Gad, H. *et al. Nature* (2014), 508, 215-221 and Saleh, A. *et al. Journal of Pharmaceutical and Biomedical Analysis* (2015), 104, 1, describe certain 2,4-diaminopyrimidines as MTH1 inhibitors. However, there is nothing that suggests that the compounds are useful for treatment of inflammatory or auto-immune diseases.

International patent application WO 2013/066839 discloses certain 6-aryl-2,4-diaminopyrimidines, which may be useful in the treatment of cancer.

Chinese patent application CN104288170 describes the natural product echinacoside as an inhibitor of MTH1. However this compound is a sugar derivative and not a pyrimidine

Kambe, T. *et al. Journal of the American Chemical Society* (2014), 136, 10777 demonstrate a tetrazole-based MTH1 ligand.

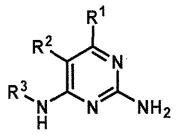
Summary

In autoimmune conditions and after organ transplantation, it is vital to eliminate the activated auto-reactive lymphocytes while preferably preserving their normal counterparts. Inhibiting MTH1 activity will kill the activated lymphocytes and thus reduce destructive inflammation. It should therefore be a promising novel therapy for autoimmunity and organ rejection, either as monotherapy or in combination with other drugs (e.g. cortisone) that are currently on the market.

We have observed that silencing the enzymatic activity of MTH1 in human lymphocytes results in selective killing of activated lymphocytes. Resting lymphocytes are not affected by the treatment. The present disclosure aims at providing a new treatment option for autoimmune conditions and transplantation patients through pharmacologic inhibition of MTH1. Diseases which may benefit from this treatment include rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, ulcerous colitis, multiple sclerosis, lymphoproliferative diseases (e.g. those caused by Epstein Barr virus and cytomegalovirus), rejection after organ transplantation, Wegener' granulomatosus, psoriasis, Mb Bechterews, Behcets disease, Guillain Barre, dermatomyositis, myositis, polymyositis, primary biliary cirrhosis, anti-phospholipid syndrome, autoimmune hepatitis, autoimmune cardiomyopathy, alopecia areata, atherosclerosis, type 1 diabetes, autoimmune

uveitis, Goodpasteure's syndrome, Graves' disease, Hashimotos disease, mixed connective tissue disease, myasthenia gravis, pemphigus vulgaris, pernicious anemia, Sjögren's syndrome, giant cell arteritis, ulcerative colitis, vasculitis, Churg–Strauss syndrome, postpolio syndrome, idiopathic thrombocytopenic purpura, Peyronie disease and Dupuytren's contracture.

In one aspect, there is provided the use of a compound of formula I,

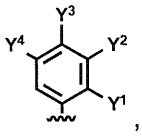


(I)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 represents

(i) , or

(ii) a 6-membered heteroaryl substituted by one or more groups selected from Y^5, or

(iii) a 5- to 10-membered monocyclic or bicyclic heteroaryl connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl, which heteroaryl is optionally substituted by one or more groups selected from Y^5, or

(iv) -ethynyl-Y^6;

R^2 represents hydrogen, halogen, -CN or C_{1-3}alkyl optionally substituted by one or more fluoro; and

R^3 represents -X-L-J, -C_{1-12}alkyl optionally substituted by one or more Z^1 or heterocycloalkyl optionally substituted by one or more groups selected from Z^2; or

R^1 represents

(v) a 3- to 8-membered nonaromatic ring, which ring optionally contains one or two heteroatoms and/or one or two double bonds, and which ring is optionally substituted by one or more groups selected from Y^7;

R^2 represents hydrogen, halogen, -CN or C_{1-3}alkyl optionally substituted by one or more fluoro; and

R^3 represents -X-L-J; or
R^1 is as defined herein above; and

R^2 and R^3 are linked together to form, along with the atoms to which they are attached, a 5- to 8-membered non-aromatic ring, wherein the link formed by R^2 and R^3 is optionally substituted by one or more groups selected from Z^3 and optionally substituted by -X-L-J;

X represents -C_{1-6}alkylene-, optionally substituted by one or more T^1, or -$(C(R^A)_2)_p$-C_{2-5}heterocycloalkylene-$(C(R^A)_2)_q$-, where the heterocycloalkylene is optionally substituted by one or more T^2;

