NOVEL HETEROARYL SUBSTITUTED BENZOTHIAZOLES

The present invention relates to novel heteroaryl substituted benzothiazole derivatives and therapeutic uses for such compounds. Furthermore, the invention relates to novel heteroaryl substituted benzothiazole derivatives that are suitable for imaging amyloid deposits in living patients, their compositions, methods of use and processes to make such compounds. More specifically, the present invention relates to a method of imaging amyloid deposits in brain *in vivo* to allow antemortem diagnosis of Alzheimer's disease as well as measureing clinical efficacy of Alzheimer's disease therapeutic agents.

Baekground of the invention

Amyloidosis is a progressive, incurable metabolic disease of unknown cause characterized by abnormal deposits of protein in one or more organs or body systems. Amyloid proteins are manufactured, for example, by malfunctioning bone marrow. Amyloidosis, which occurs when accumulated amyloid deposits impair normal body function, can cause organ failure or death. It is a rare disease, occurring in about eight of every 1,000,000 people. It affects males and females equally and usually develops after the age of 40. At least 15 types of amyloidosis have been identified. Each one is associated with deposits of a different kind of protein.

The major forms of amyloidosis are primary systemic, secondary, and familial or hereditary amyloidosis. There is also another form of amyloidosis associated with Alzheimer's disease. Primary systemic amyloidosis usually develops between the ages of 50 and 60. With about 2,000 new cases diagnosed annually, primary systemic amyloidosis is the most common form of this disease in the United States. Also known as light-chain-related amyloidosis, it may also occur in association with multiple myeloma (bone marrow cancer). Secondary amyloidosis is a result of chronic infection or inflammatory disease. It is often associated with Familial Mediterranean fever (a bacterial infection characterized by chills, weakness, headache, and reeurring fever), Granulomatous ileitis (inflammation of the small intestine), Hodgkin's disease, Leprosy, Osteomyelitis and Rheumatoid arthritis.

Familial or hereditary amyloidosis is the only inherited form of the disease. It occurs in members of most ethnic groups, and each family has a distinctive pattern of symptoms and organ involvement. Hereditary amyloidosis is though to be autosomal dominant, which means that only one copy of the defective gene is necessary to cause the disease. A child of a parent with familial amyloidosis has a 50-50 risk of developing the disease.

Amyloidosis can involve any organ or system in the body. The heart, kidneys, gastrointestinal system, and nervous system are affected most often. Other common sites of amyloid accumulation include the brain, joints, liver, spleen, pancreas, respiratory system, and skin.

Alzheimer's disease (AD) is the most common form of dementia, a neurologic disease characterized by loss of mental ability severe enough to interfere with normal activities of daily living, lasting at least six months, and not present from birth. AD usually occurs in old age, and is marked by a decline in cognitive functions such as remembering, reasoning, and planning.

Between two and four million Americans have AD; that number is expected to grow to as many as 14 million by the middle of the 21st century as the population as a whole ages. While a small number of people in their 40s and 50s develop the disease, AD predominantly affects the elderly. AD affects about 3% of all people between ages 65 and 74, about 20% of those between 75 and 84, and about 50% of those over 85. Slightly more women than men are affected with AD, even when considering women tend to live longer, and so there is a higher proportion of women in the most affected age groups.

The accumulation of amyloid Aβ-peptide in the brain is a pathological hallmark of all forms of AD. It is generally accepted that deposition of cerebral amyloid Aβ-peptide is the primary influence driving AD pathogenesis. (Hardy J and Selkoe D.J., Science. 297: 353-356, 2002).

Imaging techniques, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), are effective in monitoring the accumulation of amyloid deposits in the brain and correlating it to the progression of AD (Shoghi-Jadid et

al. The American journal of geriatrie psychiatry 2002, 10, 24; Miller, Science, 2006, 313, 1376; Coimbra *et al.* Curr. Top. Med. Chem. 2006, 6, 629; Nordberg, Laneet Neurol. 2004, 3, 519). The application of these techniques requires the development of radioligands that readily enter thc brain and selectively bind to amyloid deposits *in vivo*.

A need exists for amyloid binding compounds that are non-toxic and can cross the blood-brain barrier, and consequently, can be used in diagnostics. Furthermore, it is important to be able to monitor the efficacy of the treatment given to AD patients, by measuring the effect of said treatment by measuring changes of AD plaque level.

