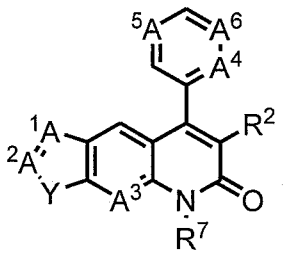
applied treatment regimens (e.g. mycophenolate mofetil, cyclophosphamide, cyclosporine A, azathioprine, etc.) resulting in a general suppression of lymphocytes, thus increasing the risk for opportunistic infections. Furthermore, longterm treatment often results in side effects reducing the overall compliance (e.g. skin atrophy and enhanced risk of osteoporosis with glucocorticoid treatment, increased risk of skin cancer and rhabdomyolysis upon topical tacrolimus treatment, nausea and vomitting with cyclophosphamide and cyclosporine A). Recent approvals of medicaments for the treatment of such diseases include several biologics (e.g. Alefacept, Natalizumab, Adalimumab, Ustekinumab, Belimumab), which display a potential for a general side effect profile known for such drugs like sensitization, anaphylactic shock, resistance, and again often showed an enhanced risk for opportunistic infections.

There is, therefore, a need for new small molecule medicaments which, compared with the aforementioned therapeutics, are particularly more selective towards specific cell subsets of the immune system and particularly avoid the aforementioned adverse effects, in particular in the therapy of the above medical conditions.

Summary

In one aspect, there is provided a compound of the general formula (III) or a salt, solvate or prodrug thereof,

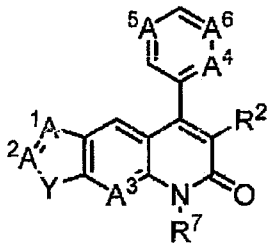


(III)

wherein A^1 is selected from the group consisting of N and C-R^8; A^2 is selected from the group consisting of N and C-R^3; A^3 is selected from the group consisting of N and C-R^9; A^4 and A^5 and A^6 are independently selected from the group consisting of N and C-R^1; R^1 is selected from the group consisting of hydrogen, (C_1-C_3)alkyl, halogen, (C_1-C_3)alkoxy and (C_1-C_3)haloalkyl; R^2 is selected from the group consisting of hydrogen, halogen and (C_1-C_3)alkyl; R^3 is selected from the group consisting of hydrogen, (C_1-C_3)alkyl, NR^4R^5, (C_1-C_3)alkyl-NR^4R^5 and cyano; wherein R^4 and R^5 are independently selected from the group consisting of hydrogen, (C_3-C_5)cycloalkyl, (C_3-C_5)heterocycloalkyl, (C_1-C_3)alkyl, or R^4 and R^5 together with the nitrogen atom to which they are attached form a 5- to 7-membered heterocyclic ring optionally comprising in addition to the aforementioned nitrogen atom a further heteroatom group selected from the group consisting of O and NR^6, wherein R^6 is selected from the group

consisting of hydrogen, methyl, acetyl and formyl; Y is selected from the group consisting of O and S; R^7 is selected from the group consisting of hydrogen, and $(C_1$-$C_3)$alkyl; R^8 is selected from the group consisting of $(C_1$-$C_4)$alkyl, $(C_3$-$C_5)$cycloalkyl, and $(C_3$-$C_5)$heterocycloalkyl; and R^9 is selected from the group consisting of hydrogen, $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$alkoxy, wherein said prodrug is selected from the group consisting of sulfenyl derivatives, sulfuryloxymethyl derivatives, phosphoryloxymethyl derivatives, or acyloxymethyl derivatives of the lactam or lactim forms of the compounds of the general formula (III).