L represents a single bond or -L^1-L^2-;
L^1 represents -$N(R^B)$-, -O-, -$S(O)_m$-, -$C(O)N(R^C)$-, -$N(R^D)C(O)$-, -$S(O)_nN(R^E)$-, -$N(R^F)S(O)_n$- or -$N(R^G)C(O)N(R^H)$-;
L^2 represents a single bond or -C_{1-6}alkylene-;

J represents

(i) a 6- to 10-membered aryl optionally substituted by D^1 and optionally substituted by one or more groups selected from R^X, or

(ii) a 5- to 11-membered monocyclic or bicyclic heteroaryl ring, which heteroaryl contains 1 to 3 nitrogen atoms, and/or one oxygen atom and/or one or two sulfur atoms and which heteroaryl is optionally substituted by D^2 and optionally substituted by one or more groups selected from R^Y;

Y^1 represents hydrogen, halogen, -CN, R^a, -A-$C(Q)R^b$, -A-$C(Q)N(R^c)R^d$, -A-$C(Q)OR^e$, -A-$S(O)_nR^f$, -A-$S(NR^g)(O)R^h$, -A-$S(O)_nN(R^i)R^j$, -A-$S(O)_nOR^k$, -$B(OR^l)_2$, -N_3, -NO_2, -OR^m -SR^n;

Y^2, Y^3 and Y^4 each independently represents hydrogen, halogen, R^a, -A-$C(Q)R^b$, -A-$C(Q)N(R^c)R^d$, -A-$C(Q)OR^e$, -A-$S(O)_nR^f$, -A-$S(NR^g)(O)R^h$, -A-$S(O)_nN(R^i)R^j$, -A-$S(O)_nOR^k$, -$B(OR^l)_2$, -N_3, -NO_2, -OH, -OR^m or -SR^n;

Y^5 represents halogen, R^a, -A-C(Q)R^b, -A-C(Q)N(R^c)R^d, -A-C(Q)OR^e, -A-S(O)$_n$$R^f$, -A-S(N$R^g$)(O)$R^h$, -A-S(O)$_n$N($R^i$)$R^j$, -A-S(O)$_nOR^k$, -B(O$R^l$)$_2$, $-N_3$, $-NO_2$, -OH, -OR^m or -SR^n;

Y^6 represents aryl or heteroaryl, both optionally substituted by one or more groups selected from halogen, -CN, R^a, -A-C(Q)R^b, -A-C(Q)N(R^c)R^d, -A-C(Q)OR^e, -A-S(O)$_n$$R^f$, -A-S(N$R^g$)(O)$R^h$, -A-S(O)$_n$N($R^i$)$R^j$, -A-S(O)$_nOR^k$, -B(O$R^l$)$_2$, $-N_3$, $-NO_2$, -OH, -OR^m and -SR^n;

Y^7 represents halogen, R^a, -A-C(Q)R^b, -A-C(Q)N(R^c)R^d, -A-C(Q)OR^e, -A-S(O)$_n$$R^f$, -A-S(O)$_n$N($R^i$)$R^j$, -A-S(O)$_nOR^k$, -OH, -O$R^m$, or Q;

Q represents =O, =S, =NR^o, =NN(R^p)R^q, =N(OR^r), =NS(O)$_2$N(R^s)R^t or $=C(H)NO_2$;

A represents a single bond, -N(R^I)-, -C(Q)N(R^J)- or -O-;

each R^a, R^f, R^h and R^m independently represents C_{1-6} alkyl optionally substituted by one or more groups selected from W^1, heterocycloalkyl optionally substituted by one or more groups selected from W^2 or aryl or heteroaryl both optionally substituted by one or more groups selected from W^3;

each R^b, R^c, R^d, R^e, R^g, R^i, R^j, R^k, R^l, R^o, R^p, R^q, R^r, R^s and R^t independently represents hydrogen, C_{1-6} alkyl optionally substituted by one or more groups selected from W^1, heterocycloalkyl optionally substituted by one or more groups selected from W^2 or aryl or heteroaryl both optionally substituted by one or more groups selected from W^3; or

any two R^c and R^d, R^i and R^j, R^p and R^q and/or R^s and R^t are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two further heteroatoms and which ring optionally is substituted by one or more groups selected from W^2, C_{1-3}alkyl optionally substituted by one or more groups selected from W^1, and =O; or

two R^l are linked together to form, along with the boron, and the oxygen atoms to which they are attached, a 5- to 8-membered heterocyclic ring, which ring optionally contains one or more further heteroatoms and which ring optionally is

substituted by one or more groups independently selected from halogen, C_{1-3}alkyl optionally substituted by one or more halogens, and =O;

