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(54) **SUBSTITUTED BENZOTHIAZOLES AND THERAPEUTIC USES THEREOF FOR THE TREATMENT OF HUMAN DISEASES**

SUBSTITUIERTE BENZOTHIAZOLE UND THERAPEUTISCHE VERWENDUNGEN DAVON ZUR BEHANDLUNG VON ERKRANKUNGEN DES MENSCHEN

BENZOTHIAZOLES SUBSTITUÉS ET LEURS UTILISATIONS THÉRAPEUTIQUES POUR LE TRAITEMENT DE MALADIES HUMAINES

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(56) References cited:
WO-A1-01/57008 **WO-A1-2005/037845**
WO-A2-2006/018662 **GB-A- 1 535 223**
US-A- 4 208 419

- **MONTE FABIO LO ET AL: "Synthesis and biological evaluation of glycogen synthase kinase 3 (GSK-3) inhibitors: An fast and atom efficient access to 1-aryl-3-benzylureas", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 21, no. 18, 18 July 2011 (2011-07-18) , pages 5610-5615, XP029121413, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2011.06.131**
- **FAIZUL AZAM ET AL: "Structure-based design, synthesis, and molecular modeling studies of 1-(benzo[]thiazol-2-yl)-3-(substituted aryl)urea derivatives as novel anti-Parkinsonian agents", MEDICINAL CHEMISTRY RESEARCH, BIRKHÄUSER-VERLAG, BOSTON, vol. 21, no. 9, 10 September 2011 (2011-09-10), pages 2630-2643, XP035092189, ISSN: 1554-8120, DOI: 10.1007/S00044-011-9786-Y**

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(Cont. next page)

- ROSANNA CAPUTO ET AL: "Synthesis of benzothiazole derivatives and their biological evaluation as anticancer agents", MEDICINAL CHEMISTRY RESEARCH, BIRKHÄUSER-VERLAG, BOSTON, vol. 21, no. 9, 10 September 2011 (2011-09-10), pages 2644-2651, XP035092199, ISSN: 1554-8120, DOI: 10.1007/S00044-011-9789-8
- FARAHNAZ REZAEI MAKHURI ET AL: "Computer-aided scaffold hopping to identify a novel series of casein kinase 1 delta (CK1d) inhibitors for amyotrophic lateral sclerosis", EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES., vol. 78, 1 October 2015 (2015-10-01), pages 151-162, XP055475419, NL ISSN: 0928-0987, DOI: 10.1016/j.ejps.2015.07.011
- IRENE G. SALADO ET AL: "Protein Kinase CK-1 Inhibitors As New Potential Drugs for Amyotrophic Lateral Sclerosis", JOURNAL OF MEDICINAL CHEMISTRY, vol. 57, no. 6, 4 March 2014 (2014-03-04), pages 2755-2772, XP055227625, US ISSN: 0022-2623, DOI: 10.1021/jm500065f

Description

SECTOR OF THE ART AND OBJECT OF THE INVENTION

[0001] The present invention relates to a family of derivatives of substituted benzothiazoles having inhibitory activity of the enzyme casein kinase 1 (CK-1), due to which they are useful for the treatment and/or prevention of diseases mediated by said enzyme, especially inflammatory, neurological, psychiatric, neurodegenerative and/or ophthalmic diseases and in certain regenerative processes, as defined in claim 1. Therefore, the invention falls within the field of pharmaceutical chemistry and pharmacology.

STATE OF THE ART

[0002] CK-1 protein kinase is a serine/threonine kinase which was first characterised in the early 70s. The CK-1 family is formed of seven isoforms CK-1α, CK-1γ1 -CK-1γ3, CK-1β, CK-1δ and CK-1ε. All isoforms retain their kinase domain (53% -98%) and differ in the C-terminal region. This kinase family does not require the phosphorylation of their activation loop, while the activity of CK-1δ/ε can be regulated by the autophosphorylation of its C-terminal region in an intramolecular-type reaction. CK-1 is found in different cell types and in many subcellular compartments, such as for example the plasma membrane, cytosol and nucleus. Due to being a widely distributed kinase, it is believed to play an essential role in regulatory processes, being involved in various biological functions such as the regulation of DNA repair, cell morphology, modulation of Wnt/β-catenin metabolic pathway and regulation of circadian rhythms.

[0003] In recent years it has been described as a pharmaceutical target of interest for the treatment of various pathologies, including neurodegenerative diseases [Perez, D. I.; Gil, C.; Martinez, A., Protein kinases CK-1 and CK-2 as new targets for neurodegenerative diseases. Med Res Rev 2011, 31 (6), 924-54] and neurological diseases, and their effect on circadian rhythm. There are also data which suggest that CK-1 is a good pharmacological target in chronic inflammatory processes as well as regenerative processes of the central nervous system and retina stem cells.

[0004] It has been shown that overexpression or excessive activation of CK-1, is related to many degenerative diseases, also including sleep disorders, inflammation and cancer. The CK-1 protein kinase phosphorylates certain proteins such as TDP-43 or tau, resulting in post-transductional changes and abnormal protein inclusions.

[0005] Amyotrophic Lateral Sclerosis (ALS) is a degenerative muscle disease that triggers the functional decline of motor neurons and death, causing progressive muscle paralysis. There is currently no effective treatment for ALS, Riluzole being (Rilutek®) the only drug approved for its treatment, which moderately slows the progression of the disease. Sporadic ALS type represents 90%-95% of cases of the disease. Both in sporadic and familial ALS, it has recently been discovered that TDP-43 protein is hyperphosphorylated in patients' brains. One of the proteins involved in the phosphorylation of TDP-43 is CK-1 enzyme. Therefore, the search for CK-1 inhibitors represents a novel therapeutic target for the treatment of this disease.

[0006] Alzheimer's disease (AD) is a neurodegenerative disease characterised in its typical form by an immediate loss of memory and other mental abilities, as nerve cells die and different areas of the brain atrophies. In Alzheimer's patients' brains, an abnormal increase in beta-amyloid and tau proteins has been observed. The so-called *tau* hypothesis argues that hyperphosphorylation of tau protein initiates the cascade of disorders inherent to Alzheimer's disease. CK-1 enzyme is considered as one of the enzymes involved in the phosphorylation of tau protein.

[0007] CK-1 enzyme is also related to inflammatory, neurological, psychiatric and/or ophthalmic diseases and in certain regenerative processes [Fumitaka, O.; Zi-Bing, J.; Yasuhiko, H.; Hanako, I.; Teruko, D.; Kiichi, W.; Yoshiki, S.; Masayo, T. In vitro differentiation of retinal cells from human pluripotent stem cells by small-molecule induction. J. Cell Sci. 2009, 122, 3169-3179].

[0008] CK-1 inhibitors with good pharmacological properties and good safety profiles can be effective drugs for treating various currently incurable human pathologies. WO2005026137 discloses a broad family of inhibitors with a benzothiazole-benzylamides structure which act as modulators of ABC transporters of cell membranes for the treatment of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease and Amyotrophic Lateral Sclerosis. The benzothiazole-benzylamides described herein differ from those described in WO2005026137 in that, besides having different substituents, they do not have any stereogenic centre and, therefore, do not give rise to racemic mixtures. This fact considerably simplifies the process of evaluation of a potential drug through the clinical phases to which they are subjected and must fulfil before being placed on the market. This is because the inactive enantiomer must be equally evaluated to demonstrate that it is not harmful to health.

[0009] The presence of a stereogenic centre at the position located on the carbon acetoamide of benzothiazole-benzylamide structures seems to indicate that said stereogenic centre may be essential to achieving the required activity, as WO2002046173 discloses a similar family to that disclosed in WO2005026137, with similar substitution at that position, whose compounds act as glucokinase enzyme activators used in the treatment of type 2 diabetes. However, the compounds of the present invention lack such stereogenic centre and, therefore, have greater structural simplicity which

facilitates their synthesis and avoids problems, such as for example toxicity, that may arise in the use of racemic mixtures of active compounds against a certain disease when conducting clinical phases of development of said compound, as mentioned in the preceding paragraph.

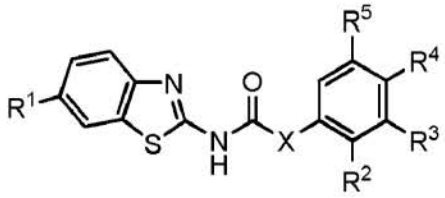
[0010] WO2012026491 discloses a family of benzothiazole-benzylamides for the treatment of cardiovascular diseases by myocardial cell differentiation.

[0011] WO-A-01/57008 discloses 2-benzothiazolyl urea derivatives as inhibitors of protein kinases, including of serine/threonine kinases. The compounds are useful for the treatment of diseases mediated by protein kinases, such as vasculitis, Crohn's disease, rheumatoid arthritis, multiple sclerosis, atherosclerosis, retinopathy and macular degeneration. Due to the need for new molecules to combat diseases for which there are no existing treatments or existing treatments can be improved, the present invention provides a group of compounds that are inhibitors of CK-1 enzyme, which is an enzyme associated with a large number of inflammatory diseases, particularly neurological, psychiatric, neurodegenerative and/or ophthalmic diseases, and in certain regenerative processes, and which are an alternative to existing drugs.

DETAILED DESCRIPTION OF THE INVENTION

[0012] The invention is defined by the claims. Any subject-matter falling outside the scope of the claims is provided for information purposes only. Any references in the description to methods of treatment refer to the compounds, pharmaceutical compositions and medicaments of the present invention for use in a method for treatment of the human or animal body by therapy. The authors of the present invention have developed a family of benzothiazole-benzylamides with greater activity than those described in the prior art and having the additional advantage over such compounds of not giving rise to racemic mixtures, on not having stereogenic centres.

[0013] In a first aspect, the present invention relates to a compound having the following formula (I):



(I)

its pharmaceutically acceptable salts, tautomers and/or solvates, wherein R^1 is CF_3,
X is selected from among NH, CH_2, CHPh, CH_2CH_2, CH_2CHPh, CH=CH, CH_2OCH_2, CH_2NHCO, $CH_2NHCOCHPh$ and $CH_2NHCOCH_2$.
R^2, R^3, R^4 and R^5 are independently selected from among H, halogen, O-alkyl (C_1-C_5) and NH_2, NHR^6, CN, NO_2, OCF_3, CO_2R^6.
R^6 is selected from among H and alkyl (C_1-C_5).
provided that when X is CHPh, CH_2CHPh or $CH_2NHCOCHPh$, then R^2, R^3, R^4 and R^5 are H;
for use for the treatment and/or prevention of a disease mediated by casein kinase 1 (CK-1) enzyme, as defined in the claims.

[0014] The term "alkyl" refers, in the present invention, to radical linear or branched hydrocarbon chains having 1 to 5 carbon atoms, and which bind to the rest of the molecule by a single bond, for example, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *terc*-butyl, *sec*-butyl, *n*-pentyl, etc. The alkyl groups may be optionally substituted by one or more substituents such as halogen, hydroxyl, alkoxyl, carboxyl, carbonyl, cyano, acyl, alkoxycarbonyl, amino, nitro, mercapto and alkylthio. The term "halogen" refers to fluoride (-F), chloride (-Cl), bromide (Br) or iodine (-1).

[0015] "Ph" stands for phenyl.

[0016] The compounds of the present invention represented by the general formula (I) may include isomers, depending on the presence of multiple bonds (for example *Z*, *E*).

[0017] Unless otherwise stated, the compounds used in the invention are intended to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the substitution of a hydrogen atom for a deuterium atom or a tritium atom, or the substitution of a carbon atom for a carbon atom enriched in ^{13}C or ^{14}C or a nitrogen atom enriched in ^{15}N fall within the scope of this invention.

[0018] The term "pharmaceutically acceptable salts or solvates thereof" relates to salts or solvates which, on being administered to the recipient, are capable of providing a compound such as that described herein. The preparation of salts and derivatives can be carried out by methods known in the state of the art. Preferably, "pharmaceutically acceptable"

relates to molecular entities and compositions that are physiologically tolerable and do not typically produce an allergic reaction or a similar unfavourable reaction, such as gastric upset, dizziness and similar side effects, when administered to a human. Preferably, the term "pharmaceutically acceptable" means approved by a regulatory agency of a federal or state government or collected in the US Pharmacopoeia or other generally recognised pharmacopeia for use in animals and, more particularly, in humans.

