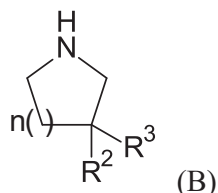


in the presence of a compound of formula (B)



and a base, wherein  $R^1$  to  $R^4$  and  $n$  are as defined herein.

In another aspect, there is provided a compound as defined herein for use as  
5 therapeutically active substance.

In another aspect, there is provided a pharmaceutical composition comprising a  
compound as defined herein and a therapeutically inert carrier.

In another aspect, there is provided use of a compound as defined herein for the  
preparation of medicaments for the treatment or prophylaxis of pain, neuropathic pain,  
10 atherosclerosis, age-related macular degeneration, diabetic retinopathy, glaucoma, diabetes  
mellitus, inflammation, inflammatory bowel disease, ischemia-reperfusion injury, acute  
liver failure, liver fibrosis, lung fibrosis, kidney fibrosis, systemic fibrosis, acute allograft  
rejection, chronic allograft nephropathy, diabetic nephropathy, glomerulonephropathy,  
cardiomyopathy, heart failure, myocardial ischemia/infarction, systemic sclerosis, thermal  
15 injury, burning, hypertrophic scars, keloids, gingivitis pyrexia, liver cirrhosis or tumors,  
regulation of bone mass, neurodegeneration, stroke, transient ischemic attack, uveitis,  
asthma, osteoporosis, psychiatric diseases, psychosis, oncology, encephalitis, malaria,  
immunological disorders, arthritis, gastrointestinal disorders, rheumatoid arthritis or  
allergy.

20 In another aspect, there is provided a compound as defined herein for use in the  
treatment or prophylaxis of pain, neuropathic pain, atherosclerosis, age-related macular  
degeneration, diabetic retinopathy, glaucoma, diabetes mellitus, inflammation,  
inflammatory bowel disease, ischemia-reperfusion injury, acute liver failure, liver fibrosis,  
lung fibrosis, kidney fibrosis, systemic fibrosis, acute allograft rejection, chronic allograft  
25 nephropathy, diabetic nephropathy, glomerulonephropathy, cardiomyopathy, heart failure,  
myocardial ischemia/infarction, systemic sclerosis, thermal injury, burning, hypertrophic  
scars, keloids, gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass,  
neurodegeneration, stroke, transient ischemic attack, uveitis, asthma, osteoporosis,

## Claims

- R1CN1=NC2=C(N1)N=CN=C2N3CC(R2)CC(R3)N3
- (I)

5 R<sup>1</sup> is a ring selected from phenyl and [1,2,5]oxadiazolyl wherein said ring is substituted with one substituent selected from halosulfonyl, halosulfonylalkyl, isothiocyanatoalkyl, isothiocyanato, aminoalkyldisulfanylalkyl, hydroxyalkyldisulfanylalkyl, hydroxyalkyldisulfanyl, aminoalkyldisulfanyl, halogen, alkyl, pyridinyldisulfanylalkyl, benzotriazolylsulfonylalkyl, 10 dihydroxyalkyldisulfanylalkyl and pyridinyldisulfanyl and optionally further substituted with cyano;

R<sup>2</sup> and R<sup>3</sup> are independently selected from hydrogen, hydroxyl, halogen, thiohydroxyl, thiohydroxyazetidiny, azido, isothiocyanato and alkyldisulfanyl; provided that at least one of R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> is a group comprising sulfonyl, 15 isothiocyanato, disulfanyl, thiohydroxyl or azido;

R<sup>4</sup> is alkyl or phenylhaloalkyl; and

n is 0 or 1;

or a pharmaceutically acceptable salt or ester thereof.

2. A compound according to claim 1, wherein R<sup>1</sup> is a ring selected from phenyl and [1,2,5]oxadiazolyl wherein said ring is substituted with one substituent selected from halosulfonyl, halosulfonylalkyl, isothiocyanatoalkyl, isothiocyanato, halogen, alkyl, hydroxyalkyldisulfanylalkyl, pyridinyldisulfanylalkyl, dihydroxyalkyldisulfanylalkyl and optionally further substituted with cyano.



