, dd, J= 1.7, 1.7 Hz), 7.65 (1H, d, J = 9.6 Hz), 7.08 (1H, dd, J = 1.8, 0.8 Hz), 6.81 (1H, dd, J= 9.3, 6.3 Hz), 6.65 (1H, dd, J = 7.3, 6.4 Hz)	++

48		300 MHz 1H NMR (DMSO-d_6) δ 8.19 (1H, dt, J = 7.4, 1.1 Hz), 7.93 (1H, dt, J = 9.4, 1.1 Hz), 7.67~7.59 (2H, m), 7.34~7.21 (3H, m), 7.06 (1H, ddd, J = 9.4, 6.4, 1.0 Hz), 6.80 (1H, ddd, J = 7.4, 6.4, 1.1 Hz)	++

Activities are based on IC_{50} values in cell-based assay, i.e., NFAT-promoter assays: +, >20uM; ++, 5~20uM; +++, <5uM.

Example 10: Measurement of inhibitory effect of 1,4-diphenyl -1,3-dihydro -imidazole-2-thione (IA-11) and derivatives thereof on TCR- or PMA/ionomycin-induced NFAT activation

Jurkat T-cells (ATCC) ($5x10^5$ cells/ml) transfected with reporter plasmids (NFAT-luciferase-pcDNA3.1) were pre-incubated with various concentrations of compounds (0.5~50 μM) for 3hrs, and activated with pre-coated anti-CD3 antibody (1~5 μg/ml) (UCHT1, Pharmingen) or phorbol 12-myristate 13-acetate (PMA) (Sigma, USA) (5 ng/ml) plus ionomycin (Sigma, USA) (500 ng/ml). Jurkat cells were further incubated for 24 hrs, harvested, lysed and centrifuged. The supernatant was assayed for luciferase activity. NFAT reporter plasmid consists of 5 repeats of NFAT binding sites and minimal promoter regions from IL-2 promoter and was inserted in front of the luciferase gene cloned in pcDNA3.1 (Invitrogen Corp., California, USA).

As a result, 1,4-diphenyl-1,3–dihydro-imidazole-2-thione (IA-11) and 1-(3-Hydr oxy-benzyl)-2H-imidazo[1,5-a]pyridine-3-thione (IB-29) inhibited TCR- induced NFAT promoter activation in a dose-dependent manner with an IC_{50} of 5~10 μM **(Fig. 1A)**. Other representative compounds (N-{4-[4-(5-Bromo -furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-phenyl}-acetamide (IA-109), 4-(1-Phenyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)-benzoic acid (IA-25), {4-[4 -(5-Methyl-furan-2-yl)-2-thioxo-2,3–dihydro-imidazol-1-yl]-phenoxy}-acetic acid ethyl ester (IA-111) and 3-[4-(5-Methyl-furan-2-yl)-2-thioxo-2,3-dihydro imidazol

-1-yl]-benzoic acid ethyl ester (IA-114)) also showed inhibitory effects on TCR-induced NFAT activation **(Fig. 1B)** and relative inhibitory effects of compounds are marked as from + to +++ in **Tables 1** and **2** above. 1,4-Diphenyl -1,3–dihydro-imidazole-2-thione (IA-11) and 1-(3-Hydroxy-benzyl)-2H-imidazo [1,5-a]pyridine-3-thione (IB-29) also inhibited PMA/ionomycin– induced NFAT reporter activity with a similar range of IC_{50}, suggesting that the target of 1,4-diphenyl-1,3–dihydro-imidazole-2-thione (IA-11) and 1-(3-Hydroxy-benzyl) -2H-imidazo[1,5-a]pyridine -3-thione (IB-29) is located in downstream of PMA/ionomycin-acting points or in other signaling pathway affecting on PMA/IA-induced signaling **(Fig. 1C)**.

Example 11: Measurement of inhibitory effect of 1,4-diphenyl-1,3-dihydro -imidazole-2-thione (IA-11) and derivatives thereof on T cell proliferation.

In order to determine whether the inhibition of NFAT activation mediated by 1,4-diphenyl-1,3-dihydro-imidazole-2-thione (IA-11) and derivatives thereof leads to the reduction in TCR-induced proliferation, splenocytes from C57BL/6 mice (Orient, Korea) were pre-incubated with 1,4-diphenyl-1,3–dihydro-imidazole-2 -thione (IA-11) and stimulated by anti-CD3 antibody.

Splenocytes from C57BL/6 mice ($1x10^6$ cells/ml) were pre-incubated with various concentrations of compounds (0.5~50 μM) for 3hrs and then transferred to the 96-well plates ($2x10^5$ cells/well) coated with anti-CD3 antibodies (0.2 g/ml, UCHT1, Pharmingen). Splenocytes were further incubated for 96hrs. [3H]thymidine (Amersham Pharmacia Biotech) (0.5 μCi) was added to each well, and plates were harvested after an additional 18hrs of culture. Incorporation of [3H] thymidine into DNA was measured by luminometer counter (PerkinElmer). 1,4-Diphenyl-1,3–dihydro-imidazole-2-thione (IA-11) and derivatives thereof , i.e., [1-(4-Methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazol-4-yl]-pyrrolidin-1-yl-met hanone (IA-83) and 4-(4-Amino-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione

IA-21), inhibited TCR-induced T cell proliferation with an IC_{50} of 4 μM~10 μM **(Fig. 2A)**, consistent with NFAT luciferase assay in Jurkat T cells. This suggests that 1,4-diphenyl-1,3-dihydro-imidazole-2-thione (IA-11) and derivatives thereof may effectively inhibit the T cell response elicited by auto-antigen, and therefore, can be used for the treatment of T-cell-mediated pathologic diseases. One way-MLRs were performed as described in Strong, D. M., *et al. J. Immunol. Methods.* 1973. *2*: 279; Sanglier, J. J., *et al. J. Antibiot. (Tokyo)* 1999. *52*: 466. Briefly, C57BL/6 (H-2b) splenocytes ($1x10^5$ cells/100 ㎕/well) were cultured with γ-irradiated (800 rads) (Gammacell 3000 Elan, MDS Nordion, Canata, Ontario, Canada) Balb/C (H-2d) splenocytes ($1x10^5$ cells/100 ㎕/well) in 96-well microplates. To examine the inhibitory effect of 1,4-diphenyl-1,3–dihydro -imidazole-2-thione (IA-11) on the resulting MLR, they were incubated for 3 days at 37°C in a 5 % CO_2 incubator in the presence or absence of 1,4-diphenyl-1,3–dihydro -imidazole-2-thione (IA-11) (0~50 μM). Then, the cells were pulsed with [^{3}H]-thymidine for 12 hrs of incubation and amount of the incorporated [^{3}H]-thymidine was measured with beta-counter (MicroBeta TriLux, PerkinElmer).

1,4-diphenyl-1,3–dihydro -imidazole-2-thione (IA-11) inhibited one-way MLR with 5 μM of IC_{50} **(Fig. 2B)**, which indicates that 1,4-diphenyl-1,3–dihydro -imidazole-2-thione (IA-11) can also inhibit allo-antigen-induced T cell proliferation and may be used for the treatment of organ transplantation rejection and GvHD. Thus such results imply that 1, 4-diphenyl-1,3–dihydro -imidazole-2-thione (IA-11) and derivatives thereof are expected to be efficacious in treating organ transplantation and GvHD.

Example 12: Measurement of *in vivo* inhibitory effect of 1,4-diphenyl -1,3–dihydro-imidazole-2-thione (IA-11) and derivatives thereof on T cell activation

1, 4-diphenyl-1,3–dihydro-imidazole-2-thione (IA-11) and representative derivatives were administered orally to Balb/c mice 3hrs before T-cell activation.

Vehicle group was administered orally with 0.2% carboxymethylcellulose only. T cells were activated by intravenous inoculation of anti-CD3 antibody (125ng/100 μℓ/mouse). After two hours from anti-CD3 injection, mice were bled via cardiac puncture, and the serum was collected and assayed for IL-2 by ELISA (BD biosciences, San Diego).

Various concentrations of 1, 4-diphenyl-1,3–dihydro-imidazole-2-thione (IA-11) (10~90 mg/kg) was administered orally to Balb/c mice 3 hrs before T-cell activation. While vehicle-treated group showed IL-2 level of 600~900 pg/ml, mice treated with 1,4-diphenyl-1,3–dihydro-imidazole-2-thione (IA-11) showed much reduced IL-2 level in a dose-dependent manner. The ED_{50} of IA-11 and IA29 for inhibition of anti-CD3-induced IL-2 production was 10 mg/kg and IL-2 production was suppressed 98% at 90 mg/kg **(Fig. 3)**. As a positive control, cyclosporine A, a currently used immunosuppressant, was used and cyclosporine A showed ED_{50} of less than 10 mg/kg. These results indicate that orally administered 1,4-diphenyl-1,3–dihydro-imidazole-2-thione (IA-11) and derivatives thereof are available and functional in inhibiting T cell activation *in vivo*.

Example 13: Measurement of *in vivo* inhibitory effect of 1,4-diphenyl-1,3–dihydro-imidazole-2-thione (IA-11) and derivatives thereof on DTH response

In order to assess the therapeutic potential in T-cell-mediated pathologic disease, inhibitory effect of 1,4-diphenyl-1,3–dihydro-imidazole-2-thione (IA-11) and its derivatives was determined in DTH model.