[0019] For example, pharmaceutically acceptable salts of the compounds previously described herein are synthesised from the previously described compound containing a basic or acidic moiety by conventional chemical methods. In general, such salts are prepared, for example, by reacting the free acid or basic forms of these compounds with a stoichiometric quantity of the appropriate base or acid in water or in an organic solvent or a mixture of both. Generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol or acetonitrile are preferred. Examples of acid addition salts include addition salts of mineral acids such as, for example, hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate and addition salts of organic acids such as, for example, acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulfonate and *p*-toluenesulfonate. Examples of alkali addition salts include inorganic salts such as, for example, sodium, potassium, calcium, ammonium, magnesium, aluminium and lithium, and organic alkaline salts such as, for example, ethylenediamine, ethanolamine, *N*-dialkylenethanolamine, glucamine and basic amino acid salts.

[0020] The compounds used in the invention may be in crystalline form, either as free compounds or as solvates (e.g.: hydrates), and it is understood that both forms fall within the scope of the present invention. Solvation methods are generally known in the state of the art. Suitable solvates are pharmaceutically acceptable solvates. In a particular embodiment, the solvate is a hydrate.

[0021] "Tautomers" are understood to be the two isomers that differ only in the position of a functional group because between the two forms there is a chemical balance in which a migration of a group or atom occurs.

[0022] The term "therapeutically effective quantity" means the necessary quantity of a compound for the treatment or prevention of the disease, disorder or condition to be effective.

[0023] In a preferred embodiment of the present invention R^2, R^3, R^4 and R^5 are independently selected from among H, halogen and O-alkyl (C_1-C_5).

[0024] In another more preferred embodiment of the present invention, X is CH_2, CH_2CH_2, CHPh or NH.

[0025] In another even more preferred embodiment of the present invention, X is CH_2.

[0026] In a more preferred embodiment, the compound of formula (I) is selected from the following group:

- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3,4-dichlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3,4,5-trimethoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-phenylacetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-(trifluoromethyl)-phenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2,2-diphenylacetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-N'-(3-chlorophenyl)urea
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2,5-dimethoxyphenyl)acetamide

and its pharmaceutically acceptable salts, solvates or tautomers.

[0027] In an even more preferred embodiment the compound of formula (I) is selected from the following group:

- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3,4-dichlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3,4,5-trimethoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-phenylacetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-(trifluoromethyl)phenyl)acetamide and its pharmaceutically acceptable salts, solvates or tautomers.

[0028] In an even more preferred embodiment, the compound of formula (1) is selected from the following group:

- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3,4,5-trimethoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-phenylacetamide

and its pharmaceutically accepted salts, solvates or tautomers.

[0029] The compounds of general formula (I) of the present invention are CK-1 enzyme inhibitors. In a preferred embodiment, CK-1 enzyme is selected from among delta CK-1 (CK-1δ) and CK-1 epsilon (CK-Iε). Therefore, these compounds may be useful for preparing medicines for the treatment and/or prevention of diseases related to the circadian rhythm, selected from among: rapid time zone change syndrome (transoceanic syndrome), night shift worker sleep disorder, delayed sleep phase syndrome and advanced sleep phase disorder.

[0030] In another aspect of the present invention, compounds of general formula (I), as CK-1 enzyme inhibitors, can be useful for preparing drugs for the treatment and/or prevention of inflammatory and autoimmune diseases, selected from among: Crohn's disease, ulcerative colitis, multiple sclerosis, encephalitis, myelitis and encephalomyelitis, vasculitis, arthritis, atherosclerosis, osteoarthritis and rheumatoid arthritis.

[0031] In another aspect of the present invention, compounds of general formula (I), as CK-1 inhibitors, can be useful for preparing drugs for the treatment and/or prevention of neurological diseases, selected from among: acute neurological disorder, bipolar disorder and conduct disorder, anxiety and depression.

[0032] In another particular embodiment, the disease mediated by CK-1 is a neurological disorder selected from among: depression and/or bipolar disorder.

[0033] In another aspect of the present disclosure, compounds of general formula (I), as CK-1 enzyme inhibitors, may be useful for preparing drugs which induce cell regeneration from the proliferation and differentiation of adult stem cells present in the nervous system, hematopoietic system, skeletal system, in the myocardium or in the retina.

[0034] In another particular embodiment, the cell regeneration mediated by CK-1 is retinal cell regeneration.

[0035] In another aspect of the present invention, compounds of general formula (I), as CK-1 enzyme inhibitors, may be useful for preparing drugs for the treatment of ophthalmic diseases selected from among: glaucoma, macular degeneration and retinitis pigmentosa.

[0036] In another particular embodiment, the ophthalmic disease mediated by CK-1 is retinitis pigmentosa.

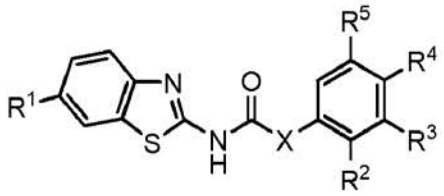
[0037] In another aspect of the present invention, compounds of general formula (I), as CK-1 enzyme inhibitors, can be useful for preparing drugs for the treatment and/or prevention of diseases that progress with protein post-translational modifications, such as hyperphosphorylation of tau protein, TDP-43, synuclein, hungtintina, etc., selected from among: Alzheimer's disease, postencephalitic Parkinsonism, Tourette syndrome, periodic limb movement pathologies, restless legs syndrome, Huntington's disease, progressive supranuclear palsy, Pick's disease, frontotemporal dementia, amyotrophic lateral sclerosis and muscular dystrophies such as Duchenne muscular dystrophy, myotonic dystrophy and distal muscular dystrophy; cerebral palsy; Friedreich's ataxia, congenital myasthenic syndrome and myasthenia gravis.

[0038] In another particular embodiment, the disease that progresses with hyperphosphorilation of tau protein mediated by CK-1 enzyme is Alzheimer's disease and frontotemporal dementia.

[0039] In another particular embodiment, the disease that progresses with hyperphosphorilation of synuclein protein mediated by CK-1 enzyme is Parkinson's disease.

[0040] In another particular embodiment, the disease that progresses with hyperphosphorilation of TDP-43 protein mediated by CK-1 enzyme is Amyotrophic Lateral Sclerosis (ALS) and frontotemporal dementia.

[0041] Another aspect of the invention relates to a compound of formula (I'):



(I')

i

ts pharmaceutically acceptable salts, tautomers and/or solvates, wherein R^1 is CF_3,
X is selected from among NH, CH_2, CHPh, CH_2CH_2, CH_2CHPh, CH=CH, CH_2OCH_2, CH_2NHCO, $CH_2NHCOCHPh$ and $CH_2NHCOCH_2$.
R^2, R^3, R^4 and R^5 are independently selected from among H, halogen and O-alkyl (C_1-C_5).

provided that:

when X is CHPh, CH_2CHPh or $CH_2NHCOCHPh$, then R^2, R^3, R^4 and R^5 are H;
R^5 is O-alkyl (C_1-C_5) when R^3 and R^4 are both O-alkyl (C_1-C_5).

[0042] In a preferred embodiment of the present invention, X is CH_2, CH_2CH_2, CHPh or NH.

[0043] In a more preferred embodiment of the present invention, X is CH_2.

[0044] In another more preferred embodiment of the present invention, R^1 is CF_3.

[0045] In a more preferred embodiment, the compound of formula (I') is selected from the following group:

- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3,4,5-trimethoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-phenylacetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2,2-diphenylacetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-*N'*-(3-chlorophenyl)urea
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2,5-dimethoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-*N'*-(4-methoxyphenyl)urea

or its pharmaceutically acceptable salts, solvates or tautomers.

[0046] In an even more preferred embodiment, the compound of formula (I') is selected from the following group:

- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3,4,5-trimethoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-phenylacetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2,2-diphenylacetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-*N'*-(3-chlorophenyl)urea
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2,5-dimethoxyphenyl)acetamide

or pharmaceutically acceptable salts, solvates or tautomers.

[0047] In a still more preferred embodiment, the compound of formula (I') is selected from the following group:

- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3,4,5-trimethoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-phenylacetamide

or pharmaceutically acceptable salts, solvates or tautomers.

[0048] Non-pharmaceutically acceptable salts may be useful for preparing pharmaceutically acceptable salts.

[0049] The compounds of the present invention are capable of crossing the blood-brain barrier, as shown in the examples below. This represents an additional advantage of the compounds when used in therapeutic treatments related

to the central nervous system, such as the aforementioned neurodegenerative, neurological, psychiatric, inflammatory and autoimmune diseases.

[0050] An additional aspect of the present invention relates to a pharmaceutical composition comprising the compounds of formula (I') as defined above and at least one excipient, adjuvant and/or pharmaceutically acceptable vehicles.

[0051] The pharmaceutical compositions can be administered by any suitable administration route, for example: oral, parenteral (subcutaneous, intraperitoneal, intravenous, intramuscular, etc.), rectal, etc.

[0052] In a particular embodiment, said pharmaceutical compositions may be in a pharmaceutical form of oral administration, either solid or liquid. Illustrative examples of pharmaceutical forms of oral administration include tablets, capsules, granules, solutions, suspensions, etc., and may contain conventional excipients such as binders, dilutes, disintegrating agents, lubricants, humectants, etc., and may be prepared by conventional methods. The pharmaceutical compositions may also be adapted for parenteral administration, in the form of, for example, solutions, suspensions or lyophilised, sterile products in the suitable dosage form; in this case, said pharmaceutical compositions will include suitable excipients, such as buffers, surfactants, etc. In any case, the excipients are chosen according to the pharmaceutical form of administration selected. A review of the different pharmaceutical forms of drug administration and their preparation can be found in the book "Treatise on Galenic Pharmacy " by C. Faulí i Trillo, 10th Edition, 1993, Luzán 5, S.A. de Ediciones, or any book of similar characteristics in each country.

[0053] In a particular embodiment, for its administration in the treatment and/or prevention of diseases wherein CK-1 enzyme is relevant, the compounds of formula (I), their pharmaceutically acceptable salts and/or solvates will be formulated in an appropriate pharmaceutical composition, in the therapeutically effective quantity, together with one or more pharmaceutically acceptable excipients, adjuvants and/or carriers.

[0054] The term "treatment or prevention" as used herein, unless otherwise indicated, relates to reversing, alleviating and inhibiting the progress of, or preventing the disorder or condition to which it applies in such terms, one or more symptoms of such disorder or condition.

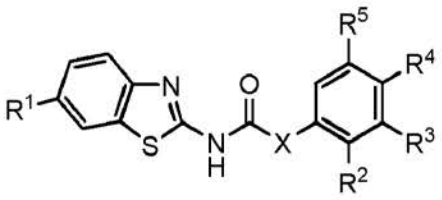
[0055] The term "excipients, adjuvants and/or carriers" relates to molecular entities or substances through which the active ingredient is administered. Such pharmaceutical excipients, adjuvants or carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and similar oils, excipients, disintegrating agents, humectants or dilutes. Suitable pharmaceutical excipients and carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin.

[0056] For its application in therapy, the compound of formula (I) will preferably be in a pharmaceutically acceptable or substantially pure form, that is, the compound of formula (I) has a pharmaceutically acceptable level of purity excluding pharmaceutically acceptable excipients and not including material considered toxic at normal dosage levels. The purity levels for a compound of formula (I) are preferably above 50%, more preferably above 70%, more preferably above 90%. In a preferred embodiment, they are above 95%.

[0057] In general, the therapeutically effective amount of the compound of formula (I) to be administered will depend, among other factors, on the individual who is to be treated, the severity of the disease suffered by the individual, the selected form of administration, etc. For this reason, the doses mentioned in this invention must be considered solely as guides for the skilled person, who must adjust the doses according to the aforementioned variables. However, a compound of formula (I) may be administered one or more times a day, for example 1, 2, 3 or 4 times a day, in a typical total daily quantity comprised between 0.1 and 1,000 mg/kg body weight/day, preferably 10 mg/kg body mass/day.

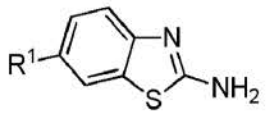
[0058] The compounds described in the present invention, their pharmaceutically acceptable tautomers, salts and solvates and pharmaceutical compositions containing them may be used together with other additional drugs to provide a combined therapy. Said additional drugs may form part of the same pharmaceutical composition or, alternatively, may be provided as a separate composition for simultaneous administration or not with the pharmaceutical composition comprising a compound of formula (I), an isomer, solvate or a pharmaceutically acceptable salt thereof.