- 2-{{5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}benzene-1-sulfonyl fluoride;
- 2-{{(2-{{5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}phenyl)methyl}disulfanyl}ethan-1-amine;
- 5 2-{{(2-{{5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}phenyl)methyl}disulfanyl}ethan-1-ol;
- 2-((2-{{5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}phenyl)disulfanyl)ethan-1-ol;
- 10 2-((2-{{5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)methyl}phenyl)disulfanyl)ethan-1-amine;
- 2-{{2-({5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}methyl)phenyl}disulfanyl}ethan-1-amine;
- 2-({2-({5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}methyl)phenyl)methyl}disulfanyl)ethan-1-amine;
- 15 2-({5-[difluoro(phenyl)methyl]-7-[(3S)-3-hydroxypyrrolidin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}methyl)benzene-1-sulfonyl fluoride;
- 2-({5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}methyl)benzene-1-sulfonyl fluoride;
- 20 [2-({5-[difluoro(phenyl)methyl]-7-[(3S)-3-hydroxypyrrolidin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}methyl)phenyl]methanesulfonyl fluoride;
- [2-({5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}methyl)phenyl]methanesulfonyl fluoride;
- (3S)-1-(5-[difluoro(phenyl)methyl]-3-{{2-(isothiocyanatomethyl)phenyl}methyl}-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)pyrrolidin-3-ol;
- 25 5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)-3-{{2-(isothiocyanatomethyl)phenyl}methyl}-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)-3-[(2-isothiocyanatophenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

- 1-{5-tert-butyl-3-[(2-chlorophenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}pyrrolidine-3-thiol;
- 1-{5-tert-butyl-3-[(2-chlorophenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}azetidine-3-thiol;
- 5 (3S)-1-{5-tert-butyl-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}pyrrolidine-3-thiol;
- (3R)-1-{5-tert-butyl-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}pyrrolidine-3-thiol;
- 10 (3S)-1-{5-tert-butyl-3-[(2-chlorophenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}pyrrolidine-3-thiol;
- (3R)-1-{5-tert-butyl-3-[(2-chlorophenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}pyrrolidine-3-thiol
- 7-(3-azidopyrrolidin-1-yl)-5-tert-butyl-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 15 5-tert-butyl-3-[(2-chlorophenyl)methyl]-7-(3-isothiocyanatopyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 5-tert-butyl-7-(3-isothiocyanatopyrrolidin-1-yl)-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 20 7-(3-azidopyrrolidin-1-yl)-5-tert-butyl-3-[(2-chlorophenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 5-[difluoro(phenyl)methyl]-7-[3-(methylsulfonyl)pyrrolidin-1-yl]-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 3-[(2-chlorophenyl)methyl]-5-[difluoro(phenyl)methyl]-7-[3-(methylsulfonyl)pyrrolidin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 25 7-(3-azidopyrrolidin-1-yl)-5-[difluoro(phenyl)methyl]-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 7-(3-azidopyrrolidin-1-yl)-3-[(2-chlorophenyl)methyl]-5-[difluoro(phenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

- 3-[(2-chlorophenyl)methyl]-5-[difluoro(phenyl)methyl]-7-(3-isothiocyanatopyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 5-[difluoro(phenyl)methyl]-7-(3-isothiocyanatopyrrolidin-1-yl)-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;
- 5 2-[[5-[difluoro(phenyl)methyl]-7-[(3S)-3-hydroxypyrrolidin-1-yl]triazolo[4,5-d]pyrimidin-3-yl]methyl]benzenesulfonyl fluoride;
- 2-[[2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]methyl]disulfanyl]ethanol;
- 10 2-[[5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]benzenesulfonyl fluoride;
- 5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)-3-[[2-[2-(pyridin-2-yl)disulfanyl]ethyl]phenyl]methyl]triazolo[4,5-d]pyrimidine;
- 2-[2-[2-[[5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]ethyl]disulfanyl]ethanol;
- 15 2-[2-[2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]ethyl]disulfanyl]ethanol;
- 3-[[2-[2-(benzotriazol-1-yl)sulfonyl]ethyl]phenyl]methyl]-5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidine;
- 20 2-[2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]ethanesulfonyl fluoride;
- 5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3-[[2-[2-(pyridin-2-yl)disulfanyl]ethyl]phenyl]methyl]triazolo[4,5-d]pyrimidine;
- 2-[2-[2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]ethyl]disulfanyl]ethanamine;
- 25 2-[2-[2-[[5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]ethyl]disulfanyl]ethanamine;
- 3-[2-[2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]ethyl]disulfanyl]propane-1,2-diol;

2-[[2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]disulfanyl]ethanol;

5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3-[[2-(pyridin-2-yl)disulfanyl]phenyl]methyl]triazolo[4,5-d]pyrimidine; and

5 2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]-3-ethynylbenzenesulfonyl fluoride.