On day 0, C57BL/6 mice were immunized intradermally with 400 μg of methylated bovine serum albumin (mBSA, Sigma) in a 1:1 emulsion with complete Freund's adjuvant (Difco, Detroit, MI). Mice were administered orally with 1,4-diphenyl-1,3–dihydro-imidazole-2-thione (IA-11) or cyclosporine A from day -1 to day 8 on a daily basis. On day 7, mice were challenged in one hind footpad with 100 μg of mBSA in 20 μℓ of PBS and in the opposite footpad with

PBS alone for control. Footpad swelling was measured after 24 hrs from challenge using a vernier caliper.

In the DTH model, footpad swelling was inhibited by 70% when 1,4-diphenyl-1,3–dihydro-imidazole-2-thione (IA-11) was given from day -1 to day 8 **(Fig 4)**. 1,4-diphenyl-1,3–dihydro-imidazole-2-thione (IA-11) inhibited footpad swelling with 30 mg/kg/day of ED_{50}. This result suggests that 1,4-diphenyl-1,3–dihydro-imidazole-2- thione (IA-11) and derivatives thereof can suppress T-cell driven inflammatory responses.

Example 14: Measurement of *in vivo* inhibitory effect of 1,4-diphenyl -1,3–dihydro-imidazole-2-thione (IA-11) and derivatives thereof on EAE

In order to evaluate the preventive or therapeutic effects of 1,4-diphenyl-1,3–dihydro-imidazole-2-thione (IA-11) and 1-(3-Hydroxy-benzyl)-2H-imidazo[1,5-a]pyridine-3-thione (IB-29) in T-cell-mediated pathologic diseases, EAE model, a standard animal model for human multiple sclerosis, was used.

To induce EAE by active immunization, female C57BL/6 mice were immunized s.c. at four sites on the flank, with a total of 100 μg of MOG_{35-55} peptide emulsified in an equal volume of CFA (Difco, Detroit, MI) containing 1 mg/ml *Mycobacterium tuberculosis* H37 RA (Difco, Detroit, MI) on day 0. Mice also received i.v. injections of 400 ng of pertussis toxin (List Biological Laboratories, Campbell, CA) on days 0 and 2 after immunization. Mice were administered orally with 1, 4-diphenyl-1,3-dihydro-imidazole-2-thione (IA-11) and derivatives thereof in 0.2% CMC from day 0 to day 30 on a daily basis. Clinical signs were daily monitored and scored based on following criteria: 0, no detectable signs of disease; 0.5, distal limp tail; 1, complete limp tail; 1.5, limp tail and hind limb weakness; 2, unilateral partial hind paralysis; 2.5, bilateral hind limb paralysis; 3, complete bilateral hind limb paralysis; 3.5, complete bilateral hind limb paralysis and unilateral forelimb; 4, total paralysis of fore and hind limbs; and

5, death.

To evaluate the prophylactic effect of 1,4-diphenyl-1,3–dihydro-imidazole-2-thione (IA-11) and 1-(3-Hydroxy-benzyl)- 2H-imidazo[1,5-a]pyridine -3-thione (IB-29) in MOG-induced EAE, C57BL/6 mice were orally administered with 1,4-diphenyl-1,3–dihydro-imidazole-2-thione (IA-11) or 1-(3-Hydroxy-benzyl)-2H-imidazo[1,5-a]pyridine-3-thione (IB-29) on the day of the first s.c. immunization with MOG_{35-55} peptide. Vehicle-treated group showed disease onset from day 11 and reached the maximal level on day 20. All the vehicle-treated mice showed moderate to severe EAE with clinical scores ranging from 3 to 4. In contrast, oral administration of 1,4-diphenyl-1,3–dihydro-imidazole-2-thione (IA-11) (100mg/kg) greatly inhibited the development of EAE and reduced the disease incidence and severity ($p<0.05$) **(Fig 5)**. One of 8 mice (25%) was entirely asymptomatic, whereas the rest (5 of 8; 62.5%) only displayed moderate symptoms **(Table 3)**. A group treated with lower dose of 1,4-diphenyl-1,3–dihydro -imidazole-2-thione (IA-11) (20mg/kg/day) seemed to reduce the clinical signs of EAE but was not statistically significant.

Further, 1-(3-Hydroxy-benzyl)-2H-imidazo[1,5-a]pyridine -3-thione (IB-29) also showed a little stronger or similar efficacy to 1,4-diphenyl-1,3–dihydro -imidazole-2-thione (IA-11), showing significant efficacy in both of groups with the treatment of 20 mg/kg/day and 100 mg/kg/day **(Table 4)**.

Table 3

EAE in Mice Treated with 1,4-diphenyl-1,3–dihydro-imidazole-2-thione (IA-11) or vehicle

Treatment	Incidence						Mean maximal score
	Severe (2.6-5)		Mild (0.5-2.5)		None (0)		
Vehicle	7	(87.5%)	1	(12.5%)	0	(0%)	3.10±0.20
IA-11(100mg)	2	(25%)	5	(62.5%)	1	(12.5%)*	1.85±0.13
IA-11(20 mg)	5	(62.5%)	2	(25%)	0	(0%)	2.65±0.19

*$p<0.05$ when compared with vehicle group as determined by one way ANOVA

Table 4

EAE in Mice Treated with 1-(3-Hydroxy-benzyl)-2H-imidazo[1,5-a]pyridine -3-thione (IB-29) or vehicle

Treatment	Incidence						Mean maximal score
	Severe (2.6-5)		Mild (0.5-2.5)		None (0)		
Vehicle	7	(87.5%)	1	(12.5%)	0	(0%)	3.06±0.20
IB-29 (100mg)	1	(12.5%)	6	(75%)	1	(12.5%)*	1.35±0.10
IB-29 (20 mg)	2	(25%)	5	(62.5%)	1	(12.5%)†	1.87±0.14

* $p<0.01$ when compared with vehicle group as determined by one way ANOVA

† $p<0.05$ when compared with vehicle group as determined by one way ANOVA

Example 15: Measurement of *in vivo* inhibitory effect of 1,4-diphenyl-1,3–dihydro-imidazole-2-thione(IA-11) on MOG-specific T cell proliferation in EAE

Immune responses can be down-regulated at many different steps. In order

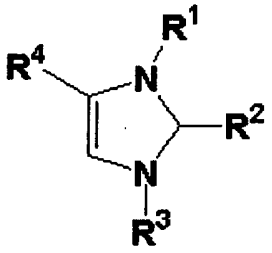
to determine if 1,4-diphenyl-1,3–dihydro-imidazole-2-thione(IA-11) inhibits MOG-specific T cell response, draining lymph node (DLN) cells were isolated from vehicle or 1,4-diphenyl-1,3–dihydro-imidazole-2-thione(IA-11)-treated mice and determined for MOG-dependent T cell response in the absence of 1,4-diphenyl-1,3–dihydro-imidazole-2-thione(IA-11). Ten days after immunization, DLN cells (auxillary and inguinal) were isolated and cultured with 25μg/ml of MOG_{35-55} peptide for 96hrs in 96-well flat-bottom plates at a concentration of 5 x 10^5 cells/well in complete RPMI 1640 medium (Life Technologies) containing 10% heat-inactivated FCS (Fetal Calf Serum), 1mM glutamine, 1% penicillin-streptomycin, 1 mM nonessential amino acids, and 5 x 10^{-5} M 2-ME (β-mercaptoethanol). Cells were pulsed with [^{3}H]thymidine (Amersham Pharmacia Biotech) at 0.5 μCi/well for the final 18 hrs before harvest. Incorporation of [^{3}H]-thymidine into DNA was measured by liquid scintillation counting (luminometer counter, PerkinElmer), and the mean was calculated from triplicate wells. For the cytokine assay, DLN cells were incubated with 25 μg/ml of MOG_{35-55} peptide for 72 hrs, culture supernatant was collected and assayed for IFN-γ with sandwich ELISA (BD biosciences, San Diego).

DLN cells isolated from vehicle-treated mice showed strong MOG-specific T cell proliferation. On the other hand, DLN cells collected from 1,4-diphenyl-1,3–dihydro-imidazole-2-thione (IA-11)-treated mice did not or weakly respond to MOG, suggesting that MOG-specific T cell activation was efficiently inhibited *in vivo* **(FIG. 6)**.

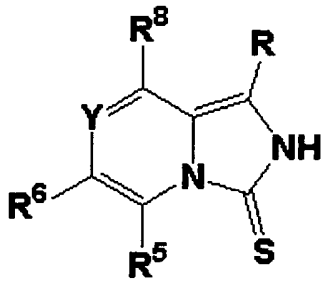
While the present invention has been described and illustrated with respect to the preferred embodiments only, various changes and modifications may be made therein without departing from the inventive concept of the present invention which should be limited only by the scope of the appended claims.