[0059] A non-claimed aspect of the disclosure relates to a procedure (hereinafter, procedure 1) for preparing a compound of formula (I') as previously defined:



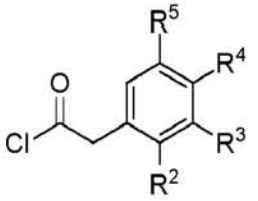
(I')

which comprises reacting a compound of formula (II):



(II)

wherein R^1 is selected from among H, alquilo (C_1-C_5), halogen, CF_3, OCF_3, OR^7, CO_2R^7, $SO_2N(R^7)_2$ and NO_2, wherein R^7 is selected from among H and alkyl (C_1-C_5),
with a compound of formula (III):



(III)

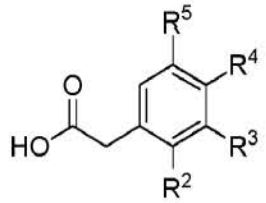
wherein R^2, R^3, R^4 and R^5 are independently selected from among H, halogen, O-alkyl (C_1-C_5),
in the presence or absence of a solvent, under microwave irradiation for a time interval comprised between 2 and 30 min, in a range of temperatures comprised between 100°C and 200°C.

[0060] In a particular embodiment, when solvent is used it is tetrahydrofuran (THF).

[0061] In a preferred embodiment, the reaction time is set between 5 and 20 min.

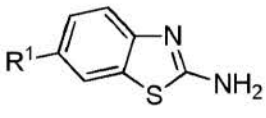
[0062] In another preferred embodiment, the reaction temperature is set between 110°C and 150°C.

[0063] The compound of formula (III) may be obtained by general procedures commonly known to a person skilled in the art based on the corresponding carboxylic acid, formula (IV) by treating it with thionyl chloride.



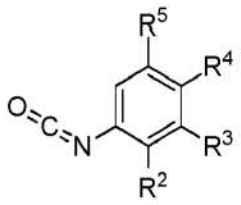
(IV)

[0064] A non-claimed alternative for preparing compounds of formula (I') consists of a process (hereinafter, procedure 2) which comprises reacting a compound of formula (II):



(II)

wherein R^1 is selected from among H, alkyl (C_1-C_5), halogen, CF_3, OCF_3, OR^7, CO_2R^7, $SO_2N(R^7)_2$ and NO_2, wherein R^7 is selected from among H and alkyl (C_1-C_5),
with a compound of formula (V);



(V)

wherein R^2, R^3, R^4 and R^5 are independently selected from H, halogen, O-alkyl (C_1-C_5),
in the presence or absence of a solvent, under microwave irradiation for a time interval comprised between 0.5 and 5 hours, over a range of temperatures comprised between 100°C and 200°C.

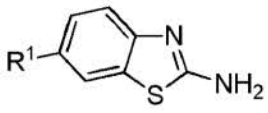
[0065] In a particular embodiment, when this solvent is used it is tetrahydrofuran (THF).

[0066] In a preferred embodiment, the reaction time is between 1 and 4 hours.

[0067] In another preferred embodiment, the reaction temperature is set between 110°C and 150°C.

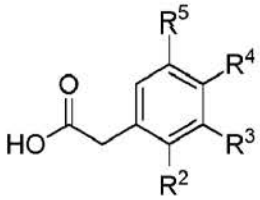
[0068] The compound of formula (V) may be obtained by general procedures commonly known to a person skilled in the art or may be purchased from a chemical supplier.

[0069] Another non-claimed alternative for preparing compounds of formula (I') is a process (hereinafter, procedure 3) which comprises adding a compound of formula (II):



(II)

wherein R^1 is selected from among H, alkyl (C_1-C_5), halogen, CF_3, OCF_3, OR^7, CO_2R^7, $SO_2N(R^7)_2$ and NO_2, wherein R^7 is selected from among H and alkyl (C_1-C_5), on a solution comprising an aprotic organic solvent, a coupling agent, a base and a compound of formula (IV),



(IV)

wherein R^2, R^3, R^4 and R^5 are independently selected from H, halogen, O-alkyl (C_1-C_5),
the reaction is completed within a time interval comprised between 0.5 and 24 hours and a temperature range is comprised between 0°C and 60°C is used.

[0070] In a particular embodiment, the solvent is selected from among tetrahydrofuran, dichloromethane and toluene.

[0071] In a particular embodiment, the coupling agent is benzotriazole-1-U-oxy-tris[pyrrolidine]phosphonium hexafluorophosphate (PyBOP).

[0072] In another particular embodiment, the base is selected from among triethylamine and diisopropylethylamine.

[0073] In a preferred embodiment, the reaction time is between 12 and 24 hours.

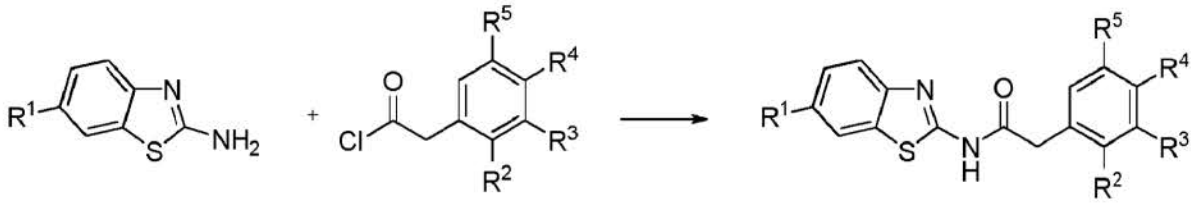
[0074] In another preferred embodiment, the temperature is set between 15°C and 35°C.

[0075] In all the procedures (1-3), the compounds are isolated and purified by methods commonly known to a person skilled in the art.

EXAMPLES

Example 1: General procedure for synthesis of compounds of the invention.

[0076]



Acid chloride formation:

[0077] The corresponding acid (1 eq) and $SOCl_2$ (1.5 eq) is introduced in a flask having a coolant and under an inert atmosphere. The reaction mixture is heated at 80°C for 6 hours. After this time has elapsed, the excess $SOCl_2$ evaporated under reduced pressure and the acid chloride obtained is used directly in the amide formation reaction.

Amide formation:

[0078] The acid chloride (1 eq) formed on the corresponding 2-aminobenzothiazole (1 eq) is added introduced in a microwave vial. The vial is introduced in the microwave reactor and heated to the temperature for the time indicated in each case. Dichloromethane (50 mL) is added and extracted with a 0.1 M HCl (50 mL) solution. Next, the organic phase is washed with saturated $NaHC0_3$ solution (50 mL) and then with saturated NaCl (50 mL) solution. The organic phase is dried over anhydrous $MgS0_4$ and the solvent removed under reduced pressure. The residue obtained was purified by flash column chromatography using Isolera One equipment. In all cases a mixture of hexane and ethyl acetate was used as eluent. All the acid chlorides required for the synthesis of the amide derivatives were synthesised in situ except: 2-(4-chlorophenyl)acetyl chloride, 2-(2,5-dimethoxyphenyl)acetyl chloride and 2-phenylbutanoyl chloride, which were purchased directly from the company Sigma Aldrich.

***N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-chlorophenyl)acetamide (1):**

[0079] Reagents: 2-(4-chlorophenyl)acetyl chloride (216.7 mg, 1.1 mmol) and 2-amino-6-trifluoromethylbenzothiazole (250 mg, 1.14 mmol). Reaction conditions: 5 min under microwave irradiation at 150°C. Purification by flash column chromatography using hexane/ethyl acetate (3:1) to obtain a white solid. Yield: 404.1 mg, 95%. Mp: 135°C-137°C ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.84 (s, 1H), 8.48 (s, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1 H), 7.49 - 7.27 (m, 4H), 3.87 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 170.4, 161.1, 151.2, 134.0, 133.4, 132.0, 131.3, 128.1, 124.5 (d, J = 272.0 Hz), 123.7 (d, J = 31.8 Hz), 122.9 (d, J = 3.9 Hz), 120.9, 1 19.9 (d, J = 4.3 Hz) 41.0. HPLC purity: >99%. ESI-MS (m/z): 371 $[M+H]^+$. Elemental analysis ($C_{16}H_{10}ClF_3N_2OS$): Theoretical %C 51.83, %H 2.72, %N 7.56, %S 8.64; Found %C 52.00, %H 2.71, %N 7.55, %S 8.49.

***N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-methoxyphenyl)acetamide (3):**

[0080] Reagents: 2-(4-methoxyphenyl)acetyl chloride (21 1.7 mg, 1.2 mmol), 2-amino-6-trifluoromethylbenzothiazole (250 mg, 1.2 mmol) and THF (1 mL). Reaction conditions: 10 min under microwave irradiation at 110°C. Purification by flash column chromatography using hexane/ethyl acetate (3:1) to obtain a yellow solid. Yield: 184.8 mg, 44%. Mp: 133°C-134°C ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.79 (s, 1H), 8.47 (s, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 3.77 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 171.0, 161.1, 158.3, 151.3, 132.0, 130.4, 126.3, 124.5 (d, J = 272.2 Hz), 123.7 (d, J = 31.9 Hz), 122.9 (d, J = 3.7 Hz), 120.9, 119.8 (d, J = 4.3 Hz), 113.9, 55.0, 40.9. HPLC purity: >99%. MS (ES) m/z: 367 $[M+H]^+$. Elemental analysis ($C_{17}H_{13}F_3N_2O_2S$): Theoretical %C 55.73, %H 3,58, %N 7,65, %S 8.75; Found %C 55.48, %H 3.31, %N 7.44, %S 8,97.

***N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-chlorophenyl)acetamide (4):**

[0081] Reagents: 2-(3-chlorophenyl)acetyl chloride (432.8 mg, 2.3 mmol), 2-amino-6-trifluoromethylbenzothiazole (500 mg, 2.3 mmol) and THF (1 mL). Reaction conditions: 10 min under microwave irradiation at 110°C. Purification by flash column chromatography using hexane / ethyl acetate (3:1) to obtain a white solid. Yield: 340 mg, 40%. Mp: 183°C-185°C ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.85 (s, 1H), 8.48 (s, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.44 (s, 1H), 7.35 (t, J = 8.1 Hz, 3H), 3.90 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 170.2, 161.1, 151.3, 136.8, 132.9, 132.0, 130.2, 129.4, 128.3, 127.0, 123.8 (d, J = 31.8 Hz), 122.9 (d, J = 3.2 Hz), 121.0, 119.9 (d, J = 4.5Hz), 41.2. HPLC purity: >99%. MS (ES) m/z: 371 $[M+H]^+$. Elemental Analysis ($C_{16}H_{10}ClF_3N_2OS$): Theoretical %C 51.83, %H 2.72, %N 7.56, %S 8.75; Found %C 51.72, %H 2.83, %N 7.27, %S 8.56.

***N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-methoxyphenyl)acetamide (6):**

[0082] Reagents: 2-(3-methoxyphenyl)acetyl chloride (211.7 mg, 1.2 mmol), 2-amino-6-trifluoromethylbenzothiazole (250 mg, 1.2 mmol) and THF (1 mL). Reaction conditions: 15 min under microwave irradiation at 110°C. Purification by flash column chromatography using hexane/ethyl acetate (3:1) to obtain a white solid. Yield: 108.1 mg, 26%. Mp: 154°C-156°C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.83 (s, 1H), 8.48 (s, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.73 (dd, J = 8.5, 1.5 Hz, 1H), 7.25 (t, J = 7.9 Hz, 1H), 6.92 (m, 2H), 6.84 (dd, J = 7.9, 2.2 Hz, 1H), 3.82 (s, 2H), 3.74 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 171.2, 161.8, 160.0, 152.0, 136.5, 132.7, 130.2, 125.2 (d, J = 271.8 Hz), 124.4 (d, J = 31.9 Hz), 123.6 (d, J = 3.6 Hz), 122.2, 121.6, 120.6 (d, J = 4.1 Hz), 115.9, 113.0, 55.7, 42.6. HPLC purity: 98%. MS (ES) m/z: 367 $[M+H]^+$. Elemental Analysis ($C_{17}H_{13}F_3N_2O_2S$): Theoretical %C 55.73, %H 3.58, %N 7.65, %S 8.75; Found %C 55.80, %H 3.41, %N 7.66, %S 9.02.N, 9.02% S.