In another aspect, there is provided a compound of the general formula (III) or a salt, or solvate thereof,



(III)

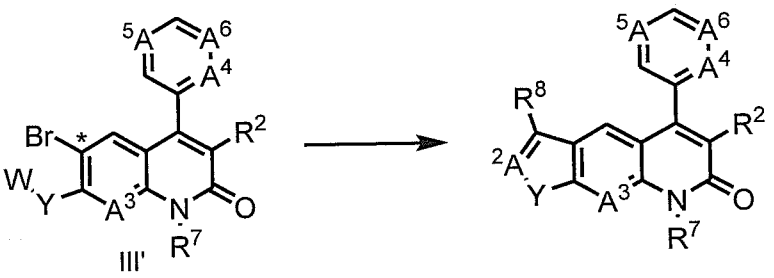
wherein A^1 is selected from the group consisting of N and C-R^8; A^2 is selected from the group consisting of N and C-R^3; A^3 is selected from the group consisting of N and C-R^9; A^4 and A^5 and A^6 are independently selected from the group consisting of N and C-R^1; R^1 is selected from the group consisting of hydrogen, $(C_1$-$C_3)$alkyl, halogen, $(C_1$-$C_3)$alkoxy and $(C_1$-$C_3)$haloalkyl; R^2 is selected from the group consisting of hydrogen, halogen and $(C_1$-$C_3)$alkyl; R^3 is selected from the group consisting of hydrogen, $(C_1$-$C_3)$alkyl, NR^4R^5, $(C_1$-$C_3)$alkyl-NR^4R^5 and cyano; wherein R^4 and R^5 are independently selected from the group consisting of hydrogen, $(C_3$-$C_5)$cycloalkyl, $(C_3$-$C_5)$heterocycloalkyl, $(C_1$-$C_3)$alkyl, or R^4 and R^5 together with the nitrogen atom to which they are attached form a 5- to 7-membered heterocyclic ring optionally comprising in addition to the aforementioned nitrogen atom a further heteroatom group selected from the group consisting of O and NR^6, wherein R^6 is selected from the group consisting of hydrogen, methyl, acetyl and formyl; Y is selected from the group consisting of O and S; R^7 is selected from the group consisting of hydrogen, and $(C_1$-$C_3)$alkyl; R^8 is selected from the group consisting of $(C_1$-$C_4)$alkyl, $(C_3$-$C_5)$cycloalkyl, and $(C_3$-$C_5)$heterocycloalkyl; and R^9 is selected from the group consisting of hydrogen, $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$alkoxy.

In another aspect, there is provided a pharmaceutical composition comprising a compound as disclosed herein and a pharmaceutically acceptable carrier or diluent.

In a further aspect, there is provided a compound as disclosed herein for use in the treatment of diseases or medical conditions.

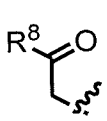
In another aspect, there is provided the use of a compound as disclosed herein for the manufacture of a pharmaceutical composition for treating diseases or medical conditions.

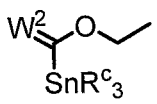
In yet another aspect, there is provided a method for producing a compound according to the general formula III as defined herein, wherein A^1 is C-R^8 and A^2 is selected from the group consisting of CH and N; and wherein said method is characterized by the following conversion:



III'

wherein A^3, A^4, A^5, A^6, R^2, R^7, R^8 and Y are as defined in claim 1;

W is selected from the group consisting of  and , wherein R^8 is as defined above, W^2 is selected from the group consisting of CH_2, $CH\text{-}CH_3$, $C(CH_3)_2$, $CH\text{-}CH_2\text{-}CH_3$, $C(CH_3)\text{-}CH_2\text{-}CH_3$, $CH\text{-}CH(CH_3)\text{-}CH_3$, and $CH\text{-}CH_2\text{-}CH_2\text{-}CH_3$, and said method further comprises the step of transition metal mediated intramolecular alkylation at the position marked with an asterisk in the above formula III'; or W is hydrogen and said method further comprises transition metal mediated acylation at the position marked with an asterisk in the above formula III' using



,

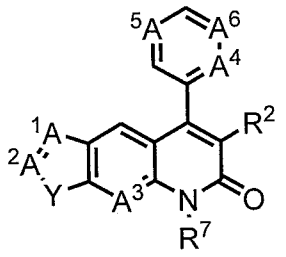
wherein W^2 is as defined above and R^c is $(C_1\text{-}C_4)$alkyl; followed by cyclization using hydroxylamine.

Detailed Description of the invention

It has now been found that such a small molecule medicament can be represented by Kv1.3 inhibitors, which, compared with the aforementioned therapeutics, are particularly more selective towards Kv1.3^{high} phenotype cells, particularly class-switched memory B-cells and/or effector memory T-cells which are of the Kv1.3^{high} phenotype, and particularly avoid the aforementioned adverse effects, in particular in the therapy of the above medical conditions.