W^1 represents halogen, -CN, $-A^1-C(O)R^{b1}$, $-A^1-C(O)N(R^{c1})R^{d1}$, $-A^1-C(O)OR^{e1}$, $-A^1-S(O)_nR^{f1}$, $-A^1-S(O)_nOR^{g1}$, $-N(R^{h1})R^{i1}$,$-OR^{j1}$ or =O;

W^2 represents halogen, -CN, R^{a1}, $-A^1-C(O)R^{b1}$, $-A^1-C(O)N(R^{c1})R^{d1}$, $-A^1-C(O)OR^{e1}$, $-A^1-S(O)_nR^{f1}$, $-A^1-S(O)_nOR^{g1}$, $-N(R^{h1})R^{i1}$, $-OR^{j1}$ or =O;

W^3 represents halogen, -CN, R^{a1}, $-A^1-C(O)R^{b1}$, $-A^1-C(O)N(R^{c1})R^{d1}$, $-A^1-C(O)OR^{e1}$, $-A^1-S(O)_nR^{f1}$, $-A^1-S(O)_nOR^{g1}$, $-OR^{j1}$, $-A^1-S(NR^{k1})(O)R^{l1}$, $-A^1-S(O)_nN(R^{m1})R^{n1}$, $-N_3$, $-NO_2$, $-SR^{o1}$ or =O;
A^1 represents a single bond, $-N(R^K)-$ or -O-;

each R^{a1}, R^{f1} and R^{l1} independently represents C_{1-6} alkyl optionally substituted by one or more fluoro;

each R^{b1}, R^{c1}, R^{d1}, R^{e1}, R^{g1}, R^{h1}, R^{i1}, R^{j1}, R^{k1}, R^{m1}, R^{n1} and R^{o1} independently represents hydrogen or C_{1-6} alkyl optionally substituted by one or more fluoro; or

any two R^{c1} and R^{d1}, R^{h1} and R^{i1} and/or R^{m1} and R^{n1} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups selected from fluoro, C_{1-3}alkyl optionally substituted by one or more fluoro, and =O;

Z^1 represents halogen, -CN, $-A^2-C(Q^1)R^{b2}$, $-A^2-C(Q^1)N(R^{c2})R^{d2}$, $-A^2-C(Q^1)OR^{e2}$, $-A^2-S(O)_nR^{f2}$, $-A^2-S(O)_nOR^{g2}$, $-A^2-S(NR^{h2})(O)R^{i2}$, $-A^2-S(O)_nN(R^{j2})R^{k2}$, $-N(R^{l2})R^{m2}$, $-OR^{n2}$, $-SR^{o2}$ or heterocycloalkyl optionally substituted by one or more groups selected from W^5;

Z^2 represents halogen, -CN, R^{a2}, $-A^2-C(Q^1)R^{b2}$, $-A^2-C(Q^1)N(R^{c2})R^{d2}$, $-A^2-C(Q^1)OR^{e2}$, $-A^2-S(O)_nR^{f2}$, $-A^2-S(O)_nOR^{g2}$, $-A^2-S(NR^{h2})(O)R^{i2}$, $-A^2-S(O)_nN(R^{j2})R^{k2}$, $-N(R^{l2})R^{m2}$, $-OR^{n2}$ or $=Q^1$;

Z^3 represents R^{a2} or $=Q^1$;

Q^1 represents =O, =S, $=NR^{p2}$, $=NN(R^{q2})R^{r2}$, $=N(OR^{s2})$, $=NS(O)_2N(R^{t2})R^{u2}$ or $=C(H)NO_2$;

A^2 represents a single bond, $-N(R^L)-$, $-C(Q^1)N(R^M)-$ or -O-;

each R^{a2}, R^{f2}, R^{i2}, R^{n2} and R^{o2} independently represents C_{1-6}alkyl optionally substituted by one or more groups selected from W^4 or heterocycloalkyl optionally substituted by one or more groups selected from W^5;