What is claimed is:

1. A compound of formula:



IA



IB

or

wherein

R^1 is H or C_1-C_4 alkyl;

R^2 is =S, -SH, =O, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_1-C_4 alkoxymethylthio, C_1-C_4 alkoxybenzylthio or -S-$(CH_2)_n$-C(=O)-O-R^g;

R^3 is phenyl optionally substituted with one or more substituents selected from the group consisting of -OH, -NO_2, -NH_2, halo, -C_1-C_4 alkyl, –C_1-C_4 alkoxy, C_1-C_4 alkylcarbonylamino, -$(CH_2)_m$-C(=O)-O-R^g and -O-CH_2-C(=O)-O-R^g,

-$CH(CH_3)$-C(=O)-NR'R", wherein R' and R" together with N atom to which they are attached may form morpholine or piperazine optionally substituted with C_1-C_4 alkoxycarbonyl,

-$(CH_2)_n$-phenyl, phenyl being optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, cyano and C_1-C_4 alkoxy,

-CH_2-pyridine,

-C_1-C_4 alkyl optionally substituted with hydroxy,

-$(CH)(CH_3)$-C(=O)-O-R^g,

-CH_2-C(=O)-NR^aR^b, wherein each of R^a and R^b is independently H, C_1-C_4 alkyl or benzyl substituted with halo, or R^a and R^b together with N atom to

which they are attached may form a five or six-membered ring selected from the group consisting of morpholine, pyrrolidine, piperidine and piperazine, that optionally substituted with C_1-C_4 alkyl or C_1-C_4 alkoxycarbonyl,

$-CH_2-C(=O)-O-R^g$,

$-(CH_2)_2-NR^cR^d$, wherein each of R^c and R^d is C_1-C_4 alkyl, or R^c and R^d together with N atom to which they are attached may form morpholine, pyrrolidine, piperidine or piperazine optionally substituted with C_1-C_4 alkyl, or

phenylcarbonyl, phenyl being optionally substituted with halo;

R^4 is phenyl optionally substituted with one or more substituents selected from the group consisting of cyano, $-NO_2$, $-NH_2$, hydroxy, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, phenyl, $-C(=O)-O-R^g$ and $-CH_2-O-R^g$,

$-C(=O)-NR^eR^f$, wherein each of R^e and R^f is independently H, C_1-C_4 alkyl or phenyl optionally substituted with C_1-C_4 alkoxy, or R^e and R^f together with N atom to which they are attached may form a five or six-membered ring selected from the group consisting of pyrrolidine, piperidine, piperazine and morpholine, that optionally substituted with C_1-C_4 alkyl or C_1-C_6 alkoxycarbonyl,

$-(CH_2)$-piperazine, piperazine being substituted with C_1-C_4 alkyl,

thienyl optionally substituted with halo or C_1-C_4 alkyl,

furyl optionally substituted with halo, C_1-C_4 alkyl or $-C(=O)-O-R^g$,

benzofuryl,

$-CH_2-O-C(=O)-C_1$-C_4 alkyl,

C_1-C_4 alkyl optionally substituted with hydroxy, or

C_1-C_4 alkoxycarbonyl;

R^g is hydrogen or C_1-C_4 alkyl;

n is 1 or 2;

m is 0 or 1;

R is C_1-C_6 alkyl,

C_1-C_6 alkenyl,

C_3-C_8 cycloalkyl,

pyridyl,

thienyl optionally substituted with halo,

-(CH_2)-pyridine,

furyl optionally substituted with C_1-C_4 alkyl or C_1-C_4 alkoxy,

isobenzofuryl,

naphthalenyl,

benzyl optionally substituted with C_1-C_4 alkoxy or hydroxy, or

phenyl optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkyl substituted with halo, C_1-C_4 alkoxy and C_1-C_4 alkoxycarbonylamino;

Y is N or CR^7, wherein R^7 is H or C_1-C_4 alkyl;

each of R^5 and R^8 is independently H or C_1-C_4 alkyl; and

R^6 is H, halo or C_1-C_4 alkyl; or

R^5 and R^6 together with the atoms to which they are attached may form a six membered aromatic ring,

or the pharmaceutically acceptable salts thereof.

2. The compound of formula IA according to claim 1, which is selected from the group consisting of:

1,4-diphenyl-1H-imidazole-2-thiol,

4-(1-phenyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)-benzonitrile,

4-(2,4-dimethoxy-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-(4-fluoro-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-(2-methoxy-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-(4-methoxy-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-biphenyl-4-yl-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-(4-chloro-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione,
1-phenyl-4-p-tolyl-1,3-dihydro-imidazole-2-thione,
3-(1,4-diphenyl-1H-imidazol-2-ylsulfanyl)-propionic acid ethyl ester,
1,4-diphenyl-1,3-dihydro-imidazole-2-thione,
3-(1,4-diphenyl-1H-imidazol-2-ylsulfanyl)-propionic acid,
(1,4-diphenyl-1H-imidazol-2-ylsulfanyl)-acetic acid ethyl ester,
(1,4-diphenyl-1H-imidazol-2-ylsulfanyl)-acetic acid,
4-phenyl-1-o-tolyl-1,3-dihydro-imidazole-2-thione,
1,4-diphenyl-1,3-dihydro-imidazol-2-one,
2-methanesulfonyl-1,4-diphenyl-1H-imidazole,
2-methylsulfanyl-1,4-diphenyl-1H-imidazole,
4-(4-methoxy-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione,
4-(4-nitro-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione,
4-(4-amino-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione,
4-(4-hydroxy-phenyl)-1-phenyl-1,3-dihydro-imidazole-2-thione,
1-(4-hydroxy-phenyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,
4-(1-phenyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)-benzoic acid methyl ester,
4-(1-phenyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)-benzoic acid,
3-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-benzoic acid ethyl ester,
3-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-benzoic acid,
4-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-benzoic acid ethyl ester,
4-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-benzoic acid,
1-(3-nitro-phenyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,
1-(3-amino-phenyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,
N-[4-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-phenyl]-acetamide,
1-(3-fluoro-benzyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,
1-benzyl-4-phenyl-1,3-dihydro-imidazole-2-thione,
1-(2-methoxy-benzyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,
1-(4-methoxy-benzyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,

1-(4-hydroxy-benzyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,
1-(2-hydroxy-benzyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,
4-[1-(4-fluoro-benzyl)-2-thioxo-2,3-dihydro-1H-imidazol-4-yl]-benzonitrile,
4-[1-(4-fluoro-benzyl)-2-thioxo-2,3-dihydro-1H-imidazol-4-yl]-benzoic acid,
1-(4-fluoro-benzyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,
4-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-ylmethyl)-benzonitrile,
1-(2-chloro-benzyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,
4-phenyl-1-pyridin-2-ylmethyl-1,3-dihydro-imidazole-2-thione,
2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-propionic acid methyl ester,
2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-propionic acid,
1-(2-hydroxy-1-methyl-ethyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,
1-morpholin-4-yl-2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-ethanone,
2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-1-piperidin-1-yl-ethanone,
1-(4-methyl-piperazin-1-yl)-2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-etha
none,
4-[2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-acetyl]-piperazine-1-carboxyli
c acid tert-butyl ester,
N,N-diethyl-2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-acetamide,
2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-1-pyrrolidin-1-yl-ethanone,
1-(2-morpholin-4-yl-ethyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,
4-phenyl-1-(2-piperidin-1-yl-ethyl)-1,3-dihydro-imidazole-2-thione,
4-phenyl-1-(2-pyrrolidin-1-yl-ethyl)-1,3-dihydro-imidazole-2-thione,
(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-acetic acid methyl ester,
(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-acetic acid,
1-methyl-4-phenyl-1,3-dihydro-imidazole-2-thione,
3-methyl-1,4-diphenyl-1,3-dihydro-imidazole-2-thione,
4-methyl-1-phenyl-1,3-dihydro-imidazole-2-thione,
1-(2-hydroxy-ethyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,
1-morpholin-4-yl-2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-propan-1-one,

4-[2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-propionyl]-piperazine-1-carbo xylic acid tert-butyl ester,

1-[2-(4-methyl-piperazin-1-yl)-ethyl]-4-phenyl-1,3-dihydro-imidazole-2-thione,

N-(4-fluoro-benzyl)-2-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-acetamide,

1-(2-diethylamino-ethyl)-4-phenyl-1,3-dihydro-imidazole-2-thione,

1-isopropyl-4-phenyl-1,3-dihydro-imidazole-2-thione,

1-[2-(4-fluoro-phenyl)-ethyl]-4-phenyl-1,3-dihydro-imidazole-2-thione,

(4-fluoro-phenyl)-[2-(4-methoxy-benzylsulfanyl)-4-phenyl-imidazol-1-yl]-methan one,

(4-fluoro-phenyl)-(2-methoxymethylsulfanyl-4-phenyl-imidazol-1-yl)-methanone,

(4-fluoro-phenyl)-(4-phenyl-2-thioxo-2,3-dihydro-imidazol-1-yl)-methanone,

1-(2-chloro-benzyl)-2-methoxymethylsulfanyl-4-phenyl-1H-imidazole,

2-(2-methoxymethylsulfanyl-4-phenyl-imidazol-1-ylmethyl)-pyridine,

4-(2-methoxymethylsulfanyl-4-phenyl-imidazol-1-ylmethyl)-pyridine,

1-(2-fluoro-benzyl)-2-methoxymethylsulfanyl-4-phenyl-1H-imidazole,

2,2-dimethyl-propionic acid 1-(4-fluoro-benzyl)-2-thioxo-2,3-dihydro-1H -imidazol-4- yl-methyl ester,

1-(4-fluoro-benzyl)-4-hydroxymethyl-1,3-dihydro-imidazole-2-thione,

1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazole-4-carboxylic acid ethyl ester,

1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazol-4-yl]-(4-methyl-piperazi n-1-yl)-methanone,