Properties of partieular interest of a detectable amyloid binding compound, besides high affinity for amyloid deposits *in vivo* and high and rapid brain entrance, include low unspeeifie binding to normal tissue and rapid clearance from the same. These properties are commonly dependant on the lipophilicity of the compound (Coimbra *et al.* Curr. Top. Med. Chem. 2006, 6, 629). Based partly on the relatively higher clearanee from normal brain tissue as compared to related analogues, [^{11}C]PIB was seleeted from amongst these for further evaluations in human suhjects (Mathis *et al.* J. Med. Chem. 2003, 46, 2740). Subsequently, a study on the use of [^{11}C]PIB for the detection of amyloid deposits in-vivo in the human by the PET-technique was condueted (Klunk *et al.* Ann Neurol. 2004, 55, 306). In this study, significant higher retention of [^{11}C]PIB in relevant regions of the brain, was observed in subjects with diagnosed AD as compared to healthy controls. Related methods and derivatives are described in WO 2002/16333 and WO 2004/083195.

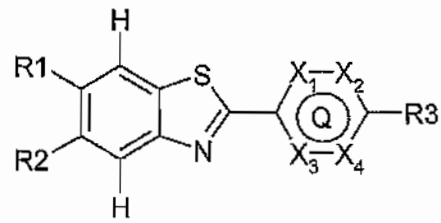
There is a need for improved compounds in order to obtain a signal-to-noise ratio high enough to allow detailed detection of amyloid deposits throughout all brain regions, and providing improved reliability in quantiative studies on amyloid plaque load in relation to drug treatments.

The present invention provides heteroaryl substituted benzothiazole derivatives that carry such unexpected improvments over known benzothiazole derivatives providing *inter alia* advantageously associated low unspecific binding and rapid brain clearance.

Disclosure of the invention

The present invention provides methods for measuring effects of amyloid binding compounds, by measuring changes of AD plaque level.

In one aspect of the invention, there is provided a compound according to formula I:



I

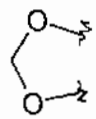
wherein

R1 is selected from hydrogen, halo, C_{1-5} alkyl, C_{1-6} fluoroalkyl, C_{1-3} alkyleneOC_{1-3} alkyl, C_{1-3} alkyleneOC_{1-3} fluorolkyl, C_{1-3} alkyleneNH_2, C_{1-3} alkyleneNHC_{1-3} alkyl, C_{1-3} alkyleneN(C_{1-3} alkyl)$_2$, C_{1-3} alkyleneNHC_{1-3} fluoroalkyl, C_{1-3} alkyleneN(C_{1-3} fluoroalkyl)$_2$, C_{1-3} alkyleneN(C_{1-3} alkyl)C_{1-3} fluoroalkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} fluoroalkoxy, amino, NHC_{1-3} alkyl, NHC_{1-3} fluoroalkyl, N(C_{1-3} alkyl)$_2$, N(C_{1-3} fluoroalkyl)$_2$, N(C_{1-3} alkyl)C_{1-3} fluoroalkyl, NH(CO)C_{1-3} alkyl, NH(CO)C_{1-3} fluorolkyl, NH(CO)C_{1-3} alkoxy, NH(CO)C_{1-3} fluoroalkoxy, NHSO_2C_{1-3} alkyl, NHSO_2C_{1-3} fluoroalkyl, (CO)C_{1-3} alkyl, (CO)C_{1-3} fluoroalkyl, COOH, (CO)C_{1-3} alkoxy, (CO)C_{1-3} fluoroalkoxy, (CO)NH_2, (CO)NHC_{1-3} alkyl, (CO)NHC_{1-3} fluoroalkyl, (CO)N(C_{1-3} alkyl)$_2$, (CO)N(C_{1-3} fluoroalkyl)$_2$, (CO)N(C_{1-3} alkyl)C_{1-3} fluoroalkyl, (CO)N(C_{4-6} alkylene), (CO)N(C_{4-6} fluoroalkylene), eyano and SO_2NH_2;