***N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2-chlorophenyl)acetamide (7):**

[0083] Reagents: 2-(2-chlorophenyl)acetyl chloride (216.6 mg, 1.2 mmol), 2-amino-6-trifluoromethylbenzothiazole (250 mg, 1.2 mmol). Reaction conditions: 5 min under microwave irradiation at 150°C. Purification by flash column chromatography using hexane/ethyl acetate (3:1) to obtain a white solid. Yield: 318.3 mg, 75%. Mp: 226°C-228°C ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.92 (s, 1H), 8.49 (s, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.74 (dd, J = 8.6, 1.9 Hz, 1 H), 7.48 - 7.45 (m, 2H), 7.38 - 7.22 (m, 2H), 4.06 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.7, 161.1, 151.3, 133.7, 132.6, 132.5, 132.0, 129.1, 127.3, 124.6 (d, J = 271.9 Hz), 125.9, 124.3, 123.8 (d, J = 31.8 Hz), 123.0 (d, J = 3.5 Hz), 123.9, 123.0, 121.0, 119.9 (d, J = 4.0 Hz), 120.0, 40.4. HPLC purity: >99%. MS (ES) m/z: 371 $[M+H]^+$. Elemental analysis ($C_{16}H_{10}ClF_3N_2OS$): Theoretical %C 51.83, %H 2.72, %N 15.37, %S 11.36; Found %C 51.68, %H 2.54, %N 7.50, %S 11.08.

***N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2-methoxyphenyl)acetamide (8):**

[0084] Reagents: 2-(2-methoxyphenyl)acetyl chloride (211.6 mg, 1.2 mmol), 2-amino-6-trifluoromethylbenzothiazole (250 mg, 1.2 mmol). Reaction conditions: 5 min under microwave irradiation at 150°C. Purification by flash column chromatography using hexane/ethyl acetate (3:1) to obtain a white solid. Yield: 366.06 mg, 54%. Mp: 174°C-175°C ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.72 (s, 1H), 8.47 (s, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 8.5 Hz, 1 H), 7.48 - 7.09 (m, 2H), 6.99 (d, J = 8.2 Hz, 1H), 6.92 (t, J = 7.4 Hz, 1H), 3.84 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 170.8, 161.2, 157.3, 151.4, 132.0, 131.2, 128.5, 124.6 (d, J = 271.8 Hz), 123.6 (d, J = 31.8 Hz), 122.9 (d, J = 5.2 Hz), 122.8, 120.8, 120.2, 119.9 (d, J = 4.2 Hz), 1 10.8, 55.5, 36.7. HPLC purity: 97%. MS (ES) m/z: 367 $[M+H]^+$. Elemental analysis ($C_{17}H_{13}F_3N_2O_2S$): Theoretical %C 55.73, %H 3.58, %N 7.65, %S 8.75; Found %C 56.02, %H 3.61, %N 7.37, %S 8.75.

***N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3,4-dichlorophenyl)acetamide (9):**

[0085] Reagents: 2-(3,4-dichlorophenyl)acetyl chloride (256 mg, 1.2 mmol), 2-amino-6-trifluoromethylbenzothiazole (250 mg, 1.2 mmol) and THF (1 mL). Reaction conditions: 10 min under microwave irradiation at 110°C. Purification by flash column chromatography using hexane/ethyl acetate (1:1) to obtain a white solid. Yield: 405.18 mg, 65%. Mp. 158°C-159°C ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.85 (s, 1H), 8.49 (s, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.64 (d, J = 1.8 Hz, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.34 (dd, J = 8.3, 1.9 Hz, 1H), 3.92 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 170.0, 161.0, 151.3, 135.4, 132.0, 131.7, 130.8, 130.4, 130.1, 129.7, 124.5 (d, J = 272.0 Hz), 123.8 (d, J = 31.8 Hz), 122.9 (d, J = 3.4 Hz), 121.0, 1 19.9 (d, J = 4.1 Hz), 40.5. HPLC purity: 97%. MS (ES) m/z: 406 $[M+H]^+$. Elemental analysis ($C_{16}H_9F_3Cl_2N_2OS$): Theoretical %C 47.42, %H 2.24, %N 14.07, %S 7.91; Found %C 47.28, %H 2.30, %N 7.04, %S 7.38.

N-6-trifluoromethylbenzothiazole-2-yl)-2-(3,4,5-trimethoxyphenyl)acetamide (10):

[0086] Reagents: 2-(3,4,5-trimethoxyphenyl)acetyl chloride (280.1 mg, 1.2 mmol), 2-amino-6-trifluoromethylbenzothiazole (250 mg, 1.2 mmol) and THF (1 mL). Reaction conditions: 10 min under microwave irradiation at 110°C. Purification by flash column chromatography using hexane/ethyl acetate (1:1) to obtain a beige solid. Yield: 89.5 mg, 18%. Mp: 223°C-224°C ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.80 (s, 1H), 8.49 (s, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.74 (d, J = 8.9 Hz, 1H), 6.69 (s, 2H), 3.79 (s, 2H), 3.77 (s, 3H), 3.64 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 171.0, 161.5, 153.1 (2C), 151.7, 136.9, 132.4, 130.2, 124.9 (d, J = 272.0 Hz), 124.1 (d, J = 31.8 Hz), 123.3 (d, J = 3.5 Hz), 121.3, 120.3 (d, J = 4.2 Hz), 107.2, 60.3, 56.2 (2C), 42.5. HPLC purity: 98%. MS (ES) m/z: 427 $[M+H]^+$. Elemental analysis ($C_{19}H_{17}F_3N_2O_4S$): Theoretical %C 53.52, %H 4.02, %N 6.57, %S 7.52; Found %C 53.60, %H 4.04, %N 6.62, %S 7.71.

***N*-(6-trifluoromethoxybenzothiazole-2-yl)-2-(3,4,5-trimethoxyphenyl)acetamide (11): (reference)**

[0087] Reagents: 2-(3,4,5-trimethoxyphenyl)acetyl chloride (261.1 mg, 1.1 mmol), 2-amino-6-trifluoromethoxybenzothiazole (250 mg, 1.1 mmol) and THF (1.5 mL). Reaction conditions: 10 min under microwave irradiation at 110°C. Purification by flash column chromatography using hexane/ethyl acetate (1:1) to obtain a brown solid. Yield: 89.3 mg, 19%. Mp: 224°C-227°C ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.66 (s, 1 H), 8.10 (d, J = 1.2 Hz, 1 H), 7.81 (d, J = 8.8 Hz, 1H), 7.41 (ddd, J = 8.8, 2.4, 0.9 Hz, 1H), 6.67 (s, 2H), 3.76 (s, 8H), 3.62 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 170.4, 159.5, 152.8 (2C), 147.5, 144.1, 136.5, 132.6, 129.9, 121.8, 120.2 (d, J = 255.8 Hz), 118.5, 115.0, 106.8 (2C), 59.9, 55.8 (2C) 42.1. HPLC purity: >99%. MS (ES) m/z: 443 $[M+H]^+$.

***N*-(6-trifluoromethylbenzothiazole-2-yl)-2-phenylacetamide (12):**

[0088] Reagents: 2-phenylacetyl chloride (176.2 mg, 1.2 mmol), 2-amino-6-trifluoromethylbenzothiazole (250 mg, 1.2 mmol). Reaction conditions: 5 min under microwave irradiation at 150°C. Purification by flash column chromatography using hexane/ethyl acetate (1:1) to obtain a white-yellow solid. Yield: 234.3 mg, 61%. Mp: 211°C-214°C ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.46 (s, 1 H), 7.67 - 7.55 (m, 3H), 7.52 (d, J = 2.1 Hz, 1H), 7.38 - 7.29 (m, 1 H), 7.00 (dd, J = 8.8, 2.2 Hz, 1H), 3.85 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 171.1, 161.5, 151.6,. 134.8, 132.4, 129.7 (2C), 128.8 (2C), 127.3, 125.8 (d, J = 36.1 Hz), 124.9 (d, J = 267.0 Hz), 123.3 (d, J = 3.3 Hz), 121.3, 120.3 (d, J = 3.8 Hz), 42.2. HPLC purity: >99%. MS (ES) m/z: 336 $[M+H]^+$.

***N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-(trifluoromethyl)phenyl)acetamide (13):**

[0089] Reagents: 2-(3-(trifluoromethyl)phenyl)acetyl chloride (253.8 mg, 1.2 mmol), 2-amino-6-trifluoromethylbenzothiazole (250 mg, 1.2 mmol) and THF (0.5 mL). Reaction conditions: 20 min under microwave irradiation at 110°C. Purification by flash column chromatography using hexane/ethyl acetate (1:1) to obtain a white solid. Yield: 194.4 mg, 42%. Mp: 138-140 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.87 (s, 1 H), 8.48 - 8.43 (m, 1 H), 7.88 (d, J = 8.5 Hz, 1H), 7.74 - 7.51 (m, 5H), 3.99 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 170.9, 161.7, 151.9, 136.4, 134.5, 132.7, 130.1, 129.7 (d, J = 31.5 Hz.), 126.9 (d, J = 3.9 Hz), 125.2 (d, J = 271.8 Hz), 124.9 (d, J = 272.1 Hz), 124.4 (d, J = 3.8 Hz), 124.4 (d, J = 31.8 Hz), 123.6 (d, J = 4.0 Hz), 121.7, 120.6 (d, J = 4.4 Hz), 41.9. HPLC purity: 96%. MS (ES) m/z: 405 $[M+H]^+$.

***N*-(6-trifluoromethylbenzothiazole-2-yl)-2,2-diphenylacetamide (15):**

[0090] Reagents: 2,2-diphenylacetyl chloride (264.6 mg, 1.2 mmol), 2-amino-6-trifluoromethylbenzothiazole (250 mg, 1.2 mmol) and THF (0.5 mL). Reaction conditions: 10 min under microwave irradiation at 110°C. Purification by flash column chromatography using hexane/ethyl acetate (3:1) to obtain a white solid. Yield: 299.3 mg, 63%. Mp. 144°C-146°C ^{1}H NMR (300 MHz, DMSO-d_6) δ: 13.11 (s, 1H), 12.72 (s, 1H), 8.52 (s, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1 H), 7.44 - 7.15 (m, 10H), 5.43 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6). δ: 171.8, 161.4, 151.6, 139.0 (2C), 132.4, 129.0 (4C), 129.0 (4C), 127.7 (2C), 124.9 (d, J = 272.0 Hz), 124.2 (d, J = 31.7 Hz), 123.4 (d, J = 3.6 Hz), 121.4, 120.3 (d, J = 4.8 Hz), 56.6. HPLC purity: 97%. MS (ES) m/z: 413 $[M+H]^+$. Elemental analysis ($C_{22}H_{15}F_3N_2OS$): Theoretical %C 64.07, %H 3.67, %N 6.79, %S 7.77; Found %C 65.33, %H 4.08, %N 6.11, %S 6.52.

***N*-(benzothiazole-2-yl)-2-(3-chlorophenyl)acetamide (20): (reference)**

[0091] Reagents: 2-(3-chlorophenyl)acetyl chloride (629.5 mg, 3.3 mmol), 2-aminobenzothiazole (500 mg, 3.3 mmol) and THF (1 mL). Reaction conditions: 10 min under microwave irradiation at 110°C. Purification by flash column chromatography using hexane/ethyl acetate (3:1) to obtain a white solid. Yield: 205.3 mg, 20%. Mp: 155°C-157°C ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.60 (s, 1H), 7.96 (d, J = 7.2 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.53 - 7.19 (m, 6H), 3.86 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.9, 159.2, 147.7, 134.8, 134.7, 131.9, 130.1, 129.4, 127.9, 127.3, 126.5, 124.2, 121.7, 120.4, 42.6. HPLC purity: >99%. MS (ES) m/z: 304 $[M+H]^+$. Elemental analysis ($C_{15}H_{11}ClN_2OS$): Theoretical %C 59.50, %H 3.66, %N 9.25, %S 10.59; Found %C 59.80, %H 3.59, %N 9.27, %S 10.31.