[1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazol-4-yl]-morpholin-4-yl-methanone,

[1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazol-4-yl]-piperidin-1-yl-met hanon,

[1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazol-4-yl]-pyrrolidin-1-yl-m ethanone,

1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazole-4-carboxylic acid diethylamide,

4-[1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazole-4-carbonyl]-piperazine-1- carboxylic acid tert-butyl ester,

1-(4-methoxy-phenyl)-4-(4-methyl-piperazin-1-yl-methyl)-1,3-dihydro-imidazole-2-thione,

1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazole-4-carboxylic acid phenylamide,

1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazole-4-carboxylic acid (4-methoxy-phenyl)-amide,

1-phenyl-4-thiophen-2-yl-1,3-dihydro-imidazole-2-thione,

1-phenyl-4-thiophen-3-yl-1,3-dihydro-imidazole-2-thione,

4-(5-bromo-thiophen-2-yl)-1-(4-methoxy-phenyl)-1,3-dihydro-imidazole-2-thione,

4-(3-methyl-thiophen-2-yl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

3-[4-(5-bromo-thiophen-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-benzoic acid,

3-[4-(5-bromo-thiophen-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-benzoic acid ethyl ester,

4-(5-bromo-thiophen-2-yl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-(5-chloro-thiophen-2-yl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-(2,5-dimethyl-thiophen-3-yl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-furan-2-yl-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-(5-methyl-furan-2-yl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-(5-bromo-furan-2-yl)-1-phenyl-1,3-dihydro-imidazole-2-thione,

4-benzofuran-2-yl-1-phenyl-1,3-dihydro-imidazole-2-thione,

3-[4-(5-bromo-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-benzoic acid ethyl ester,

3-[4-(5-bromo-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-benzoic acid,

1-(4-methoxy-phenyl)-4-(5-methyl-furan-2-yl)-1,3-dihydro-imidazole-2-thione,

N-{3-[4-(5-methyl-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-phenyl}-acetamide,

N-{4-[4-(5-methyl-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-phenyl}-acetamide,

N-{3-[4-(5-bromo-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-phenyl}-acetamide,

5-(1-phenyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)-furan-2-carboxylic acid methyl ester,

N-{4-[4-(5-bromo-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-phenyl}-acetamide,

5-(1-phenyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)-furan-2-carboxylic acid,

{4-[4-(5-methyl-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-phenoxy}-acetic acid ethyl ester,

{4-[4-(5-methyl-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-phenoxy}-acetic acid,

{4-[4-(5-methyl-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-phenyl}-acetic acid methyl ester,

3-[4-(5-methyl-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-benzoic acid ethyl ester,

3-[4-(5-methyl-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-benzoic acid,

5-[1-(4-methoxy-phenyl)-2-thioxo-2,3-dihydro-1H-imidazol-4-yl]-furan-2-carboxylic acid methyl ester and

{4-[4-(5-methyl-furan-2-yl)-2-thioxo-2,3-dihydro-imidazol-1-yl]-phenyl}-acetic acid, and

the pharmaceutically acceptable salts thereof.

3. The compound of formula IB according to claim 1, which is selected from the group consisting of:

1-(2-methoxy-phenyl)-2H-imidazo[1,5-a]pyridine-3-thione,

1-(3-methoxy-phenyl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-(4-methoxy-phenyl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-(4-hydroxy-phenyl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-(4-fluoro-phenyl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-(4-chloro-phenyl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-(4-trifluoromethyl-phenyl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-(4-bromo-phenyl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-p-tolyl-2H-imidazo[1,5-a]pyridine-3-thione,
6-chloro-1-phenyl-2H-imidazo[1,5-a]pyridine-3-thione,
1-phenyl-2H-imidazo[1,5-a]pyridine-3-thione,
1-pyridin-4-yl-2H-imidazo[1,5-a]pyridine-3-thione,
[4-(3-thioxo-2,3-dihydro-imidazo[1,5-a]pyridin-1-yl)-phenyl]-carbamic acid tert-butyl ester,
1-naphthalen-1-yl-2H-imidazo[1,5-a]pyridine-3-thione,
1-naphthalen-2-yl-2H-imidazo[1,5-a]pyridine-3-thione,
6-chloro-1-phenyl-2H-imidazo[1,5-a]pyridine-3-thione,
1-(4-methoxy-phenyl)-8-methyl-2H-imidazo[1,5-a]pyridine-3-thione,
1-(4-methoxy-phenyl)-7-methyl-2H-imidazo[1,5-a]pyridine-3-thione,
1-(4-methoxy-phenyl)-6-methyl-2H-imidazo[1,5-a]pyridine-3-thione,
1-(4-methoxy-phenyl)-5-methyl-2H-imidazo[1,5-a]pyridine-3-thione,
3-p-tolyl-2H-imidazo[1,5-a]quinoline-1-thione,
1-phenyl-2H-imidazo[1,5-a]pyrazine-3-thione,
1-benzyl-2H-imidazo[1,5-a]pyridine-3-thione,
1-(2-methoxy-benzyl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-(3-methoxy-benzyl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-(4-methoxy-benzyl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-(2-hydroxy-benzyl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-(3-hydroxy-benzyl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-(4-hydroxy-benzyl)-2H-imidazo[1,5-a]pyridine-3-thione,

1-pyridin-4-ylmethyl-2H-imidazo[1,5-a]pyridin-3-one,
4-(3-thioxo-2,3-dihydro-imidazo[1,5-a]pyridin-1-ylmethyl)-pyridinium chloride,
1-methyl-2H-imidazo[1,5-a]pyridine-3-thione,
1-ethyl-2H-imidazo[1,5-a]pyridine-3-thione,
1-isopropyl-2H-imidazo[1,5-a]pyridine-3-thione,
1-tert-butyl-2H-imidazo[1,5-a]pyridine-3-thione,
1-allyl-2H-imidazo[1,5-a]pyridine-3-thione,
1-butyl-2H-imidazo[1,5-a]pyridine-3-thione,
1-(3-methyl-butyl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-cyclohexyl-2H-imidazo[1,5-a]pyridine-3-thione,
1-thiophen-2-yl-2H-imidazo[1,5-a]pyridine-3-thione,
1-thiophen-3-yl-2H-imidazo[1,5-a]pyridine-3-thione,
1-(5-bromo-thiophen-2-yl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-furan-2-yl-2H-imidazo[1,5-a]pyridine-3-thione,
1-(5-methyl-furan-2-yl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-(5-methoxy-furan-2-yl)-2H-imidazo[1,5-a]pyridine-3-thione,
1-furan-3-yl-2H-imidazo[1,5-a]pyridine-3-thione, and
1-benzofuran-2-yl-2H-imidazo[1,5-a]pyridine-3-thione, and
the pharmaceutically acceptable salts thereof.

4. A pharmaceutical composition comprising the compound according to any one of claims 1 to 3 or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier.

5. A method for the treatment and/or prophylaxis of T-cell mediated diseases which comprises administering the compound according to any one of claims 1 to 3 to a human being or an animal.

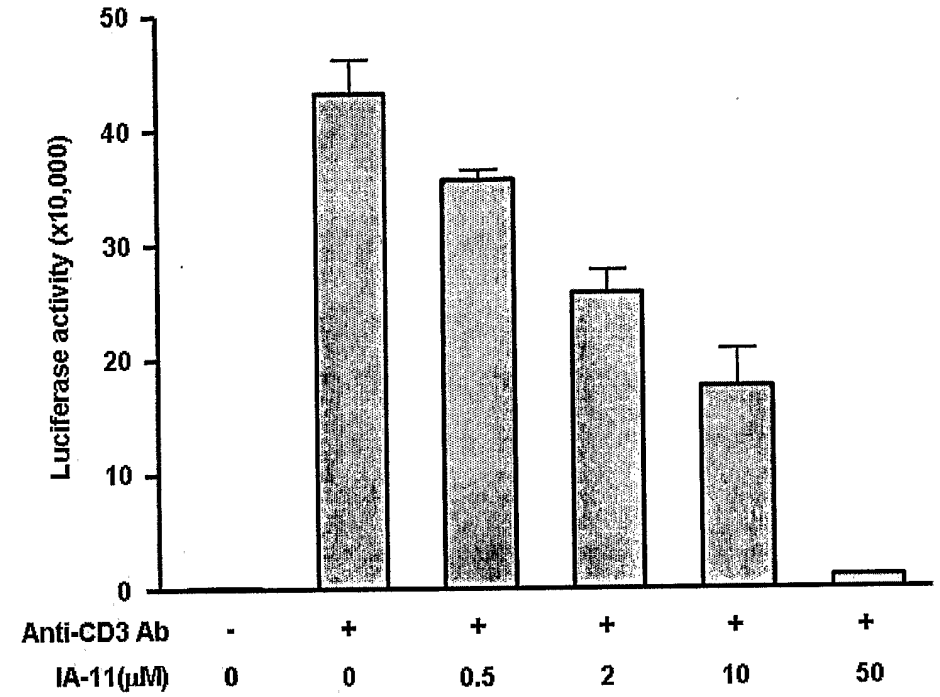
6. A use of the compound according to any one of claims 1 to 3 for the preparation

of medicaments for the treatment and/or prophylaxis of T-cell mediated diseases.

7. The use according to claim 6 wherein the T-cell mediated diseases are selected from the group consisting of graft rejection, Graft versus Host Disease, asthma, atopic diseases and autoimmune diseases.