Embodiments of the present invention are detailed in the following items:

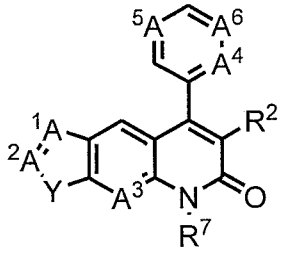
1. A compound of the general formula (III) or a salt, solvate or prodrug thereof,



III

Claims

1. A compound of the general formula (III) or a salt, solvate or prodrug thereof,



(III)

wherein

A^1 is selected from the group consisting of N and C-R^8;

A^2 is selected from the group consisting of N and C-R^3;

A^3 is selected from the group consisting of N and C-R^9;

A^4 and A^5 and A^6 are independently selected from the group consisting of N and C-R^1;

R^1 is selected from the group consisting of hydrogen, (C_1-C_3)alkyl, halogen, (C_1-C_3)alkoxy and (C_1-C_3)haloalkyl;

R^2 is selected from the group consisting of hydrogen, halogen and (C_1-C_3)alkyl;

R^3 is selected from the group consisting of hydrogen, (C_1-C_3)alkyl, NR^4R^5, (C_1-C_3)alkyl-NR^4R^5 and cyano;

wherein R^4 and R^5 are independently selected from the group consisting of hydrogen, (C_3-C_5)cycloalkyl, (C_3-C_5)heterocycloalkyl, (C_1-C_3)alkyl, or R^4 and R^5 together with the nitrogen atom to which they are attached form a 5- to 7-membered heterocyclic ring optionally comprising in addition to the aforementioned nitrogen atom a further heteroatom group selected from the group consisting of O and NR^6, wherein R^6 is selected from the group consisting of hydrogen, methyl, acetyl and formyl;

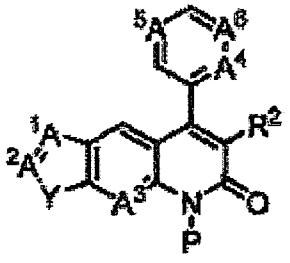
Y is selected from the group consisting of O and S;

R^7 is selected from the group consisting of hydrogen, and (C_1-C_3)alkyl;

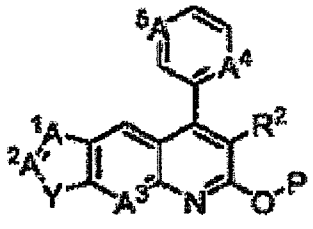
R^8 is selected from the group consisting of (C_1-C_4)alkyl, (C_3-C_5)cycloalkyl, and (C_3-C_5)heterocycloalkyl; and

R^9 is selected from the group consisting of hydrogen, $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$alkoxy, wherein said prodrug is selected from the group consisting of sulfenyl derivatives, sulfuryloxymethyl derivatives, phosphoryloxymethyl derivatives, or acyloxymethyl derivatives of the lactam or lactim forms of the compounds of the general formula (III).

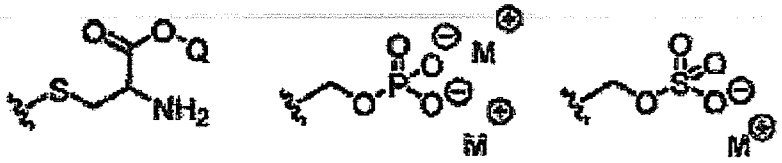
2. The compound according to claim 1, wherein the prodrug has either of the following formulae:



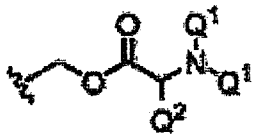
or,



wherein
P is



or



and wherein

Q, Q_1 and Q_2 are each independently selected from the group consisting of H and $(C_1$-$C_3)$alkyl and M^+ is a cationic counterion.

3. A compound according to claim 1 or 2, or a salt, solvate or prodrug thereof, wherein if Y is O, at least one of A^1, A^2 or A^3 is N.

4. A compound according to claim 1 or 2, or a salt, solvate or prodrug thereof, wherein A^1 is C-R^8; A^2 is C-R^3; A^3 is C-R^9; and Y is O.