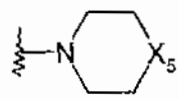
R2 is selected from hydrogen, halo, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-3} alkyleneOC_{1-3} alkyl, C_{1-3} alkyleneOC_{1-3} fluorolkyl, C_{1-3} alkyleneNH_2, C_{1-3} alkyleneNHC_{1-3} alkyl, C_{1-3} alkyleneN(C_{1-3} alkyl)$_2$, C_{1-3} alkyleneNHC_{1-3} fluoroalkyl, C_{1-3} alkyleneN(C_{1-3} fluoroalkyl)$_2$, C_{1-3} alkyleneN(C_{1-3} alkyl)C_{1-3} fluoroalkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} fluoroalkoxy, amino, NHC_{1-3} alkyl, NHC_{1-3} fluoroalkyl, N(C_{1-3} alkyl)$_2$, N(C_{1-3} fluoroalkyl)$_2$, N(C_{1-3} alkyl)C_{1-3} fluoroalkyl, NH(CO)C_{1-3} alkyl, NH(CO)C_{1-3} fluoroalkyl, NH(CO)C_{1-3} alkoxy, NH(CO)C_{1-3} fluoroalkoxy, NHSO_2C_{1-3} alkyl, NHSO_2C_{1-3} fluoroalkyl, (CO)C_{1-3} alkyl, (CO)C_{1-3}

fluoroalkyl, COOH, $(CO)C_{1-3}$ alkoxy, $(CO)C_{1-3}$ fluoroalkoxy, $(CO)NH_2$, $(CO)NHC_{1-3}$ alkyl, $(CO)NHC_{1-3}$ fluoroalkyl, $(CO)N(C_{1-3}$ alkyl$)_2$, $(CO)N(C_{1-3}$ fluoroalkyl$)_2$, $(CO)N(C_{1-3}$ alkyl$)C_{1-3}$ fluoroalkyl, $(CO)N(C_{4-6}$ alkylene), $(CO)N(C_{4-6}$ fluoroalkylene) and cyano; or

R1 and R2 together forms a ring;



R3 is selected from fluoro, bromo, iodo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, trifluoromethyl, C_{1-3} alkyleneOC_{1-3} alkyl, C_{1-3} alkyleneOC_{1-3} fluoroalkyl, C_{1-3} alkyleneNH$_2$, C_{1-3} alkyleneNHC_{1-3} alkyl, C_{1-3} alkyleneN(C_{1-3} alkyl$)_2$, C_{1-3} alkyleneNHC_{1-3} fluoroalkyl, C_{1-3} alkyleneN(C_{1-3} fluoroalkyl$)_2$, C_{1-3} alkyleneN(C_{1-3} alkyl)C_{1-3} fluoroalkyl, hydroxy, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, amino, NHC_{1-3} alkyl, NHC_{1-3} fluoroalkyl, N(C_{1-3} alkyl$)_2$, N(C_{1-3} fluoroalkyl$)_2$, N(C_{1-3} alkyl)C_{1-3} fluoroalkyl, NH(C_{0-3} alkylene)G2, N(C_{0-1} alkyl)N(C_{0-1} alkyl$)_2$, N(C_{0-1} alkyl)OC_{0-1} alkyl, NH(CO)C_{1-3} alkyl, NH(CO)C_{1-3} fluoroalkyl, NH(CO)G2, $(CO)C_{1-3}$ alkyl, $(CO)C_{1-3}$ fluorolkyl, $(CO)C_{1-3}$ alkoxy, $(CO)C_{1-3}$ fluoroalkoxy, $(CO)NH_2$, $(CO)NHC_{1-3}$ alkyl, $(CO)NHC_{1-3}$ fluoroalkyl, $(CO)N(C_{1-3}$ alkyl$)_2$, $(CO)N(C_{1-3}$ fluoroalkyl$)_2$, $(CO)N(C_{1-3}$ alkyl)C_{1-3} fluoroalkyl, $(CO)N(C_{4-6}$ alkylene), $(CO)N(C_{4-6}$ fluoroalkylene), $(CO)NH_2$G2, SO_2NH_2, SO_2NHC_{1-3} alkyl, SO_2NHC_{1-3} fluoroalkyl, $SO_2N(C_{1-3}$ alkyl$)_2$, $SO_2N(C_{1-3}$ fluoroalkyl$)_2$, $SO_2N(C_{1-3}$ alkyl)C_{1-3} fluoroalkyl, cyano, SO_2C_{1-6} alkyl, SC_{1-6} alkyl, SC_{1-6} fluoroalkyl, N(C_{4-6} alkylene) and G1, wherein G1 is;



G1

X_5 is selected from O, NH, NC_{1-3} alkyl and NC_{1-3} fluoroalkyl;
G2 is phenyl or a 5- or 6-membered aromatic heterocycle, optionally suhstituted with a substituent selected from fluoro, bromo, iodo, methyl and methoxy;