***N*-(6-methoxybenzothiazole-2-yl)-2-(3-chlorophenyl)acetamide (22): (reference)**

[0092] Reagents: 2-(3-chlorophenyl)acetyl chloride (314.6 mg, 1.7 mmol), 2-amino-6-methoxybenzothiazole (300 mg, 1.7 mmol) and THF (1 mL). Reaction conditions: 15 min under microwave irradiation at 110°C. Purification by flash column chromatography using hexane/ethyl acetate (3:1) to obtain a white solid. Yield: 418 mg, 76%. Mp: 173°C-175°C ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.47 (s, 1H), 7.63 (d, 1H, J = 8.9Hz), 7.52 (d, 1H, J = 2.5Hz), 7.41 (m, 1H) 7.38-7.2 (m, 3H), 7.00 (dd, 1H, J = 8.9Hz, J = 2.6Hz), 3.82 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.7, 156.4,

156.0, 142.7, 137.3, 133.1, 132.9, 130.5, 129.5, 128.4, 127.1, 121.4 1 15.2, 104.9, 55.8, 41.4. HPLC purity: >99%. MS (ES) m/z: 333 $[M+H]^+$. Elemental analysis ($C_{16}H_{13}ClN_2O_2S$): Theoretical %C 57.74, %H 3.94, %N 8.42, %S 9.63; Found %C 57.46, %H 3.90, %N 8.27, %S 9.44.

***N*-(6-trifluoromethoxybenzothiazole-2-yl)-2-(3-chlorophenyl)acetamide (23): (reference)**

[0093] Reagents: 2-(3-chlorophenyl)acetyl chloride (201.7 mg, 1.1 mmol), 2-amino-6-trifluoromethoxybenzothiazole (250 mg, 1.1 mmol). Reaction conditions: 5 min under microwave irradiation at 150°C. Purification by flash column chromatography using hexane/ethyl acetate (1:1) to obtain a white solid. Yield: 386.7 mg, 48%. Mp: 174°C-176°C ^1H NMR (300 MHz, DMSO-d_6) δ: 12.74 (s, 1H), 8.11 (t, J = 1.8 Hz, 1H), 7.82 (dd, J = 8.8, 1.7 Hz, 1 H), 7.47 - 7.25 (m, 5H), 3.88 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 170.7, 160.0, 148.2, 144.7, 137.5, 133.6, 133.3,. 130.9, 130.1, 128.9, 127.6, 122.2, 120.9 (d, J = 256.1 Hz), 119.6, 115.7, 41.8. HPLC purity: 98%. MS (ES) m/z: 387 $[M+H]^+$. Elemental Analysis ($C_{16}H_{10}ClF_3N_2O_2S$): Theoretical %C 49.68, %H 2.61, %N 7.24, %S 8.29; Found %C 49.81, %H 2.45, %N 7.32, %S 7.99.

***N*-(6-trifluoromethoxybenzothiazole-2-yl)-2-(3,4-dichlorophenyl)acetamide (28): (reference)**

[0094] Reagents: 2-(3,4-dichlorophenyl)acetyl chloride (238.5 mg, 1.1 mmol), 2-amino-6-trifluoromethoxybenzothiazole (250 mg, 1.1 mmol) and THF (0.3 mL). Reaction conditions: 10 min under microwave irradiation at 110°C. Purification by flash column chromatography using hexane/ethyl acetate (1:1) to obtain a white solid. Yield: 203.1 mg, 45%. Mp: 170°C-172°C ^1H NMR (300 MHz, DMSO-d_6) δ: 7.97 (s, 1 H), 7.76 - 7.64 (m, 1 H), 7.65 - 7.52 (m, 2H), 7.33 (dd, J = 8.1, 1.7 Hz, 2H), 3.82 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 171.4, 162.0, 148.1, 143.5, 136.7, 132.9, 131.5, 130.6, 130.3, 130.0, 129.3, 121.9, 120.2 (d, J = 255.9 Hz), 118.5, 114.6, 41.7. HPLC purity: >99%. MS (ES) m/z: 422 $[M+H]^+$. Elemental analysis ($C_{16}H_9Cl_2F_3N_2O_2S$): Theoretical %C 45.62, %H 2.15, %N 6.65, %S 7.62; Found %C 45.38, %H 1.97, %N 6.48, %S 7.47.

***N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2,5-dimethoxyphenyl)acetamide (29):**

[0095] Reagents: 2-(2,5-dimethoxyphenyl)acetyl chloride (246 mg, 1.2 mmol), 2-amino-6-trifluoromethylbenzothiazole (250 mg, 1.2 mmol). Reaction conditions: 7 min under microwave irradiation at 150°C. Purification by flash column chromatography using hexane/ethyl acetate (3:1) to obtain a beige solid. Yield: 141.7 mg, 31%. Mp. 146°C-147°C ^1H NMR (300 MHz, DMSO-d_6) δ: 8.26 (d, J = 24.7 Hz, 1H), 7.63 (dd, J = 32.9, 7.4 Hz, 2H), 6.82 (dd, J = 30.0, 9.1 Hz, 3H), 3.68 (s, 8H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 174.0, 165.95, 152.9, 152.6, 151.5, 132.5, 125.9, 121.9 (d, J = 2.25 Hz), 121.6 (d, J = 37.2 Hz), 119.2, 118.8 (d, J = 3.6 Hz), 117.4, 111.7 (2C), 56.0, 55.3, 38.4. HPLC purity: >99%. MS (ES) m/z: 397 $[M+H]^+$

***N*-(6-methylbenzothiazole-2-yl)-2-(2-methoxyphenyl)acetamide (30): (reference)**

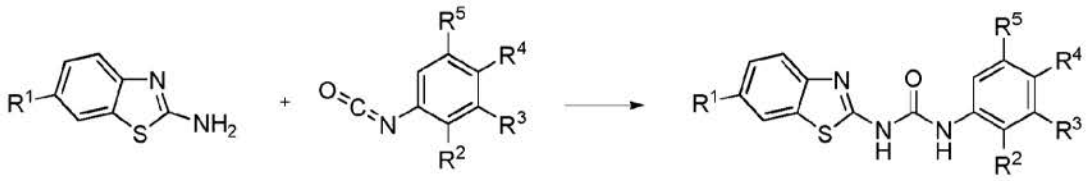
[0096] Reagents: 2-(2-methoxyphenyl)acetyl chloride (280.8 mg, 1.5 mmol), 2-amino-6-methylbenzothiazole (250 mg, mmol). Reaction conditions: 5 min under microwave irradiation at 150°C. Purification by flash column chromatography using hexane/ethyl acetate (1:1) to obtain an orange-brown solid. Yield: 93.45 mg, 20%. Mp: 165°C-167°C ^1H NMR (300 MHz, DMSO-d_6) δ: 12.38 (s, 1 H), 7.73 (s, 1 H), 7.61 (d, J = 8.2 Hz, 1 H), 7.32 - 7.16 (m, 1 H), 6.98 (d, J = 7.7 Hz, 1H), 6.91 (td, J = 7.4, 10.0 Hz, 1 H), 3.79 (s, 1H), 3.74 (s, 1H), 2.39 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 170.1, 157.2, 157.1, 146.5, 132.8, 131.5, 131.1, 128.4, 127.3, 123.0 121.0, 120.2, 120.1, 110.8, 55.4, 36.6, 20.9. HPLC purity: >99%. MS (ES) m/z: 312 $[M+H]^+$.

***N*-(6-methoxybenzothiazole-2-yl)-2-(3,4-dichlorophenyl)acetamide (53): (reference)**

[0097] Reagents: 2-(3,4-dichlorophenyl)acetyl chloride (310 mg, 10.4 mmol), 2-Amino-6-methoxybenzothiazole (250 mg, 1.4 mmol) and THF (0.4 mL). Reaction conditions: 10 min under microwave irradiation at January 10°C. Purification by flash column chromatography using hexane/ethyl acetate (1:1) to obtain a beige solid. Yield: 100 mg, 20%. Mp: 198°C-199°C ^1H NM R (300 MHz, DMSO-d_6) δ: 12.47 (s, 1H), 7.64-7.58 (m, 3H), 7.55 (d, J = 2.7 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.01 (dd, J = 8.8, 2.7 Hz, 1H), 3.85 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 169.8, 156.9, 156.4, 143.3, 136.5, 133.4, 132.3, 131 0.5, 131 0.1, 130.7, 130.3, 121.9 1 15.7, 105.4, 56.3, 41.2. HPLC purity: >99%. MS (ES) m/z: 368 $[M+H]^+$. Elemental analysis ($C_{16}H_{12}Cl_2N_2O_2S$): Theoretical %C 52.33, %H 3.29, %N 7.63,%S 8.73. Found %C 52.05, %H 3.09, %N 7.38, %S 8.53.

Example 2: General procedure for synthesis of compounds 24 and 46.

[0098]



[0099] **General methodology:** In a microwave vial benzothiazole derivative and the corresponding isocyanate is added in each case. Next, THF is added as solvent. The vial is introduced into the microwave reactor and heated to the temperature for the time indicated in each case. After the reaction time, ethyl acetate (50 mL) and water (50 mL) is added. The organic phase is dried over anhydrous $MgS0_4$ and the solvent is removed under reduced pressure. The obtained residue was purified by flash column chromatography using Isolera One equipment, in all cases a mixture of hexane and ethyl acetate as eluent was used.

***N*-(6-trifluoromethylbenzothiazole-2-yl)-*N'*-(3-chlorophenyl)urea (24):**

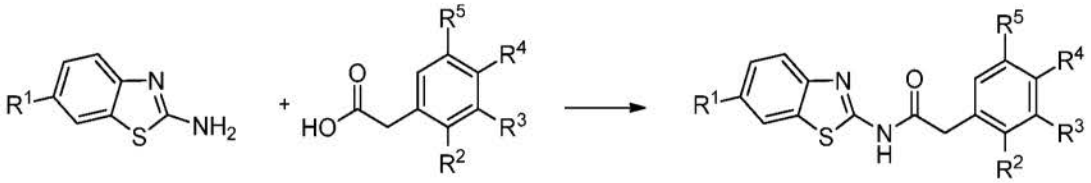
[0100] Reagents: 1-isocianato-3-chlorobenzene (175.8 mg, 1.2 mmol), 2-amino-6-trifluoromethylbenzothiazole (250 mg, 1.2 mmol) and THF (0.4 mL). Reaction conditions: 3 hours and 30 min under microwave irradiation at 110°C. Purification by flash column chromatography using hexane/ethyl acetate (3:1) to obtain a white solid. Yield: 43.2 mg, 10%. Mp: 222°C-223°C ^{1}H NMR (500 MHz, DMSO-d_6) δ: 11.16 (s, 1H), 9.38 (s, 1H), 8.41 (s, 1H), 7.73 (s, 1H), 7.69 (dd, J = 8.5, 1.9 Hz, 1H), 7.38 (s, 1H), 7.35 (t, J = 7.9 Hz, 2H), 7.11 (d, J = 8.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 162.6, 152.0, 140.3, 133.7, 131.0, 125.0 (q, J = 271.7 Hz), 123.6 (d, J = 31.8 Hz), 123.5, 123.4 (d, J = 2.5 Hz), 120.1 (d, J = 4.3 Hz), 118.8, 117.9. HPLC purity: >99%. MS (ES) m/z: 372 $[M+H]^+$.

***N*-(6-trifluoromethylbenzothiazole-2-yl)-*N'*-(4-methoxyphenyl)urea (46):**

[0101] Reagents: 1-isocianato-4-methoxybenzene (170.9 mg, 1.2 mmol), 2-amino-6-trifluoromethylbenzothiazole (250 mg, 1.2 mmol) and 0.4 mL of THF. Reaction conditions: 1 hour under microwave irradiation at 110°C. Purification by flash column chromatography using hexane/ethyl acetate (3:1) to obtain a white solid. Yield: 208.7 mg, 50%. Mp: 194°C-196°C ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.97 (s, 1H), 8.99 (s, 1H), 8.39 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.72 - 7.62 (m, 1H), 7.41 (d, J = 8.9 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 3.72 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.6, 160.8, 155.4, 151.8, 132.3, 131.1, 125.3 (d, J = 39.6 Hz), 124.8 (d, J = 242.6 Hz), 122.8 (d, J = 2.7 Hz), 120.9 (2C), 119.5 (d, J = 4.2 Hz), 119.5, 114.1 (2C), 55.2. HPLC purity: >99%. MS (ES) m/z: 368 $[M+H]^+$. Elemental analysis ($C_{16}H_{12}F_3N_3O_2S$): Theoretical %C 52.31, %H 3.29, %N 11.44. Found %C 50.27, %H 4.08, %N 11.54.

Example 3: General procedure for synthesis of compounds 35, 37 and 38.