5. A compound according to any one of claims 1 to 4 or a salt, solvate or prodrug thereof, wherein

R^1 is selected from the group consisting of hydrogen, methyl, chloro, fluoro, methoxy, ethoxy and trifluoromethyl;

R^2 is selected from the group consisting of hydrogen, bromo and methyl;

R^3 is selected from the group consisting of hydrogen, methyl, morpholinyl, morpholinomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl and cyano;

R^7 is selected from the group consisting of hydrogen and methyl;

R^8 is selected from the group consisting of methyl, ethyl and cyclopropyl; and

R^9 is selected from the group consisting of hydrogen, methyl and methoxy.

6. A compound according to any one of claims 1 to 5 or a salt, solvate or prodrug thereof, wherein

A^1 is C-CH_3;

Y is O;

A^2 is selected from the group consisting of N and CH;

A^3 is selected from the group consisting of N and C-CH_3;

A^4 and A^5 and A^6 are independently selected from the group consisting of N and C-R^1;

R^1 is selected from the group consisting of hydrogen, methyl, chloro, fluoro and methoxy;

R^2 is selected from the group consisting of hydrogen, methyl and bromo; and

R^7 is selected from the group consisting of hydrogen and methyl.

7. A compound according to any one of claims 1, and 4 to 6 or a salt, solvate or prodrug thereof, wherein

A^1 is C-CH_3; A^2 is C-H; A^3 is C-CH_3; Y is O;

A^4 and A^5 and A^6 are independently selected from the group consisting of N and C-R^1;

R^1 is selected from the group consisting of hydrogen, methyl, chloro, fluoro and methoxy;

R^2 is selected from the group consisting of hydrogen, methyl and bromo; and

R^7 is selected from the group consisting of hydrogen and methyl.

8. A compound according to any one of claims 1 to 7 or a salt, solvate or prodrug thereof, wherein

A^4 and A^5 and A^6 are independently selected from the group consisting of N and CH; and

R^2 is selected from the group consisting of hydrogen and methyl.

9. A compound according to claim 1 or a salt, solvate or prodrug thereof, which is selected from the group consisting of

6-bromo-3,9-dimethyl-5-phenylfuro[3,2-g]quinolin-7(8H)-one,

6-bromo-5-(2-fluorophenyl)-3,9-dimethylfuro[3,2-g]quinolin-7(8H)-one,

6-bromo-3,9-dimethyl-5-(o-tolyl)furo[3,2-g]quinolin-7(8H)-one,

3,9-dimethyl-5-(o-tolyl)furo[3,2-g]quinolin-7(8H)-one,

5-(2-fluorophenyl)-3,6,9-trimethylfuro[3,2-g]quinolin-7(8H)-one,

3,6,9-trimethyl-5-phenylfuro[3,2-g]quinolin-7(8H)-one,

3,8,9-trimethyl-5-phenylfuro[3,2-g]quinolin-7(8H)-one,

6-bromo-3,8,9-trimethyl-5-phenylfuro[3,2-g]quinolin-7(8H)-one,

3,6,8,9-tetramethyl-5-phenylfuro[3,2-g]quinolin-7(8H)-one,

3,6,9-trimethyl-5-phenylisoxazolo[4,5-g]quinolin-7(8H)-one,

5-(2-chlorophenyl)-3,6,9-trimethylfuro[3,2-g]quinolin-7(8H)-one,

3,6,8-trimethyl-5-phenylfuro[2,3-b][1,8]naphthyridin-7(8H)-one,

3,9-dimethyl-5-phenylisoxazolo[4,5-g]quinolin-7(8H)-one,

3,6,8,9-tetramethyl-5-phenylisoxazolo[4,5-g]quinolin-7(8H)-one,

3,6,9-trimethyl-5-(pyridin-3-yl)furo[3,2-g]quinolin-7(8H)-one,

3,6,8,9-tetramethyl-5-(pyridin-3-yl)furo[3,2-g]quinolin-7(8H)-one,

3,6,8,9-tetramethyl-5-(pyridin-3-yl)isoxazolo[4,5-g]quinolin-7(8H)-one,

3,6,8,9-tetramethyl-5-(o-tolyl)furo[3,2-g]quinolin-7(8H)-one,

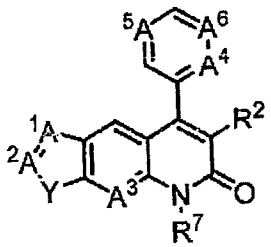
5-(2-chlorophenyl)-3,6,8,9-tetramethylfuro[3,2-g]quinolin-7(8H)-one,