R^{m2} represents C_{2-6}alkyl optionally substituted by one or more groups selected from W^4;

each R^{b2}, R^{c2}, R^{d2}, R^{e2}, R^{g2}, R^{h2}, R^{j2}, R^{k2}, R^{l2}, R^{p2}, R^{q2}, R^{r2}, R^{s2}, R^{t2} and R^{u2} independently represents hydrogen, C_{1-6}alkyl optionally substituted by one or more groups selected from W^4, heterocycloalkyl optionally substituted by one or more groups selected from W^5; or

any two R^{c2} and R^{d2}, R^{j2} and R^{k2}, R^{l2} and R^{m2}, R^{q2} and R^{r2} and/or R^{t2} and R^{u2} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two further heteroatoms and which ring optionally is substituted by one or more groups selected from W^5, C_{1-3}alkyl optionally substituted by one or more groups selected from W^4, and =O;

W^4 represents halogen, -CN, $-A^3-C(O)R^{b3}$, $-A^3-C(O)N(R^{c3})R^{d3}$, $-A^3-C(O)OR^{e3}$, $-A^3-S(O)_nR^{f3}$, $-A^3-S(O)_nOR^{g3}$, $-OR^{h3}$, =O or W^6;

W^5 represents halogen, -CN, R^{a3}, $-A^3-C(O)R^{b3}$, $-A^3-C(O)N(R^{c3})R^{d3}$, $-A^3-C(O)OR^{e3}$, $-A^3-S(O)_nR^{f3}$, $-A^3-S(O)_nOR^{g3}$, $-OR^{h3}$, =O or W^6;

W^6 represents phenyl or heteroaryl, both optionally substituted by one or more groups selected from halogen and R^{a3};

A^3 represents a single bond, $-N(R^L)-$ or -O-;

each R^{a3} and R^{f3} independently represents C_{1-6} alkyl optionally substituted by one or more fluoro;

each R^{b3}, R^{c3}, R^{d3}, R^{e3}, R^{g3} and R^{h3} independently represents hydrogen or C_{1-6}alkyl optionally substituted by one or more fluoro; or

R^{c3} and R^{d3} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatoms and which ring optionally is substituted by one or more groups selected from fluoro, C_{1-3}alkyl optionally substituted by one or more fluoro, and =O;

D^1 and D^2 represent R^{a4}, $-A^4-C(Q^2)R^{b4}$, $-A^4-C(Q^2)N(R^{c4})R^{d4}$, $-A^4-C(Q^2)OR^{e4}$, $-A^4-S(O)_nR^{f4}$, $-A^4-S(O)_nC(O)R^{g4}$, $-A^4-S(NR^{h4})(O)R^{i4}$, $-A^4-S(O)_nN(R^{j4})R^{k4}$, $-A^4-S(O)_nOR^{l4}$, $-B(OR^{m4})_2$, $-N_3$, $-N(R^{n4})R^{o4}$, -N(H)CN, $-NO_2$, $-ONO_2$, $-OR^{p4}$, $-SR^{q4}$ or, when J is partly aromatic, $=Q^2$;

Q^2 represents =O, =S, $=NR^{r4}$, $=NN(R^{s4})R^{t4}$, $=N(OR^{u4})$, $=NS(O)_2N(R^{v4})R^{w4}$ or $=C(H)NO_2$;

A^4 represents a single bond, $-N(R^M)-$, $-C(Q)N(R^N)-$ or -O-;

each R^X and R^Y independently represent halogen, -CN, R^{a4}, $-N(R^{n4})R^{o4}$, $-NO_2$, $-OR^{p4}$ or =O;

R^{c4} represents hydrogen, R^{a4}, $-C(O)OR^{e4}$, $-S(O)_nR^{f4}$, $-S(O)_nN(R^{j4})R^{k4}$, $-N(R^{n4})R^{o4}$ or $-OR^{p4}$;

each R^{a4}, R^{f4} and R^{i4} independently represent C_{1-6}alkyl optionally substituted by one or more groups selected from G^1, heterocycloalkyl optionally substituted by one or more groups selected from G^2, aryl optionally substituted by one or more groups selected from G^3 or heteroaryl optionally substituted by one or more groups selected from G^4;