8. The use according to claim 7 wherein the autoimmune diseases are selected from the group consisting of multiple sclerosis, psoriasis, inflammatory bowl disease, rheumatoid arthritis, lupus, and type I diabetes.

FIG. 1A


Luciferase activity (x10,000)
50
40
30
20
10
0
Anti-CD3 Ab - + + + + +
IA-11(μM) 0 0 0.5 2 10 50

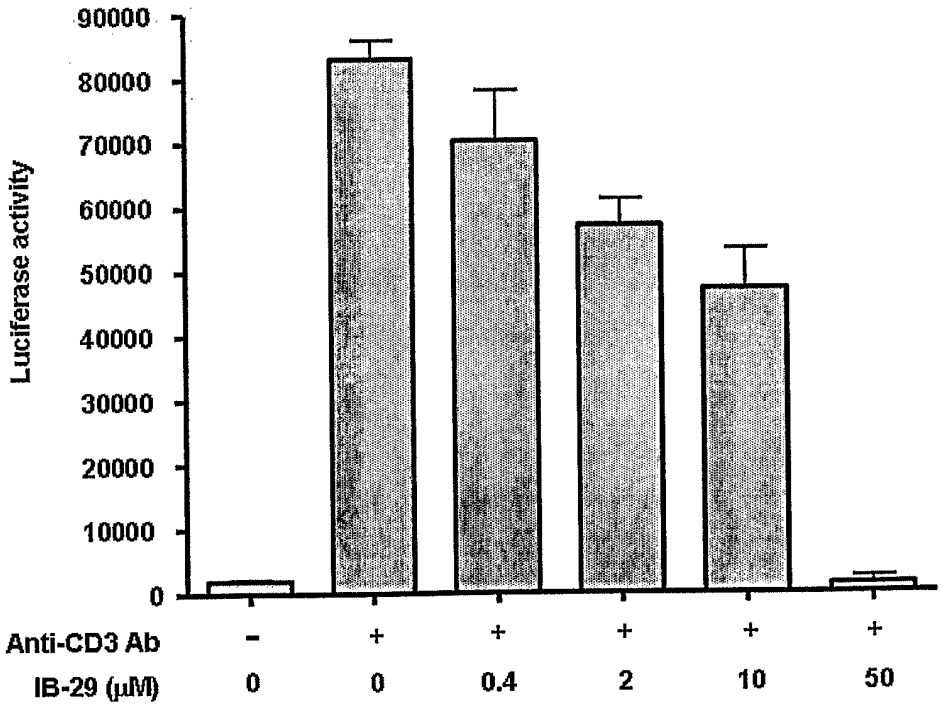

Luciferase activity
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
Anti-CD3 Ab - + + + + +
IB-29 (μM) 0 0 0.4 2 10 50

FIG. 1B

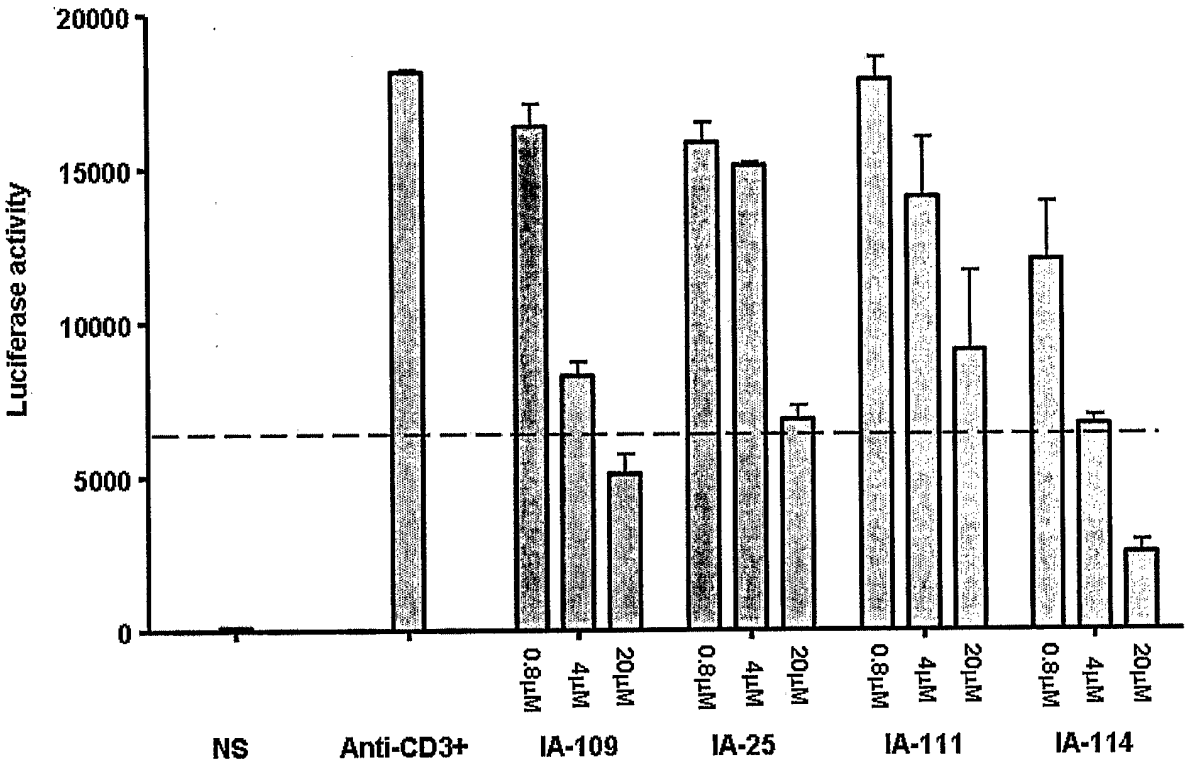
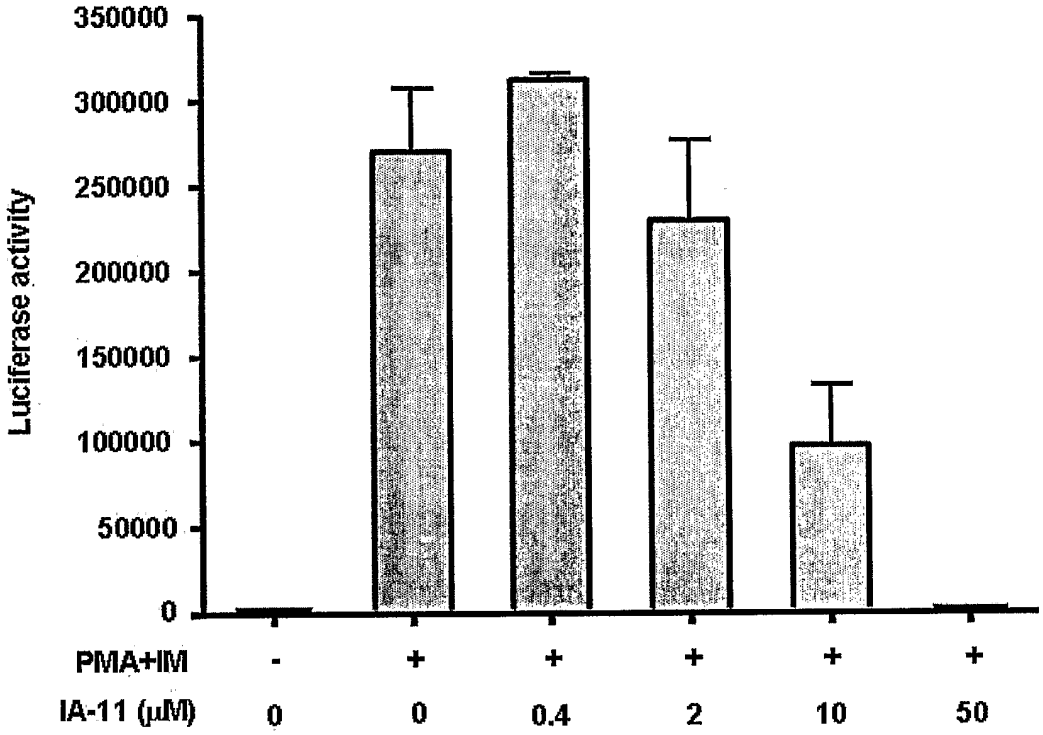

Luciferase activity
20000
15000
10000
5000
0
0.8μM
4μM
20μM
NS
Anti-CD3+
IA-109
IA-25
IA-111
IA-114

FIG. 1C


Luciferase activity
350000
300000
250000
200000
150000
100000
50000
0
PMA+IM - + + + + +
IA-11 (μM) 0 0 0.4 2 10 50