5-(2-fluorophenyl)-3,6,8,9-tetramethylfuro[3,2-g]quinolin-7(8H)-one, and

5-(2-methoxypyridin-3-yl)-3,6,8,9-tetramethylfuro[3,2-g]quinolin-7(8H)-one,

or a salt, solvate or prodrug thereof.

10. A compound of the general formula (III) or a salt, or solvate thereof,



(III)

wherein

A^1 is selected from the group consisting of N and C-R^8;

A^2 is selected from the group consisting of N and C-R^3;

A^3 is selected from the group consisting of N and C-R^9;

A^4 and A^5 and A^6 are independently selected from the group consisting of N and C-R^1;

R^1 is selected from the group consisting of hydrogen, $(C_1$-$C_3)$alkyl, halogen, $(C_1$-$C_3)$alkoxy and $(C_1$-$C_3)$haloalkyl;

R^2 is selected from the group consisting of hydrogen, halogen and $(C_1$-$C_3)$alkyl;

R^3 is selected from the group consisting of hydrogen, $(C_1$-$C_3)$alkyl, NR^4R^5, $(C_1$-$C_3)$alkyl- NR^4R^5 and cyano;

wherein R^4 and R^5 are independently selected from the group consisting of hydrogen, $(C_3$-$C_5)$cycloalkyl, $(C_3$-$C_5)$heterocycloalkyl, $(C_1$-$C_3)$alkyl, or R^4 and R^5 together with the nitrogen atom to which they are attached form a 5- to 7-membered heterocyclic ring optionally comprising in addition to the aforementioned nitrogen atom a further heteroatom group selected from the group consisting of O and NR^6, wherein R^6 is selected from the group consisting of hydrogen, methyl, acetyl and formyl;

Y is selected from the group consisting of O and S;

R^7 is selected from the group consisting of hydrogen, and $(C_1$-$C_3)$alkyl;

R^8 is selected from the group consisting of $(C_1$-$C_4)$alkyl, $(C_3$-$C_5)$cycloalkyl, and $(C_3$-$C_5)$heterocycloalkyl; and

R^9 is selected from the group consisting of hydrogen, $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$alkoxy.

11. A pharmaceutical composition comprising a compound according to any of claims 1 to 10 and a pharmaceutically acceptable carrier or diluent.

12. A compound according to any one of claims 1 to 10 for use in the treatment of diseases or medical conditions.

13. Use of a compound according to any one of claims 1 to 10 for the manufacture of a pharmaceutical composition for treating diseases or medical conditions.

14. The compound according to claim 12, wherein said disease or medical condition is a disease or medical condition wherein the inhibition of the voltage-gated potassium channel Kv1.3 is beneficial.

15. The use according to claim 13, wherein said disease or medical condition is a disease or medical condition wherein the inhibition of the voltage-gated potassium channel Kv1.3 is beneficial.

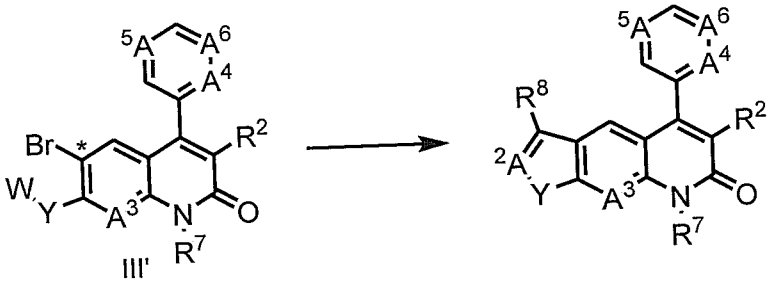
16. The compound according to claim 14, wherein said disease or medical condition is selected from the group consisting of psoriasis, psoriatric arthritis, autoimmune