each R^{b4}, R^{d4}, R^{e4}, R^{g4}, R^{h4}, R^{j4}, R^{k4}, R^{l4}, R^{m4}, R^{n4}, R^{o4}, R^{p4}, R^{q4}, R^{r4}, R^{s4}, R^{t4}, R^{u4}, R^{v4} and R^{w4} independently represent hydrogen, C_{1-6}alkyl optionally substituted by one or more groups selected from G^1, heterocycloalkyl optionally substituted by one or more groups selected from G^2, aryl optionally substituted by one or more groups selected from G^3 or heteroaryl optionally substituted by one or more groups selected from G^4; or

any two R^{c4} and R^{d4}, R^{j4} and R^{k4}, R^{n4} and R^{o4}, R^{s4} and R^{t4} and/or R^{v4} and R^{w4} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one heteroatom and which ring optionally is substituted by one or more groups selected from fluoro, C_{1-3}alkyl optionally substituted by one or more fluoro, and =O; or

two R^{m4} are linked together to form, along with the boron, and the oxygen atoms to which they are attached, a 5- to 8-membered heterocyclic ring, which ring optionally contains one or more further heteroatoms and which ring optionally is substituted by one or more groups independently selected from halogen, C_{1-3}alkyl optionally substituted by one or more halogens, and =O;

each G^1 is independently selected from halogen, -CN, $-N(R^{b5})R^{c5}$, $-N(H)C(O)R^{d5}$, $-N(H)S(O)_nR^{h5}$, $-OR^{k5}$, $-S(O)_mR^{l2}$ or =O;

each G^2 is independently selected from halogen, R^{a5}, -CN, $-N(R^{b5})R^{c5}$, $-N(H)C(O)R^{d5}$, $-N(H)S(O)_nR^{h5}$, $-OR^{k5}$, $-S(O)_mR^{l2}$ or =O;

each G^3 and G^4 are independently selected from halogen, -CN, R^{a5}, $-N(R^{b5})R^{c5}$, $-A^5-C(O)R^{d5}$, $-A^5-C(O)N(R^{e5})R^{f5}$, $-A^5-C(O)OR^{g5}$, $-A^5-S(O)_nR^{h5}$, $-A^5-S(O)_nN(R^{i5})R^{j5}$, $-OR^{k5}$ or =O;

A^5 represents a single bond or -N(H)-;

R^{a5} represents C_{1-6} alkyl optionally substituted by one or more halogens;

each R^{b5}, R^{c5}, R^{d5}, R^{e5}, R^{f5}, R^{g5}, R^{h5}, R^{i5}, R^{j5}, R^{k5} and R^{l5} independently represents hydrogen or C_{1-6} alkyl optionally substituted by one or more halogens; or

any two R^{b5} and R^{c5}, R^{e5} and R^{f5} and/or R^{i5} and R^{j5} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups selected from halogen, C_{1-3}alkyl optionally substituted by one or more halogens, and =O;

each R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, R^K, R^L, R^M and R^N independently represents hydrogen or C_{1-3} alkyl optionally substituted by one or more fluoro;

T^1 represents halogen, -CN, $-N(R^{b6})R^{c6}$ or $-OR^{d6}$;

T^2 represents halogen, -CN, R^{a6}, $-OR^{d6}$ or =O;

each R^{a6} independently represents C_{1-6}alkyl optionally substituted by one or more halogens;

each R^{b6}, R^{c6} and R^{d6} independently represents hydrogen or C_{1-6}alkyl optionally substituted by one or more halogens; or

R^{b6} and R^{c6} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring;

each p and q independently represents 0, 1 or 2, provided that the sum of p and q is 0, 1 or 2;

each m independently represents 0, 1 or 2;

each n independently represents 1 or 2;
provided that when X represents $-CH_2CH_2-$, L represents $-L^1-L^2-$, L^1 represents -N(H)- or -N(Me)-, L^2 represents a single bond and J represents 4-pyrimidinyl, and said 4-pyrimidinyl is unsubstituted or substituted with $-CH_3$, $-NH_2$ or $-N(H)CH_2CH(CH_3)_2$, then R^1 does not represent phenyl, 3-chlorophenyl, 3,5-dichlorophenyl or 5-chloro-2-methoxyphenyl, and

provided that formula I does not represent
(*S*)-*N*^{4}-(1-(2,4-difluorophenyl)ethyl)-6-(pyrazolo[1,5-*a*]pyrimidin-3-yl)pyrimidine-2,4-diamine,
in the manufacture of a medicament for treating autoimmune diseases and inflammatory conditions.