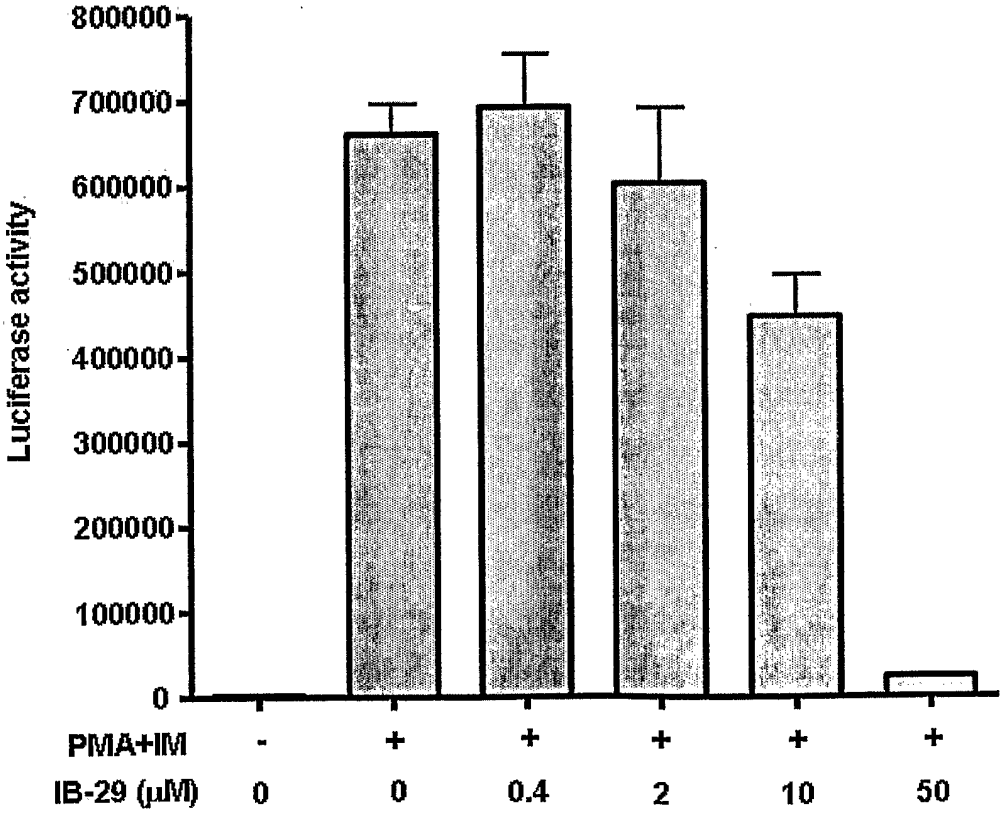
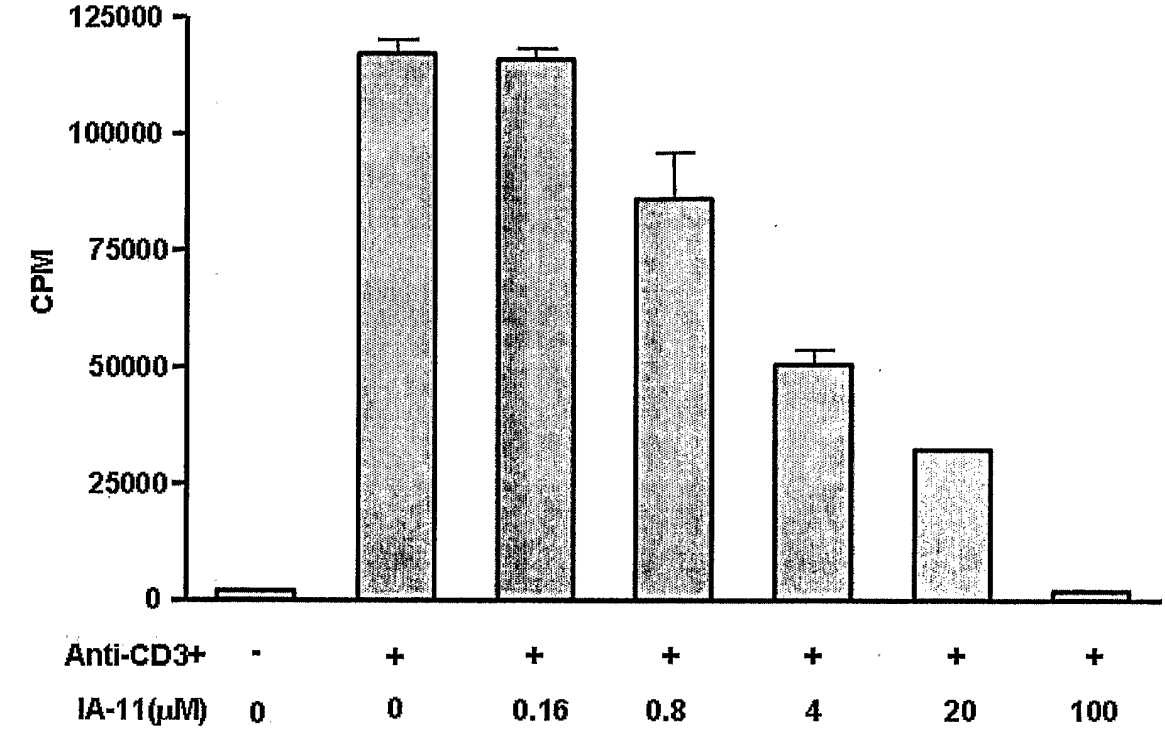

Luciferase activity
800000
700000
600000
500000
400000
300000
200000
100000
0
PMA+IM - + + + + +
IB-29 (μM) 0 0 0.4 2 10 50

FIG. 2A


125000
100000
75000
50000
25000
0
CPM
Anti-CD3+ - + + + + + +
IA-11(μM) 0 0 0.16 0.8 4 20 100

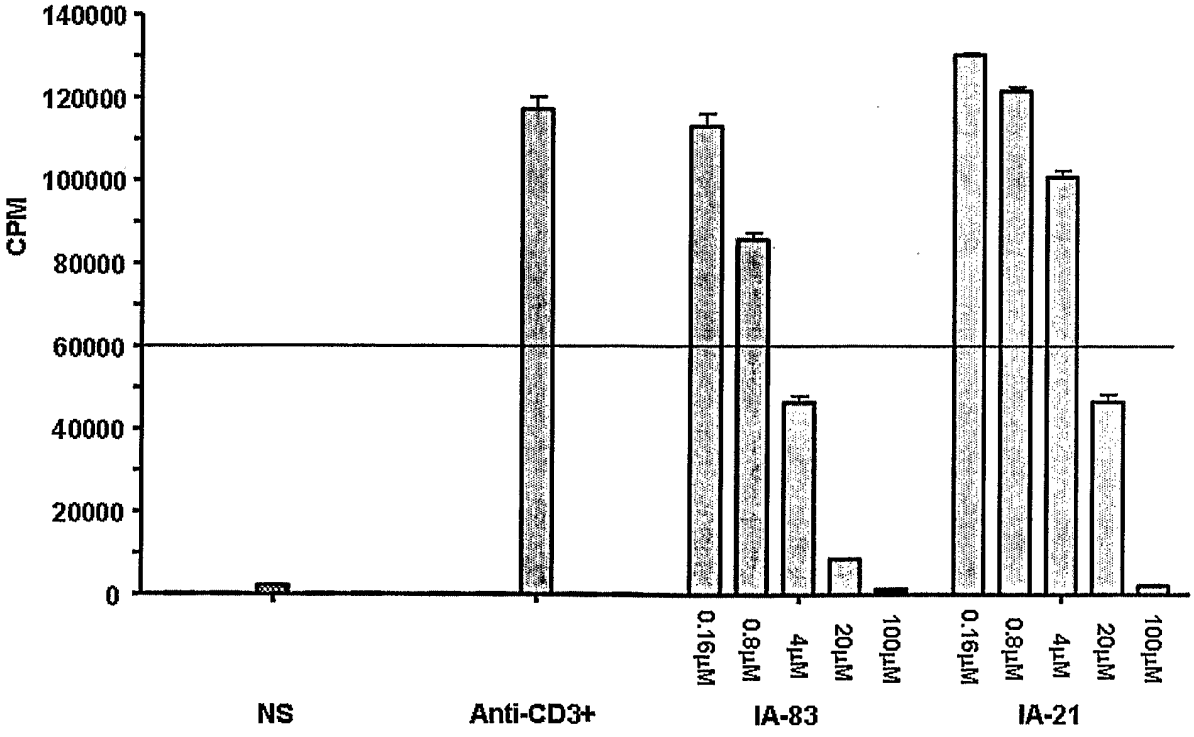

140000
120000
100000
80000
60000
40000
20000
0
CPM
0.16μM
0.8μM
4μM
20μM
100μM
0.16μM
0.8μM
4μM
20μM
100μM
NS
Anti-CD3+
IA-83
IA-21