9. A compound according to any one of claims 1 to 8 selected from

2-({5-tert-butyl-7-[(3S)-3-hydroxypyrrolidin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}methyl)benzene-1-sulfonyl fluoride;

10 (2-{{5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}methyl}phenyl)methanesulfonyl fluoride;

5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3-{2-(isothiocyanatomethyl)phenyl}methyl}-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

15 (3S)-1-(5-tert-butyl-3-{2-(isothiocyanatomethyl)phenyl}methyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}pyrrolidin-3-ol;

5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3-[(2-isothiocyanatophenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

2-{5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}methyl}benzene-1-sulfonyl fluoride;

20 1-{5-tert-butyl-3-[(2-chlorophenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}pyrrolidine-3-thiol;

(3S)-1-{5-tert-butyl-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}pyrrolidine-3-thiol;

25 7-(3-azidopyrrolidin-1-yl)-5-tert-butyl-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

5-tert-butyl-7-(3-isothiocyanatopyrrolidin-1-yl)-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

5-[difluoro(phenyl)methyl]-7-[3-(methyl)disulfanyl]pyrrolidin-1-yl]-3-[(4-methyl-1,2,5-oxadiazol-3-yl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

7-(3-azidopyrrolidin-1-yl)-3-[(2-chlorophenyl)methyl]-5-[difluoro(phenyl)methyl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine;

2-[[5-[difluoro(phenyl)methyl]-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]benzenesulfonyl fluoride;

5 2-[2-[2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]ethyldisulfanyl]ethanol;

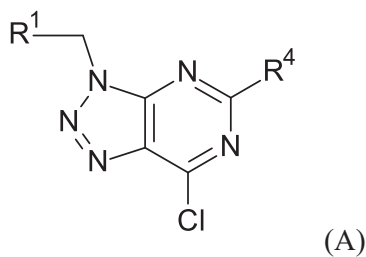
2-[2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]ethanesulfonyl fluoride;

10 5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)-3-[[2-[2-(pyridin-2-yl)disulfanyl]ethyl]phenyl]methyl]triazolo[4,5-d]pyrimidine;

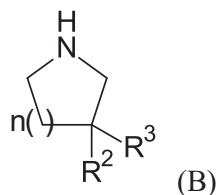
3-[2-[2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]phenyl]ethyldisulfanyl]propane-1,2-diol; and

2-[[5-tert-butyl-7-(3,3-difluoropyrrolidin-1-yl)triazolo[4,5-d]pyrimidin-3-yl]methyl]-3-ethynylbenzenesulfonyl fluoride.

15 10. A process for the manufacture of a compound according to any one of claims 1 to 9 comprising the reaction of a compound of formula (A)



in the presence of a compound of formula (B)



20 and a base, wherein R¹ to R⁴ and n are as defined in any one of claims 1 to 7.

11. A compound according to any one of claims 1 to 9 for use as therapeutically active substance.

12. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 9 and a therapeutically inert carrier.
13. The use of a compound according to any one of claims 1 to 9 for the preparation of medicaments for the treatment or prophylaxis of pain, neuropathic pain,  
5 atherosclerosis, age-related macular degeneration, diabetic retinopathy, glaucoma, diabetes mellitus, inflammation, inflammatory bowel disease, ischemia-reperfusion injury, acute liver failure, liver fibrosis, lung fibrosis, kidney fibrosis, systemic fibrosis, acute allograft rejection, chronic allograft nephropathy, diabetic nephropathy, glomerulonephropathy, cardiomyopathy, heart failure, myocardial  
10 ischemia/infarction, systemic sclerosis, thermal injury, burning, hypertrophic scars, keloids, gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass, neurodegeneration, stroke, transient ischemic attack, uveitis, asthma, osteoporosis, psychiatric diseases, psychosis, oncology, encephalitis, malaria, immunological disorders, arthritis, gastrointestinal disorders, rheumatoid arthritis or allergy.
- 15 14. A compound according to any one of claims 1 to 9 for use in the treatment or prophylaxis of pain, neuropathic pain, atherosclerosis, age-related macular degeneration, diabetic retinopathy, glaucoma, diabetes mellitus, inflammation, inflammatory bowel disease, ischemia-reperfusion injury, acute liver failure, liver fibrosis, lung fibrosis, kidney fibrosis, systemic fibrosis, acute allograft rejection,  
20 chronic allograft nephropathy, diabetic nephropathy, glomerulonephropathy, cardiomyopathy, heart failure, myocardial ischemia/infarction, systemic sclerosis, thermal injury, burning, hypertrophic scars, keloids, gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass, neurodegeneration, stroke, transient ischemic attack, uveitis, asthma, osteoporosis, psychiatric diseases, psychosis, oncology,  
25 encephalitis, malaria, immunological disorders, arthritis, gastrointestinal disorders, rheumatoid arthritis or allergy.

\*\*\*