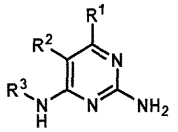
In another aspect, there is provided a combination product comprising:
(A) a compound as defined herein, or a pharmaceutically acceptable salt thereof; and
(B) one or more other therapeutic agent(s) that is/are useful in the treatment of a disease as defined herein,
wherein each one of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

Brief description of the drawings

Figure 1. An MTH1 inhibitor (example 297) selectively kills activated T-lymphocytes while unactivated T-lymphocytes are unaffected.

Detailed description of the Invention

There is provided a compound of formula I,

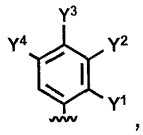


(I)

or a pharmaceutically acceptable salt thereof,

for use in the treatment of autoimmune diseases and inflammatory conditions, wherein:

R^1 represents

(i) , or

(ii) a 6-membered heteroaryl substituted by one or more groups selected from Y^5, or

(iii) a 5- to 10-membered monocyclic or bicyclic heteroaryl connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl, which heteroaryl is optionally substituted by one or more groups selected from Y^5, or

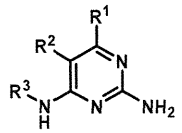
(iv) -ethynyl-Y^6;

R^2 represents hydrogen, halogen, -CN or C_{1-3}alkyl optionally substituted by one or more fluoro; and

R^3 represents -X-L-J, -C_{1-12}alkyl optionally substituted by one or more Z^1 or heterocycloalkyl optionally substituted by one or more groups selected from Z^2; or

Claims

1. The use of a compound of formula I,

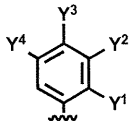


(I)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 represents

(i) , or

(ii) a 6-membered heteroaryl substituted by one or more groups selected from Y^5, or

(iii) a 5- to 10-membered monocyclic or bicyclic heteroaryl connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl, which heteroaryl is optionally substituted by one or more groups selected from Y^5, or

(iv) -ethynyl-Y^6;

R^2 represents hydrogen, halogen, -CN or C_{1-3}alkyl optionally substituted by one or more fluoro; and

R^3 represents -X-L-J, -C_{1-12}alkyl optionally substituted by one or more Z^1 or heterocycloalkyl optionally substituted by one or more groups selected from Z^2; or

R^1 represents

(v) a 3- to 8-membered nonaromatic ring, which ring optionally contains one or two heteroatoms and/or one or two double bonds, and which ring is optionally substituted by one or more groups selected from Y^7;

R^2 represents hydrogen, halogen, -CN or C_{1-3}alkyl optionally substituted by one or more fluoro; and

R^3 represents -X-L-J; or

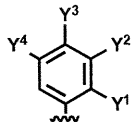
R^1 is as defined herein above; and

and said 4-pyrimidinyl is unsubstituted or substituted with $-CH_3$, $-NH_2$ or $-N(H)CH_2CH(CH_3)_2$, then R^1 does not represent phenyl, 3-chlorophenyl, 3,5-dichlorophenyl or 5-chloro-2-methoxyphenyl, and

provided that formula I does not represent (*S*)-*N*^{4}-(1-(2,4-difluorophenyl)ethyl)-6-(pyrazolo[1,5-*a*]pyrimidin-3-yl)pyrimidine-2,4-diamine, in the manufacture of a medicament for treating autoimmune diseases and inflammatory conditions.

2. The use as claimed in Claim 1 wherein

R^1 represents

(i) , or

(ii) a 6-membered heteroaryl substituted by one or more groups selected from Y^5, or

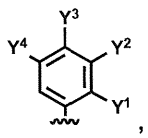
(iii) a 5- to 10-membered monocyclic or bicyclic heteroaryl connected to the pyrimidine of formula I via a carbon atom of the heteroaryl ring, which heteroaryl ring is optionally substituted by one or more groups selected from Y^5;

R^2 represents hydrogen or C_{1-3}alkyl optionally substituted by one or more fluoro; and

R^3 represents -X-L-J, $-C_{1-12}$alkyl optionally substituted by one or more groups selected from Z^1 or heterocycloalkyl optionally substituted by one or more groups selected from Z^2.