[0102]



[0103] **General methodology:** A solution of the corresponding carboxylic acid (1.2 eq) in dichloromethane (10 mL) is added in a round-bottomed flask. Next, the coupling agent (1.2 eq) and triethylamine (2 eq) is added. The reaction mixture is stirred for 1 hour at room temperature. After this time period has elapsed, the 2-aminobenzothiazole derivative (1 eq) is added and stirred at room temperature for the time indicated in each case. The solvent is removed under reduced pressure and the reaction crude is purified by the method indicated in each case.

***N*-(benzothiazole-2-yl)-2-benzyloxyacetamide (35): (reference)**

[0104] It is obtained according to the general method described above. Reagents: 2-(benzyloxy)acetic acid (200 mg, 1.2 mmol), PyBOP (592 mg, 1.2 mmol), 2-aminobenzothiazole (147 mg, 1 mmol), TEA (0.26 mL, 1.9 mmol). Reaction conditions: stirring at room temperature for 12 hours. Purification: suspended solid filtration and washed with CH_2Cl_2 to obtain a white solid. Yield: 215 mg, 76%. Mp: 75.6°C ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.71-7.66 (m, 2H), 7.36-7.15 (m, 4H), 4.56 (s, 2H), 4.12 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.4, 156.2, 146.7, 134.7, 130.6, 127.7, 127.5, 126.9, 124.9, 122.7, 120.4, 119.8, 72.7, 67.1. HPLC purity: >95%. MS (m/z): 299 $(M+H)^+$. Elemental analysis ($C_{16}H_{14}N_2O_2S$): Theoretical %C 64.41, %H 4.73, %N 9.39, %S 10.75; Found %C 64.32, %H 4.80, %N 9.27, %S 10.62.

***N*-(benzothiazole-2-yl)-2-(2,2-diphenylacetamide)acetamide (37): (reference)**

[0105] It is obtained according to the general method described above. Reagents: 2-(2,2'-diphenylacetamide)acetic acid (150 mg, 0.6 mmol) which was previously obtained by reduction of 2-(2,2'-diphenylacetamide)benzyl acetate; PyBOP (288 mg, 0.6 mmol), 2-aminobenzothiazole (72 mg, 0.5 mmol), TEA (0.2 mL, 1.1 mmol). Reaction conditions: stirring at room temperature for 24 hours. Purification: flash column chromatography using Isolera One equipment, using hexane/ethyl acetate as eluent (6:1) to obtain a white solid. Yield: 18 mg, 10%. Mp. 208.2°C-209.0°C ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.87 (d, J = 7.4 Hz, 1H), 7.76 (d, J = 8.6 Hz, 1H), 7.50-7.30 (m, 12H), 5.32 (s, 1H), 4.19 (d, J = 5.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.8, 158.4, 148.5, 147.5, 137.9, 132.6, 129.5, 129.3, 128.4, 126.8, 124.6, 121.9, 121.2, 49.4, 40.1. HPLC purity: 98%. MS (m/z): 402 $(M+H)^+$. Elemental analysis ($C_{23}H_{19}N_3O_2S$): Theoretical %C 68.81, %H 4.77, %N 10.47, %S 7.99; Found %C 68.53, %H 4.48, %N 10.71, %S 7.86.

***N*-(benzothiazole-2-yl)-2-(2-phenylacetamide)acetamide (38): (reference)**

[0106] EDC (296 mg, 1.6 mmol) along with DMAP (58 mg, 0.5 mmol) was added to a solution of 2-(2-phenylacetamide)acetic acid (305 mg, 1.6 mmol) in dichloromethane (10 mL) and stirred for 1 hour. Next, 2-aminobenzothiazole (200 mg, 1.3 mmol) was added and stirred at room temperature for 12 hours. Lastly, the solvent was removed by vacuum filtration. The residue obtained was purified by washing with CH_2Cl_2 to obtain a white solid. Yield: 327 mg, 78%. Mp: 247.2°C-249.9°C ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.56 (t, J = 5.7 Hz, 1 H), 7.96 (d, J = 8.0 Hz, 1 H), 7.72 (d, J = 8.1 Hz, 1 H), 7.41 (t, J = 8.4 Hz, 1 H), 7.30-7.19 (m, 5H), 3.51 (s, 2H), 4.05 (d, J = 5.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.5, 169.8, 158.9, 158.4, 149.1, 136.7, 129.8, 128.8, 127.1, 126.7, 124.2, 122.3, 42.9, 42.6. HPLC purity: >99%. MS (m/z): 326 $(M+H)^+$. Elemental analysis ($C_{17}H_{15}N_3O_2S$): Theoretical %C 62.75, %H 4.65, %N 12.91, %S 9.85; Found %C 62.47, %H 4.58, %N 12.67, %S 9.57.

Example 2: Measurement of the inhibition of CK-1 in the compounds of the invention

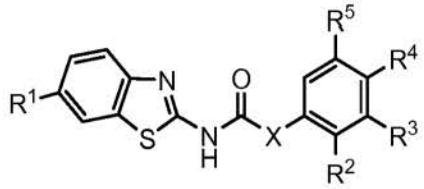
[0107] Enzyme inhibition assays were performed using the Luminometer Kinase-GLO® method. Recombinant human enzyme CK-1δ was purchased from Millipore Iberica SAU and recombinant human enzyme CK-1ε was purchased from Invitrogen. The phosphorylation substration chosen was casein. The Luminescent Kinase Kit (catalogue no. V6711) was obtained from Promega. ATP and other reagents were purchased from Sigma-Aldrich (St. Louis, MO).

[0108] The assays were conducted in buffer using 96-well plates. In a typical assay: 10 μL of the test compound (dissolved in dimethylsulfoxide at a concentration of 1 mM and, in turn, dissolved in buffer to the required concentration for the experiment) and 10 μL (16 ng) of the CK-1δ enzyme or 10 μL (50 ng) of the CK-1ε enzyme row were added to each well followed by 20 μL of buffer containing 0.1% casein as substrate and 4 μM of ATP. The assay buffer contained: 50 mM HEPES, pH 7.5; 0.01% Brij-35; 10 mM $MgCl_2$; 1 mM EGTA and 0.01% NaN3. The final concentration of DMSO in the experiment did not exceed 1%. After incubating for 60 minutes at 30°C, the enzymatic reaction was stopped using 40 μL of Kinase-GLO® reagent. Luminescence was measured after ten minutes using a FLUOstar Optima (BMG Labtechnologies GmbH, Offenburg, Germany) multimode reader. The activity was proportional to the difference between the total and consumed ATP. Inhibition activities were calculated in accordance with the maximum activity measured in the absence of inhibitor. IC_{50} is defined as the concentration of each compound that reduces enzyme activity by 50% with respect to that obtained without inhibitor.

Table 1. Inhibitory Concentration 50 (IC_{50}) of the compounds of the invention.

Only the compounds wherein $R^1 = CF_3$ are within the scope of the invention.

(continued)



No.	R^1	X	R^2	R^3	R^4	R^5	CK-1δ μM	CK-1ε μM
1	CF_3	CH_2	H	H	Cl	H	0.065	0.55
2	Cl	CH_2	H	H	OMe	H	0.070	0.50
3	CF_3	CH_2	H	H	OMe	H	0.033	0.70
4	CF_3	CH_2	H	Cl	H	H	0.023	0.84
5	Me	CH_2	H	Cl	H	H	0.083	0.88
6	CF_3	CH_2	H	OMe	H	H	0.042	0.69
7	CF_3	CH_2	Cl	H	H	H	0.068	7.73
8	CF_3	CH_2	OMe	H	H	H	0.010	0.80
9	CF_3	CH_2	H	Cl	Cl	H	0.056	0.87
10	CF_3	CH_2	H	OMe	OMe	OMe	0.015	0.37
11	OCF_3	CH_2	H	OMe	OMe	OMe	0.079	0.94
12	CF_3	CH_2	H	H	H	H	0.047	0.76
13	CF_3	CH_2	H	CF_3	H	H	0.087	0.72
14	H	CH_2	H	H	H	H	0.33	2.31
15	CF_3	CHPh	H	H	H	H	0.26	2.75
16	OMe	CHPh	H	H	H	H	0.84	5.07
17	NO_2	CH_2CH_2	H	H	H	H	0.57	9.40
18	H	CH_2	H	H	F	H	0.53	3.08
19	OMe	CH_2	H	H	OMe	H	0.57	2.41
20	H	CH_2	H	Cl	H	H	0.85	2.86
21	OMe	CH_2	H	H	Cl	H	0.75	8.75
22	OMe	CH_2	H	Cl	H	H	0.53	3.73
23	OCF_3	CH_2	H	Cl	H	H	0.54	1.02
24	CF_3	NH	H	Cl	H	H	0.74	10.95
25	OMe	CH_2	H	OMe	H	H	0.42	2.43
26	OEt	CH_2	H	OMe	H	H	0.99	8.97
27	OCF_3	CH_2	OMe	H	H	H	0.62	7.39
28	OCF_3	CH_2	H	Cl	Cl	H	0.59	0.93
29	CF_3	CH_2	OMe	H	H	OMe	0.19	3.14
30	Me	CH_2	OMe	H	H	H	0.29	4.93
31	Cl	CH_2	OMe	H	H	H	0.32	1.15
32	Br	CH_2	OMe	H	H	H	0.26	1.03
33	H	CHPh	H	H	H	H	1.96	7.31

(continued)

No.	R^1	X	R^2	R^3	R^4	R^5	CK-1δ μM	CK-1ε μM
34	H	CH_2CHPh	H	H	H	H	2.50	9.73
35	H	CH_2OCH_2	H	H	H	H	4.37	48% @ 10 μM
36	H	CH_2NHCO	H	H	H	H	7.29	36% a 10 μM
37	H	$CH_2NHCOCHPh$	H	H	H	H	1.93	13
38	H	$CH_2NHCOCH_2$	H	H	H	H	6.33	37% @ 10 μM
39	OEt	CHPh	H	H	H	H	2.82	7.86
40	CO_2Et	CHPh	H	H	H	H	6.68	1.60
41	SO_2NH_2	CHPh	H	H	H	H	10% @ 10 μM	10% @ 10 μM
42	SO_2NHEt	CHPh	H	H	H	H	10% @ 10 μM	10% @ 10 μM
43	SO_2NHBu	CHPh	H	H	H	H	10% @ 10 μM	10% @ 10 μM
44	SO_2NEt_2	CHPh	H	H	H	H	9.83	3.47
45	OEt	CH_2	H	H	OMe	H	1.09	9.49
46	CF_3	NH	H	H	OMe	H	5.50	29% @ 10 μM
47	H	CH_2CH_2	H	Cl	H	H	3.58	31% @10 μM
48	OEt	CH_2	H	Cl	H	H	1.21	9.75
49	OMe	CH_2	Cl	H	H	H	9.71	30% @ 10 μM
50	OEt	CH_2	Cl	H	H	H	17.43	20% @ 10 μM
51	OMe	CH_2	OMe	H	H	H	2.22	33% @ 10 μM
52	OEt	CH_2	OMe	H	H	H	5.76	46% @10 μM
53	OMe	CH_2	H	Cl	Cl	H	1.24	16.49
54	OEt	CH_2	H	Cl	Cl	H	3.43	14.20
55	OMe	CH_2	H	OMe	OMe	OMe	6.65	17.73
56	OEt	CH_2	H	OMe	OMe	OMe	1.43	9.83
57	SO_2NMe_2	CHCH	H	OMe	OMe	OMe	10% @10 μM	10% @10 μM
58	H	CHCH	OMe	H	H	OMe	49% @10 μM	25% @ 10 μM
59	F	CH_2	OMe	H	H	H	1.17	4.51

Example 3: Central nervous system (CNS) permeation of the compounds of the invention using parallel artificial membranes (PAMPA).

[0109] The prediction of central nervous system (CNS) permeation of the various compounds, passage of the blood-brain barrier, was determined using parallel artificial membrane (PAMPA) methodology [Di, L.; Kerns, E. H.; Fan, K.; McConnell, O. J.; Carter, G. T. "High throughput artificial membrane permeability assay for blood-brain barrier" Eur. J. Med. Chem., 2003, 38 (3), 223-232]. To filter the samples, PVDF membrane filters (diameter: 30 mm, pore size: 0.45 μm) were used.