thyroiditis, Hashimoto's disease, Grave's disease, rheumatoid arthritis, vitiligo, Crohn's disease, ulcerative colitis, inflammatory bowel disease, ankylosing spondylitis (Morbus Bechterew), periodontal disease, diabetes type I, multiple sclerosis, systemic lupus erythematosus, anti-glomerular basement membrane glomerulonephritis, rapidly progressive glomerulonephritis, advanced chronic renal failure, chronic kidney disease, renal fibrosis, uveitis, pars planitis, asthma, pemphigus foliaceus, inclusion body myositis, dermatomyositis, scleroderma, Behcet disease, atopic dermatitis, allergic and irritant contact dermatitis, Lichen planus, Sjögren's syndrome, Graft-versus-Host-Reaction, Host-versus-Graft-Reaction, transplant rejection, end-stage renal disease, vascularized composite allotransplantation rejection, alopecia areata, inflammatory bone resorption disease, anti-neutrophil cytoplasmic autoantibody-associated vasculitis, osteoarthritis, diseases associated with intimal hyperplasia, breast cancer, leukemia, human lung adenocarcinoma, cutaneous T-cell lymphoma, chronic lymphocytic leukemia, osteosarcoma, neuroblastoma, ovarian cancer and melanoma, neuroinflammatory disorders, neurodegeneration, HIV-1-associated neurocognitive disorders (HAND), microglia-induced oxidative stress in Alzheimer's disease, obesity, and insulin resistance, restenosis/neointimal hyperplasia, atherosclerosis (arteriosclerotic vascular disease or ASVD), acute coronary syndrome, acute ischemic stroke, hypertension.

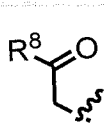
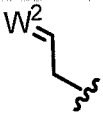
17. The use according to claim 15, wherein said disease or medical condition is selected from the group consisting of psoriasis, psoriatric arthritis, autoimmune thyroiditis, Hashimoto's disease, Grave's disease, rheumatoid arthritis, vitiligo, Crohn's disease, ulcerative colitis, inflammatory bowel disease, ankylosing spondylitis (Morbus Bechterew), periodontal disease, diabetes type I, multiple sclerosis, systemic lupus erythematosus, anti-glomerular basement membrane glomerulonephritis, rapidly progressive glomerulonephritis, advanced chronic renal failure, chronic kidney disease, renal fibrosis, uveitis, pars planitis, asthma, pemphigus foliaceus, inclusion body myositis, dermatomyositis, scleroderma, Behcet disease, atopic dermatitis, allergic and irritant contact dermatitis, Lichen planus, Sjogren's syndrome, Graft-versus-Host-Reaction, Host-versus-Graft-Reaction, transplant rejection, end-stage renal disease, vascularized composite allotransplantation rejection, alopecia areata, inflammatory bone resorption disease, anti-neutrophil cytoplasmic autoantibody-associated vasculitis, osteoarthritis, diseases associated with intimal hyperplasia, breast cancer, leukemia, human lung

adenocarcinoma, cutaneous T-cell lymphoma, chronic lymphocytic leukemia, osteosarcoma, neuroblastoma, ovarian cancer and melanoma, neuroinflammatory disorders, neurodegeneration, HIV-1-associated neurocognitive disorders (HAND), microglia-induced oxidative stress in Alzheimer's disease, obesity, and insulin resistance, restenosis/neointimal hyperplasia, atherosclerosis (arteriosclerotic vascular disease or ASVD), acute coronary syndrome, acute ischemic stroke, hypertension.

18. A method for producing a compound according to the general formula III defined in claim 1, wherein A^1 is C-R^8 and A^2 is selected from the group consisting of CH and N; and wherein said method is characterized by the following conversion:



wherein A^3, A^4, A^5, A^6, R^2, R^7, R^8 and Y are as defined in claim 1;

W is selected from the group consisting of  and , wherein R^8 is as defined above, W^2 is selected from the group consisting of CH_2, $CH\text{-}CH_3$, $C(CH_3)_2$, $CH\text{-}CH_2\text{-}CH_3$, $C(CH_3)\text{-}CH_2\text{-}CH_3$, $CH\text{-}CH(CH_3)\text{-}CH_3$, and $CH\text{-}CH_2\text{-}CH_2\text{-}CH_3$, and said method