3. The use as claimed in Claim 2 wherein

R^1 represents

,

at least one of Y^1, Y^2, Y^3 and Y^4 is other than hydrogen;

R^2 represents hydrogen or methyl;

R^3 represents -X-L-J or $-C_{1-6}$alkyl optionally substituted by one or more Z^1 or heterocycloalkyl optionally substituted by one or more Z^2;

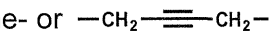
Y^1 represents hydrogen, halogen, -CN, R^a or $-OR^m$; and

Y^2, Y^3 and Y^4 each independently represent hydrogen, halogen, R^a, -A-C(Q)R^b, -C(Q)N(R^c)R^d, -C(Q)OR^e, -A-S(O)$_n$$R^f$, -S(O)$_n$N($R^i$)$R^j$, -OH or -O$R^m$.

4. The use as claimed in Claim 3 wherein
at least two of Y^1, Y^2, Y^3 and Y^4 are other than hydrogen.

5. The use as claimed in Claim 4 wherein
Y^3 and Y^4 are hydrogen; and
Y^1 and Y^2 are independently selected from fluoro, chloro, -Me or -CF_3.

6. The use as claimed in any one of Claims 1 to 5 wherein
R^3 represents -X-L-J.

7. The use as claimed in Claim 6 wherein
X represents $-CH_2-$, $-CH_2CH_2-$, -CH(Me)-, $-C(Me)_2-$, $-CH_2CH(Me)-$, $-CH(Me)CH_2-$, $-CH_2CH_2CH_2-$, $-CH(Me)CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, -cyclopropylene- or .

8. The use as claimed in Claim 7
wherein X represents $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or -cyclopropylene-.

9. The use as claimed in any one of Claims 1 to 8 wherein
L represents $-L^1-L^2-$.

10. The use as claimed in Claim 9 wherein
L^1 represents -N(H)-, -O-, $-SO_2-$, -C(O)N(H)-, $-SO_2N(H)-$ or -N(H)C(O)N(H)-.

11. The use as claimed in Claim 10 wherein

L^1 represents -N(H)-, -O- or -N(H)C(O)N(H)-.

12. The use as claimed in any one of Claims 1 to 11 wherein
L^2 represents a single bond.

13. The use as claimed in any one of Claims 1 to 8 wherein
L represents a single bond.

14. The use as claimed in any one of Claims 1 to 13 wherein
J represents phenyl optionally substituted by D^1 and optionally substituted by one or more groups selected from R^X.

15. The use as claimed in any one of Claims 1 to 13 wherein
J represents a 5- to 11-membered monocyclic or bicyclic heteroaryl ring, which ring contains 1 to 3 nitrogen atoms, and/or one oxygen atom and/or one or two sulfur atoms and which ring is optionally substituted by D^2 and optionally substituted by one or more groups selected from R^Y.

16. The use as claimed in any one of Claims 1 to 15, wherein the condition is selected from rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, ulcerous colitis, multiple sclerosis, lymphoproliferative diseases (e.g. those caused by Epstein Barr virus and cytomegalovirus), rejection after

organ transplantation, Wegener' granulomatosus, psoriasis, Mb Bechterews, Behcets disease, Guillain Barre, dermatomyositis, myositis, polymyositis, primary biliary cirrhosis, anti-phospholipid syndrome, autoimmune hepatitis, autoimmune cardiomyopathy, alopecia areata, atherosclerosis, type 1 diabetes, autoimmune uveitis, Goodpasteure's syndrome, Graves' disease, Hashimotos disease, mixed connective tissue disease, myasthenia gravis, pemphigus vulgaris, pernicious anemia, Sjögren's syndrome, giant cell arteritis, ulcerative colitis, vasculitis, Churg–Strauss syndrome, postpolio syndrome, idiopathic thrombocytopenic purpura, Peyronie disease and Dupuytren's contracture.

17. The use as claimed in Claim 16 wherein the condition is selected from the group consisting of rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis, rejection after organ transplantation and atherosclerosis.

18. The use as claimed in Claim 16, wherein the condition is psoriasis.

19. A combination product comprising:
(A) a compound as defined in any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof; and
(B) one or more other therapeutic agent(s) that is/are useful in the treatment of a disease as defined in any one of the Claims 1 to 18,
wherein each one of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

20. A combination product as claimed in Claim 19, wherein component (B) is selected from the group consisting of glucocorticoids, TNF-alpha inhibitors, anti-CD20, immunosupressants or antimetabolites.