FIG. 2B

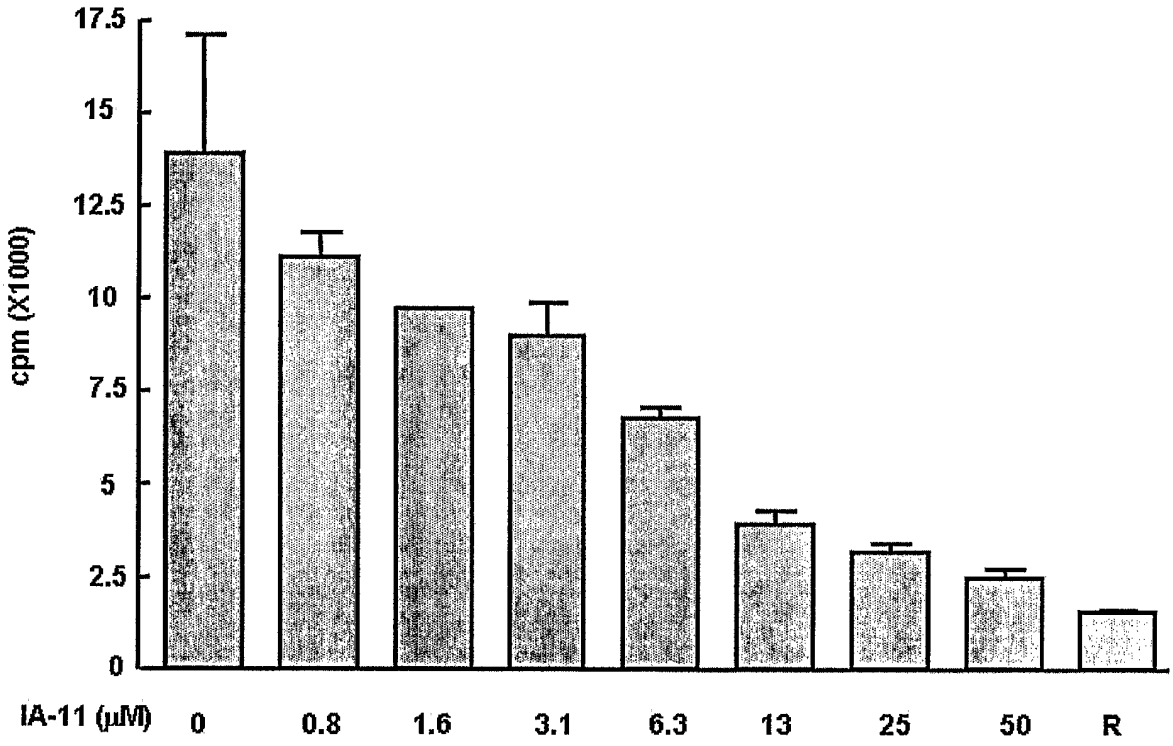


FIG. 3

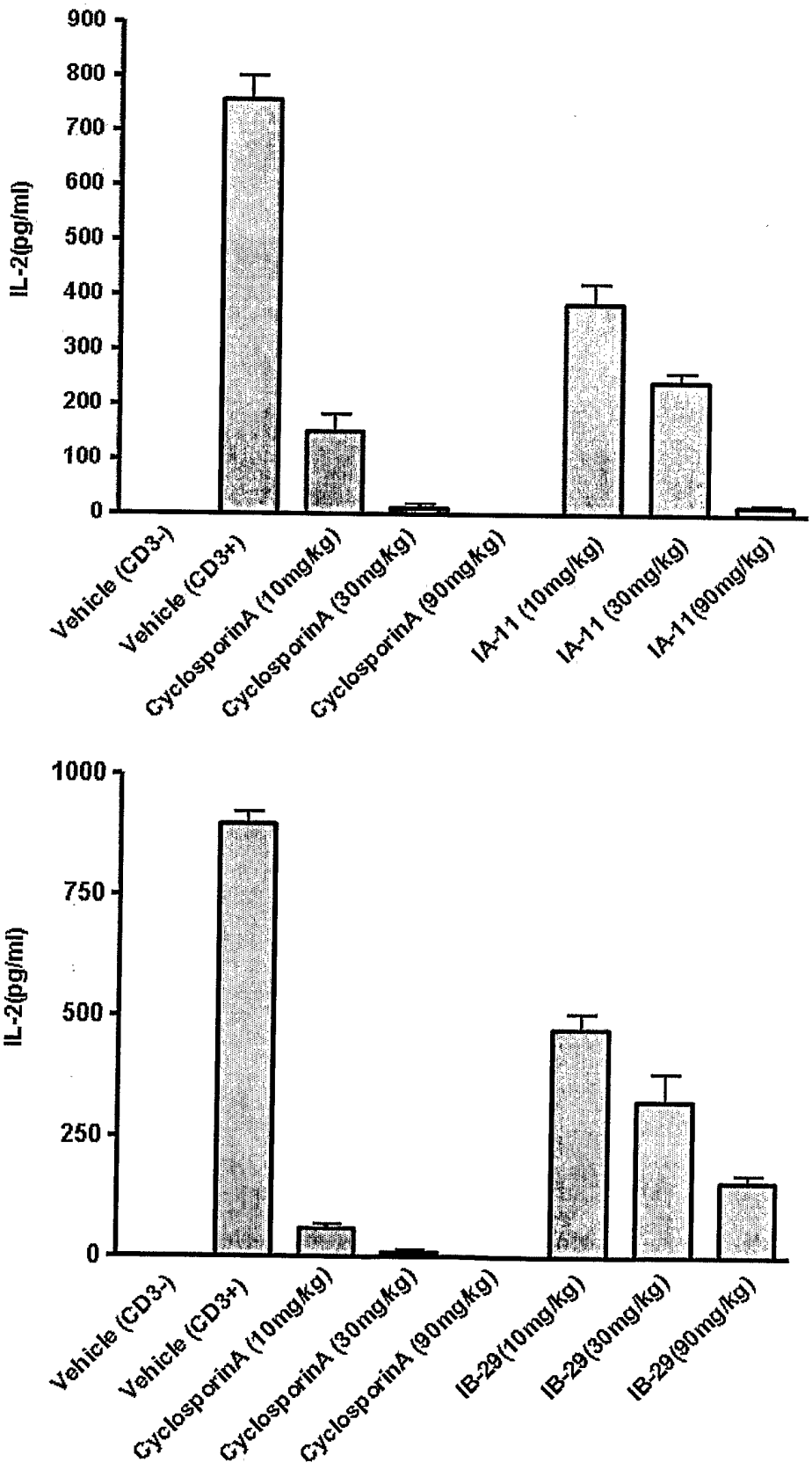

IL-2(pg/ml)
900
800
700
600
500
400
300
200
100
0
Vehicle (CD3-)
Vehicle (CD3+)
CyclosporinA (10mg/kg)
CyclosporinA (30mg/kg)
CyclosporinA (90mg/kg)
IA-11 (10mg/kg)
IA-11 (30mg/kg)
IA-11(90mg/kg)
IL-2(pg/ml)
1000
750
500
250
0
Vehicle (CD3-)
Vehicle (CD3+)
CyclosporinA (10mg/kg)
CyclosporinA (30mg/kg)
CyclosporinA (90mg/kg)
IB-29(10mg/kg)
IB-29(30mg/kg)
IB-29(90mg/kg)

FIG. 4

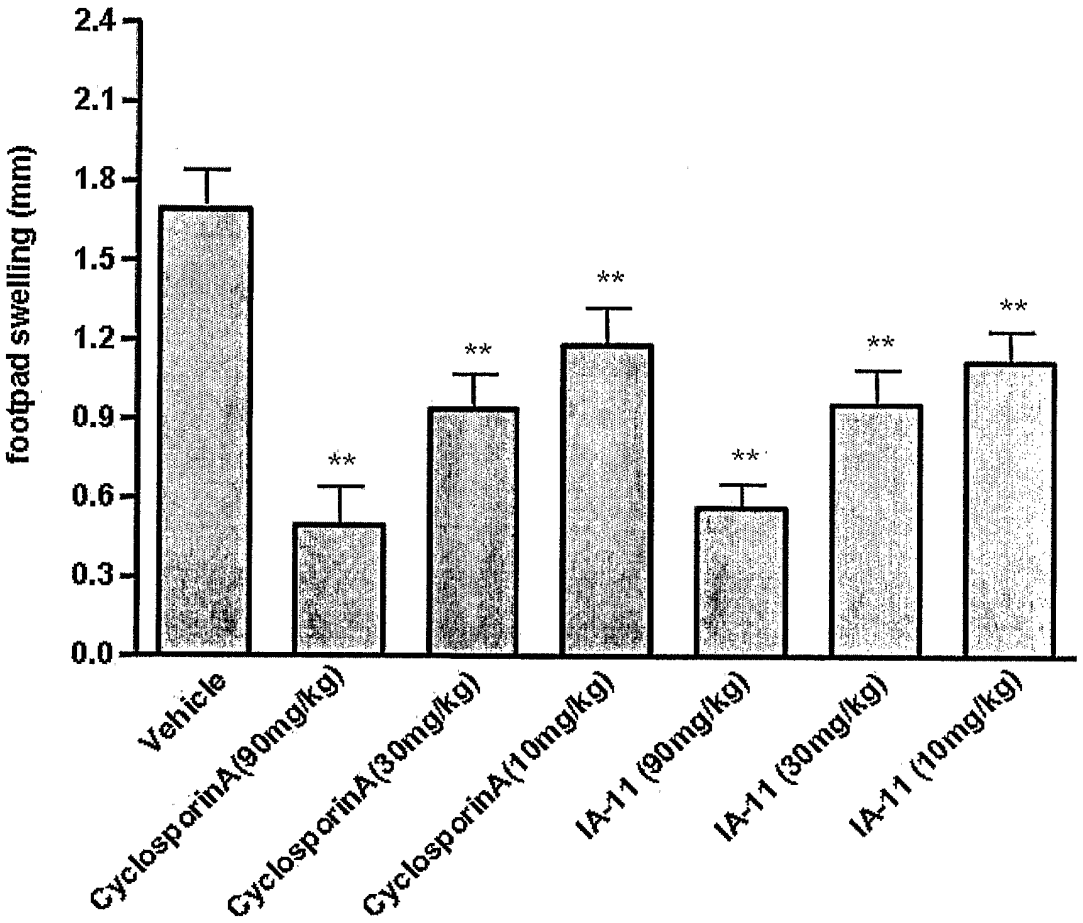

footpad swelling (mm)
2.4
2.1
1.8
1.5
1.2
0.9
0.6
0.3
0.0
**
**
**
**
**
**
Vehicle
CyclosporinA(90mg/kg)
CyclosporinA(30mg/kg)
CyclosporinA(10mg/kg)
IA-11 (90mg/kg)
IA-11 (30mg/kg)
IA-11 (10mg/kg)