[0110] Ten reference compounds were selected, whose blood-brain barrier passage is known and public, in order to validate the experiment. Different quantities of the same 3-5 mg of caffeine, enoxacin, hydrocortisone, desipramine, ofloxacin, piroxicam and testosterone, 12 mg of promazine and 25 mg of verapamil and atenolol were taken, which were dissolved in ethanol (1000 μL). 100 μL of these solutions were taken and ethanol 1,400 μL of ethanol and 3,500 μL of PBS (pH=7.4) were added in order to reach a final concentration of 30% ethanol solution. The solutions were filtered. Next, 180 μL of a PBS/ethanol (70/30) solution were added to each well of the acceptor plate. The donor plate was impregnated with 4 μL of a porcine brain lipid solution dissolved in dodecane (20 mg mL^{-1}). After 5 min, 180 μL of dissolution of each compound were added to this plate. Of the compounds whose penetration into the central nervous

system was to be assessed, between 1-2 mg were taken and dissolved in 1,500 μL of ethanol and 3,500 μL of PBS (pH=7.4), filtered and added to the donor 96-well plate. The donor plate was then placed on the acceptor forming a kind of "sandwich" and allowed to incubate for 2 hours and 30 min at 25°C. The compounds, by passive transport, will move from the donor plate through the porcine brain lipid to the acceptor plate. After 2 hours and 30 min, it was carefully removed from the donor plate. The concentration and absorbance, both of the commercial compounds and the synthesised derivatives evaluated in the acceptor and donor plates were determined using a UV absorbance reader. Each sample was analysed at different wavelengths (3 to 5) in three wells and in at least two independent experiments. The results are the average of the measurements [±standard deviation] of the different experiments performed.

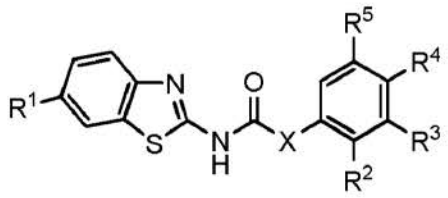
[0111] In relation to the ten reference commercial compounds used in each experiment to validate the method, a good correlation between the experimental (*Pe*) and described permeation values, *Pe* (exptl) = 1.1512 (bibl) - 0.8973 (R^2 = 0.977) was found. Based on this equation and following the pattern described in the literature [Crivori, P.; Cruciani, G.; Testa, B. "Predicting Blood-Brain Barrier Permeation from Three-Dimensional Molecular Structure." J. Med. Chem., 2000, 43, 2204-2216] for the prediction of permeation of the blood-brain barrier, the compounds can be classified as permeable to the central nervous system (CNS) when having a permeability > 3.71 x 10^{-6} cm^{-1}. The results are shown in Table 2, where it can be observed how some of the compounds tested are capable of penetrating the blood-brain barrier.

Table 2. PAMPA-blood-brain barrier permeation (*Pe* 10^{-6} cm s^{-1}) of ten compounds used to validate the experiment, and different compounds of the invention with its corresponding prediction of penetration into the central nervous system (SNC). Compounds 5, 14, 20, 30 and 51 are reference compounds.

Compound	[a]Bibl.	[b]*Pe* (10^{-6} cm s^{-1})	Permeation prediction
Atenolol	0.8	0.2 ± 0.1	
Caffeine	1.3	0.8 ± 0.1	
Desipramine	12	8.0 ± 1.0	
Enoxacin	0.9	0.7 ± 0.2	
Hydrocortisone	1.9	0.3 ± 0.3	
Ofloxacin	0.8	0.2 ± 0.1	
Piroxicam	2.5	0.2 ± 0.1	
Promazine	8.8	8.5 ± 0.1	
Testosterone	17	17.2 ± 0.6	
Verapamil	16	14.7 ± 1.1	
1		9.6 ± 0.1	SNC +
3		14.6 ± 0.1	SNC +
4		5.9 ± 0.5	SNC +
5		5.6 ± 0.8	SNC +
6		11.2 ± 2.0	SNC +
8		11.3 ± 2.1	SNC +
10		10.6 ± 0.1	SNC+
12		10.4 ± 3.9	SNC+
14		12.7 ± 1.2	SNC+
20		10.6 ± 0.3	SNC+
30		6.2 ± 0.5	SNC+
51		11.2 ± 0.9	SNC+
[a]Di et al, 2003. [b]Average data ± standard deviation of at least two independent experiments.			

Claims

1. Compound of formula (I):



(I)

its pharmaceutically acceptable salts, tautomers and/or solvates, wherein
R^1 is CF_3,
X is selected from among CH_2, NH, CHPh, CH_2CH_2, CH_2CHPh, CH=CH, CH_2OCH_2, CH_2NHCO, $CH_2NHCOCHPh$ and $CH_2NHCOCH_2$,
R^2, R^3, R^4 and R^5 are independently selected from among H, halogen and O-alkyl (C_1-C_5), NH_2, NHR^6, CN, NO_2, OCF_3 and CO_2R^6,
R^6 is selected from among H and alkyl (C_1-C_5),
provided that that when X is CHPh, CH_2CHPh or $CH_2NHCOCHPh$, then R^2, R^3, R^4 and R^5 are H,
for use for the treatment and/or prevention of a disease mediated by the CK-1 enzyme, wherein the disease mediated by CK-1 enzyme is a disease selected from among transoceanic syndrome, night shift worker sleep disorder, delayed sleep phase syndrome, advanced sleep phase disorder, Crohn's disease, ulcerative colitis, multiple sclerosis, encephalitis, myelitis, encephalomyelitis, vasculitis, arthritis, atherosclerosis, osteoarthritis, rheumatoid arthritis, neurological disorder, bipolar disorders, behavioural disorders, anxiety, depression, glaucoma, macular degeneration, retinitis pigmentosa, Alzheimer's disease, Parkinson's disease, postencephalitic Parkinsonism, Tourette syndrome, periodic limb movement pathologies, restless legs syndrome, Huntington's disease, progressive supranuclear palsy, Pick's disease, frontotemporal dementia, amyotrophic lateral sclerosis, muscular dystrophy, myotonic dystrophy and distal muscular dystrophy; cerebral palsy; Friedreich's ataxia, congenital myasthenic syndrome and myasthenia gravis; preferably the disease is selected from among depression, bipolar disorder, retinitis pigmentosa, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis or frontotemporal dementia.

2. Compound for use according to claim 1, wherein R^2, R^3, R^4 and R^5 are independently selected from among H, halogen and O-alkyl (C_1-C_5).

3. Compound for use according to claim 1 or 2, wherein X is CH_2, CH_2CH_2, CHPh or NH.

4. Compound for use according to claim 3, wherein X is CH_2.

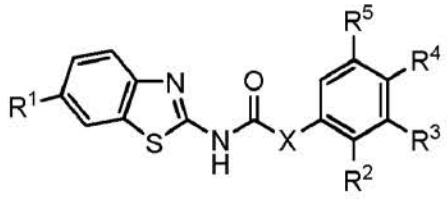
5. Compound for use according to claim 1 or 2, wherein said compound is selected from the following group:

- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3,4-dichlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3,4,5-trimethoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-phenylacetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-(trifluoromethyl)phenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2,2-diphenylacetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2,5-dimethoxyphenyl)acetamide and its pharmaceutically acceptable salts, solvates or tautomers.

6. Compound for use according to claim 5, wherein said compound is selected from the following group:

- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3,4,5-trimethoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-phenylacetamide and its salts, tautomers or pharmaceutically acceptable solvates.

7. A compound of formula (I'):



its pharmaceutically acceptable salts, tautomers and/or solvates,
wherein
R^1 is CF_3,
X is selected from among CH_2, NH, CHPh, CH_2CH_2, CH_2CHPh, CH=CH, CH_2OCH_2, CH_2NHCO, $CH_2NHCOCHPh$ and $CH_2NHCOCH_2$,
R^2, R^3, R^4 and R^5 are independently selected from among H, halogen and O-alkyl (C_1-C_5),
provided that:

when X is CHPh, CH_2CHPh or $CH_2NHCOCHPh$, then R^2, R^3, R^4 and R^5 are H,
when R^3 and R^4 are both O-alkyl (C_1-C_5), then R^5 is O-alkyl (C_1-C_5).

8. A compound according to claim 7, wherein X is CH_2, CH_2CH_2, CHPh or NH.

9. A compound according to claim 8, wherein X is CH_2

10. A compound according to claim 7, wherein said compound is selected from among the following group:

- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(4-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(3,4,5-trimethoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-phenylacetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2,2-diphenylacetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-*N'*-(3-chlorophenyl)urea
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-2-(2,5-dimethoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-yl)-*N'*-(4-methoxyphenyl)urea

or its pharmaceutically acceptable salts, solvates or tautomers.

11. A compound according to claim 10, wherein said compound is selected from among the following group:

- *N*-(6-trifluoromethylbenzothiazole-2-l)-2-(4-chlorophenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-l)-2-(4-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-l)-2-(3-chlorophenyl)acetamide

- *N*-(6-trifluoromethylbenzothiazole-2-l)-2-(3-methoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-l)-2-(2-methoxyphenyl)acetamide
- N-(6-trifluoromethylbenzothiazole-2-l)-2-(3,4,5-trimethoxyphenyl)acetamide
- *N*-(6-trifluoromethylbenzothiazole-2-l)-2-phenylacetamide

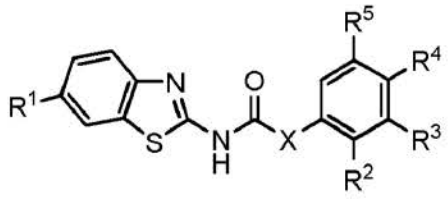
or its pharmaceutically acceptable salts, solvates or tautomers.

12. A pharmaceutical composition comprising a compound of formula (I'), as defined in any one of claims 7 to 11.

13. A composition according to claim 12, further comprising another active ingredient.

Patentansprüche

1. Verbindung der Formel (I):



(I)

deren pharmazeutisch verträglichen Salze, Tautomere und/oder Solvate, wobei R^1 CF_3 ist,
X ist ausgewählt aus CH_2, NH, CHPh, CH_2CH_2, CH_2CHPh, CH=CH, CH_2OCH_2, CH_2NHCO, $CH_2NHCOCHPh$ und $CH_2NHCOCH_2$,
R^2, R^3, R^4 und R^5 unabhängig voneinander ausgewählt sind aus H, Halogen und O-Alkyl (C_1-C_5), NH_2, NHR^6, CN, NO_2, OCF_3 und CO_2R^6,
R^6 ist ausgewählt aus H und Alkyl (C_1-C_5),
mit der Maßgabe, dass, wenn X CHPh, CH_2CHPh oder $CH_2NHCOCHPh$ ist, R^2, R^3, R^4 und R^5 H sind,
zur Verwendung für die Behandlung und/oder Vorbeugung einer durch das Enzym CK-1 vermittelten Krankheit, wobei die durch das Enzym CK-1 vermittelte Krankheit eine Krankheit ist, die ausgewählt ist aus Jetlag, Schlafstörung der Nachtschichtarbeiter, verzögertes Schlafphasensyndrom, vorverlagertes Schlafphasensyndrom, Morbus Crohn, Colitis ulcerosa, multiple Sklerose, Enzephalitis, Myelitis, Enzephalomyelitis, Vaskulitis, Arthritis, Atherosklerose, Osteoarthritis, rheumatoide Arthritis, neurologische Störung, bipolare Störungen, Verhaltensstörungen, Angstzustände, Depression, Glaukom, Makuladegeneration, Retinitis pigmentosa, Alzheimer-Krankheit, Morbus Parkinson, postenzephalitischer Parkinsonismus, Tourette-Syndrom, pathologische periodische Beinbewegungen, Restless-Legs-Syndrom, Huntington-Krankheit, progressive supranukleäre Paralyse, Pick-Krankheit, frontotemporale Demenz, amyotrophe Lateralsklerose, Muskeldystrophie, myotone Dystrophie und distale Muskeldystrophie; Gehirnlähmung; Friedreich-Ataxie, kongenitales myasthenes Syndrom und Myasthenia gravis; vorzugsweise wird die Krankheit ausgewählt aus Depression, bipolare Störung, Retinitis pigmentosa, Alzheimer-Krankheit, Morbus Parkinson, amyotropher Lateralsklerose oder frontotemporaler Demenz.

2. Verbindung zur Verwendung nach Anspruch 1, wobei R^2, R^3, R^4 und R^5 unabhängig voneinander ausgewählt sind aus H, Halogen und O-Alkyl (C_1-C_5).

3. Verbindung zur Verwendung nach Anspruch 1 oder 2, wobei X CH_2, CH_2CH_2, CHPh oder NH ist.

4. Verbindung zur Verwendung nach Anspruch 3, wobei X CH_2 ist.

5. Verbindung zur Verwendung nach Anspruch 1 oder 2, wobei die Verbindung ausgewählt ist aus der folgenden Gruppe:

- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(4-chlorphenyl)acetamid

- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(4-methoxyphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(3-chlorphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(3-methoxyphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(2-chlorphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(2-methoxyphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(3,4-dichlorphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(3,4,5-trimethoxyphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-phenylacetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(3-(trifluormethyl)phenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2,2-diphenylacetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(2,5-dimethoxyphenyl)acetamid

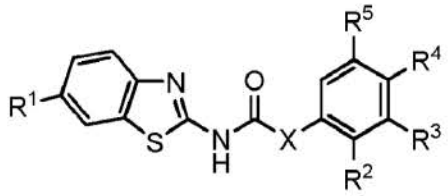
und deren pharmazeutisch verträglichen Salze, Tautomere oder Solvate.

6. Verbindung zur Verwendung nach Anspruch 5, wobei die Verbindung ausgewählt ist aus der folgenden Gruppe:

- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(4-chlorphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(4-methoxyphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(3-chlorphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(3-methoxyphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(2-methoxyphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(3,4,5-trimethoxyphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-phenylacetamid

und deren Salze, Tautomere oder pharmazeutisch verträglichen Solvate.

7. Verbindung der Formel (I'):



deren pharmazeutisch verträglichen Salze, Tautomere und/oder Solvate,
wobei
R^1 CF_3 ist,
X ist ausgewählt aus CH_2, NH, CHPh, CH_2CH_2, CH_2CHPh, CH=CH, CH_2OCH_2, CH_2NHCO, $CH_2NHCOCHPh$ und $CH_2NHCOCH_2$,
R^2, R^3, R^4 und R^5 unabhängig voneinander ausgewählt sind aus H, Halogen und O-Alkyl (C_1-C_5), mit der Maßgabe, dass:

wenn X CHPh, CH_2CHPh oder $CH_2NHCOCHPh$ ist, R^2, R^3, R^4 und R^5 H sind,
wenn R^3 und R^4 beide O-Alkyl (C_1-C_5) sind, R^5 O-Alkyl (C_1-C_5) ist.

8. Verbindung nach Anspruch 7, wobei X CH_2, CH_2CH_2, CHPh oder NH ist.

9. Verbindung nach Anspruch 8, wobei X CH_2 ist.

10. Verbindung nach Anspruch 7, wobei die Verbindung ausgewählt ist aus der folgenden Gruppe:

- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(4-chlorphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(2-chlorphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(3-chlorphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(4-methoxyphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(3-methoxyphenyl)acetamid

- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(2-methoxyphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(3,4,5-trimethoxyphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-phenylacetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2,2-diphenylacetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-*N'*-(3-chlorphenyl)harnstoff
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-2-(2,5-dimethoxyphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-yl)-*N'*-(4-methoxyphenyl)harnstoff

oder deren pharmazeutisch verträglichen Salze, Tautomere oder Solvate.

11. Verbindung nach Anspruch 10, wobei die Verbindung ausgewählt ist aus der folgenden Gruppe:

- *N*-(6-Trifluormethylbenzothiazol-2-I)-2-(4-chlorphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-I)-2-(4-methoxyphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-I)-2-(3-chlorphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-I)-2-(3-methoxyphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-I)-2-(2-methoxyphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-I)-2-(3,4,5-trimethoxyphenyl)acetamid
- *N*-(6-Trifluormethylbenzothiazol-2-I)-2-phenylacetamid

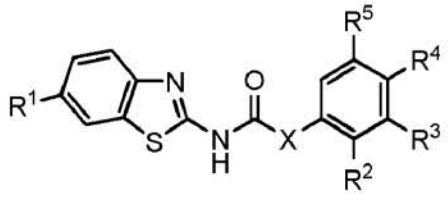
oder deren pharmazeutisch verträglichen Salze, Tautomere oder Solvate.

12. Pharmazeutische Zusammensetzung, umfassend eine Verbindung der Formel (I'), wie sie in einem der Ansprüche 7 bis 11 definiert ist.

13. Zusammensetzung nach Anspruch 12, ferner umfassend einen weiteren Wirkstoff.

Revendications

1. Composé de formule (I) :



(I)

ses sels, tautomères et/ou solvates pharmaceutiquement acceptables, dans lequel R^1 est CF_3,
X est choisi parmi CH_2, NH, CHPh, CH_2CH_2, CH_2CHPh, CH=CH, CH_2OCH_2, CH_2NHCO, $CH_2NHCOCHPh$ et $CH_2NHCOCH_2$,
R^2, R^3, R^4 et R^5 sont indépendamment choisis parmi H, l'halogène et O-alkyle (C_1-C_5), NH_2, NHR^6, CN, NO_2, OCF_3 et CO_2R^6,
R^6 est choisi parmi H et l'alkyle (C_1-C_5),
étant donné que lorsque X est CHPh, CH_2CHPh ou $CH_2NHCOCHPh$, puis R^2, R^3, R^4 et R^5 sont H ,
pour son utilisation pour le traitement et/ou la prévention d'une maladie régulée par l'enzyme CK-1, dans lequel la maladie régulée par l'enzyme CK-1 est une maladie choisie parmi le syndrome transocéanique, les troubles du sommeil du travailleur de nuit, le syndrome de retard de phase du sommeil, syndrome d'avance de phase du sommeil, la maladie de Crohn, la colite ulcéreuse, le sclérose en plaques, l'encéphalite, la myélite, l'encéphalomyélite, les vascularités, l'arthrite, l'athérosclérose, l'ostéoarthrite, l'arthrite rhumatoïde, les troubles neurologiques, les troubles bipolaires, les troubles comportementaux, l'anxiété, la dépression, le glaucome, la dégénération maculaire, la ritinite pigmentaire, la maladie d'Alzheimer, la maladie de Parkinson, le Parkinsonisme postencéphalitique, le syndrome de la Tourette, les pathologies des mouvements périodiques des membres, le syndrome des jambes sans repos, la maladie de Huntington, la paralysie supranucléaire progressive,

la maladie de Pick, la démence frontotemporelle, la sclérose latérale amyotrophique, la dystrophie musculaire, la dystrophie myotonique et la dystrophie musculaire distale ; la paralysie cérébrale ; l'ataxie de Friedreich, les syndromes myasthéniques congénitaux et la myasthénie grave ; de préférence la maladie est choisie parmi la dépression, le trouble bipolaire, la ritinite pigmentaire, la maladie d'Alzheimer, la maladie de Parkinson, la sclérose latérale amyotrophique ou la démence frontotemporelle.

2. Composé pour son utilisation selon la revendication 1, dans lequel R^2, R^3, R^4 et R^5 sont indépendamment choisis parmi H, l'halogène et O-alkyle (C_1-C_5).

3. Composé pour son utilisation selon la revendication 1 ou 2, dans lequel X est CH_2, CH_2CH_2, CHPh ou NH.

4. Composé pour son utilisation selon la revendication 3, dans lequel X est CH_2.

5. Composé pour son utilisation selon la revendication 1 ou 2, dans lequel ledit composé est choisi dans le groupe suivant :

- *N*- (6-trifluorométhylbenzothiazole-2-yl)-2-(4-chlorophényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(4-méthoxyphényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(3-chlorophényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(3-méthoxyphényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(2-chlorophényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(2-méthoxyphényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(3,4-dichlorophényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(3,4,5-triméthoxyphényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-phénylacétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(3-(trifluorométhyl)phényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2,2-diphénylacétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(2,5-diméthoxyphényl)acétamide

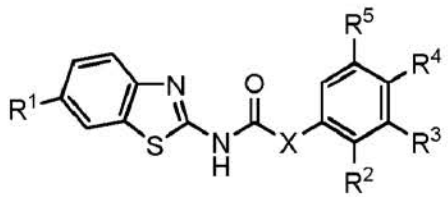
et ses sels, solvates ou tautomères pharmaceutiquement acceptables.

6. Composé pour son utilisation selon la revendication 5, dans lequel ledit composé est choisi dans le groupe suivant :

- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(4-chlorophényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(4-méthoxyphényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(3-chlorophényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(3-méthoxyphényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(2-méthoxyphényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(3,4,5-triméthoxyphényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-phénylacétamide

et ses sels, tautomères ou solvates pharmaceutiquement acceptables.

7. Composé de formule (I') :



ses sels, tautomères et/ou solvates pharmaceutiquement acceptables,
dans lequel
R^1 est CF_3,
X est choisi parmi CH_2, NH, CHPh, CH_2CH_2, CH_2CHPh, CH=CH, CH_2OCH_2, CH_2NHCO, $CH_2NHCOCHPh$ et $CH_2NHCOCH_2$,

R^2, R^3, R^4 et R^5 sont indépendamment choisis parmi H, l'halogène et O-alkyle (C_1-C_5), étant donné que : lorsque X est CHPh, CH_2CHPh ou $CH_2NHCOCHPh$, puis R^2, R^3, R^4 et R^5 sont H , lorsque R^3 et R^4 sont tous les deux O-alkyle (C_1-C_5), puis R^5 est O-alkyle (C_1-C_5).

8. Composé selon la revendication 7, dans lequel X est CH_2, CH_2CH_2, CHPh ou NH.

9. Composé selon la revendication 8, dans lequel X est CH_2.

10. Composé selon la revendication 7, dans lequel ledit composé est choisi dans le groupe suivant parmi :

- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(4-chlorophényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(2-chlorophényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(3-chlorophényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(4-méthoxyphényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(3-méthoxyphényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(2-méthoxyphényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(3,4,5-triméthoxyphényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-phénylacétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2,2-diphénylacétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-*N'*(3-chlorophényl)urée
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-2-(2,5-diméthoxyphényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-yl)-*N'*(4-méthoxyphényl)urée

ou ses sels, solvates ou tautomères pharmaceutiquement acceptables.

11. Composé selon la revendication 10, dans lequel ledit composé est choisi dans le groupe suivant parmi :

- *N*-(6-trifluorométhylbenzothiazole-2-l)-2-(4-chlorophényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-l)-2-(4-méthoxyphényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-l)-2-(3-chlorophényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-l)-2-(3-méthoxyphényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-l)-2-(2-méthoxyphényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-l)-2-(3,4,5-triméthoxyphényl)acétamide
- *N*-(6-trifluorométhylbenzothiazole-2-l)-2-phénylacétamide

ou ses sels, solvates ou tautomères pharmaceutiquement acceptables.

12. Composition pharmaceutique comprenant un composé de formule (I'), tel que définie dans l'une quelconque des revendications 7 à 11.

13. Composition selon la revendication 12, comprenant en outre un autre ingrédient actif.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 2005026137 A **[0008] [0009]**
- WO 2002046173 A **[0009]**
- WO 2012026491 A **[0010]**
- WO 0157008 A **[0011]**

Non-patent literature cited in the description

- **PEREZ, D. I. ; GIL, C. ; MARTINEZ, A.** Protein kinases CK-1 and CK-2 as new targets for neurodegenerative diseases. *Med Res Rev*, 2011, vol. 31 (6), 924-54 **[0003]**
- **FUMITAKA, O. ; ZI-BING, J. ; YASUHIKO, H. ; HANAKO, I. ; TERUKO, D. ; KIICHI, W. ; YOSHIKI, S. ; MASAYO, T.** In vitro differentiation of retinal cells from human pluripotent stem cells by small-molecule induction. *J. Cell Sci.,* 2009, vol. 122, 3169-3179 **[0007]**
- **C. FAULÍ I TRILLO.** Treatise on Galenic Pharmacy. 1993 **[0052]**
- **DI, L. ; KERNS, E. H. ; FAN, K. ; MCCONNELL, O. J. ; CARTER, G. T.** High throughput artificial membrane permeability assay for blood-brain barrier. *Eur. J. Med. Chem,* 2003, vol. 38 (3), 223-232 **[0109]**
- **CRIVORI, P. ; CRUCIANI, G. ; TESTA, B.** Predicting Blood-Brain Barrier Permeation from Three-Dimensional Molecular Structure. *J. Med. Chem.*, 2000, vol. 43, 2204-2216 **[0111]**