FIG. 5

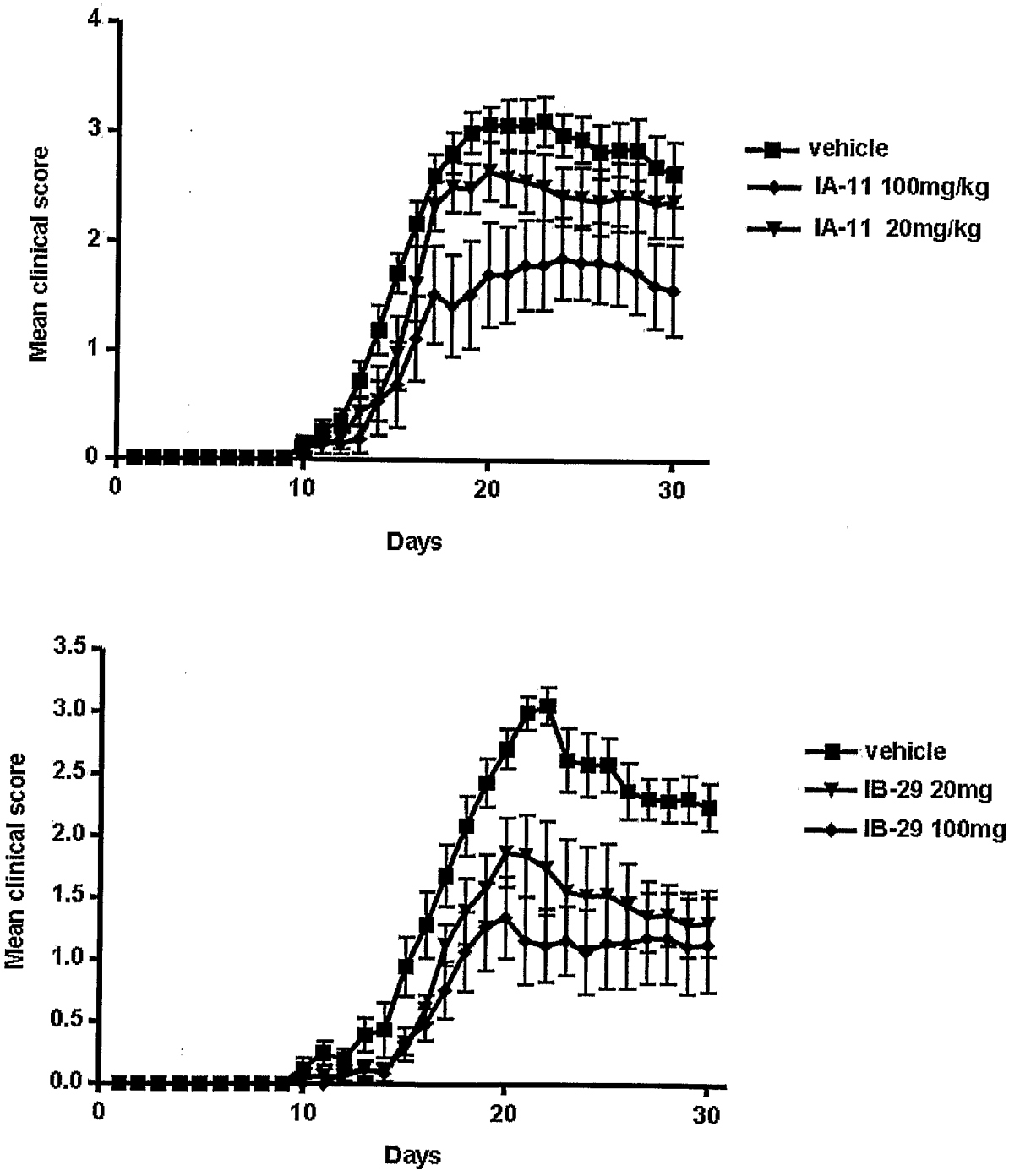
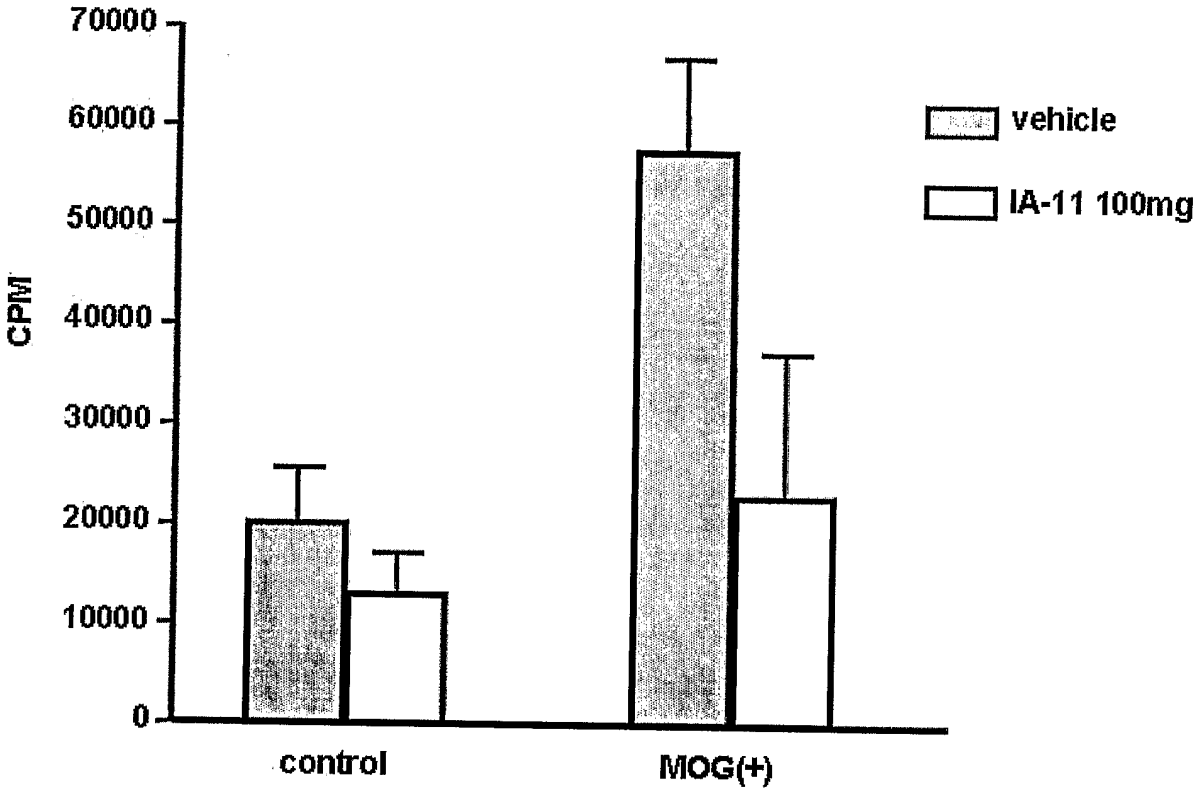

Mean clinical score
Days
vehicle
IA-11 100mg/kg
IA-11 20mg/kg
Mean clinical score
Days
vehicle
IB-29 20mg
IB-29 100mg

FIG. 6


70000
60000
50000
40000
30000
20000
10000
0
CPM
control
MOG(+)
vehicle
IA-11 100mg

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2008/000195

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 5
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 5 pertain to methods for treatment of the human or animal body by therapy, as well as diagnostic methods, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of PCT and Rile 39.1(iv) of the Regulations under the PCT, to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2008/000195

A. CLASSIFICATION OF SUBJECT MATTER

C07D 235/18(2006.01)i, C07D 235/26(2006.01)i, C07D 401/12(2006.01)i, C07D 413/12(2006.01)i, A61K 31/4164(2006.01)i, A61P 37/00(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 8 C07D 401/04, 471/04, A61K 31/541, A61P 37/00

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

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

eKIPASS(KIPO internal), PubMed, JPO, USPTO

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 20040116416 A1(STEFAN LAUFER et al.) 17 June 2004 See Abstract, Formula I of claim 1, Paragraphs 0084-0085.	1-4, 6-8
A	US 4419516 A(PETER H. L. WEI. AND STANLEY C. BELL) 6 December 1983 See Column 1 line 8- column 2 line 12, claim 1.	1-4, 6-8
A	KR 100528760 B1(F. HOFFMANN-LA ROCHE AG) 15 November 2005 See Abstract, Formula I on page 2, pages 1-19.	1-4, 6-8

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 APRIL 2008 (17.04.2008)	**17 APRIL 2008 (17.04.2008)**

Name and mailing address of the ISA/KR

Korean Intellectual Property Office
Government Complex-Daejeon, 139 Seonsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer

PARK, Yeong Gwan

Telephone No. 82-42-481-8407

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2008/000195

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO0200242279A1	30.05.2002
		ZA200303690A	13.08.2004