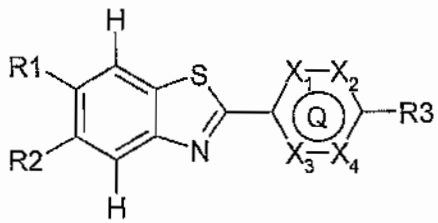
Q is a 6-membered aromatic heterocycle containing either one or two N-atoms, wherein X_1, X_2, X_3 and X_4 are independently selected from N or C, and wherein one or two of X_1,

X_2, X_3 and X_4 is N and the remaining is C, and if X_4 is C, said C is optionally substituted with fluoro or iodo;

and one or more of the atoms of formula I is optionally a detectable isotope;

as a free base or a pharmaceutieally acceptahle salt, solvate or solvate of a salt thereof, with the proviso that when R1 and R2 both are H, R3 is not methyl, hydroxy, amino, aminophenyl, aminoacetyl or methoxy.

In another aspect of the invention, there is provided a compound according to formula I



I

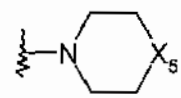
wherein

R1 is selected from hydrogen, halo, C_{1-5} alkyl, C_{1-6} fluoroalkyl, C_{1-3} alkyleneOC_{1-3} alkyl, C_{1-3} alkyleneOC_{1-3} fluorolkyl, C_{1-3} alkyleneNH$_2$, C_{1-3} alkyleneNHC_{1-3} alkyl, C_{1-3} alkyleneN(C_{1-3} alkyl)$_2$, C_{1-3} alkylcneNHC_{1-3} fluoroalkyl, C_{1-3} alkyleneN(C_{1-3} fluoroalkyl)$_2$, C_{1-3} alkyleneN(C_{1-3} alkyl)C_{1-3} fluoroalkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} fluoroalkoxy, amino, NHC_{1-3} alkyl, NHC_{1-3} fluoroalkyl, N(C_{1-3} alkyl)$_2$, N(C_{1-3} fluoroalkyl)$_2$, N(C_{1-3} alkyl)C_{1-3} fluoroalkyl, NH(CO)C_{1-3} alkyl, NH(CO)C_{1-3} fluorolkyl, NH(CO)C_{1-3} alkoxy, NH(CO)C_{1-3} fluoroalkoxy, NHSO$_2$$C_{1-3}$ alkyl, NHSO$_2$$C_{1-3}$ fluoroalkyl, (CO)C_{1-3} alkyl, (CO)C_{1-3} fluoroalkyl, COOH, (CO)C_{1-3} alkoxy, (CO)C_{1-3} fluoroalkoxy, (CO)NH$_2$, (CO)NHC_{1-3} alkyl, (CO)NHC_{1-3} fluoroalkyl, (CO)N(C_{1-3} alkyl)$_2$, (CO)N(C_{1-3} fluoroalkyl)$_2$, (CO)N(C_{1-3} alkyl)C_{1-3} fluoroalkyl, (CO)N(C_{4-6} alkylene), (CO)N(C_{4-6} fluoroalkylene) and cyano;

R2 is selected from hydrogen, halo, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-3} alkyleneOC_{1-3} alkyl,

C_{1-3} alkyleneOC_{1-3} fluorolkyl, C_{1-3} alkyleneNH_2, C_{1-3} alkyleneNHC_{1-3} alkyl, C_{1-3} alkylene$N(C_{1-3}$ alkyl$)_2$, C_{1-3} alkyleneNHC_{1-3} fluoroalkyl, C_{1-3} alkylene$N(C_{1-3}$ fluoroalkyl$)_2$, C_{1-3} alkylene$N(C_{1-3}$ alkyl$)C_{1-3}$ fluoroalkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} fluoroalkoxy, amino, NHC_{1-3} alkyl, NHC_{1-3} fluoroalkyl, $N(C_{1-3}$ alkyl$)_2$, $N(C_{1-3}$ fluoroalkyl$)_2$, $N(C_{1-3}$ alkyl$)C_{1-3}$ fluoroalkyl, $NH(CO)C_{1-3}$ alkyl, $NH(CO)C_{1-3}$ fluoroalkyl, $NH(CO)C_{1-3}$ alkoxy, $NH(CO)C_{1-3}$ fluoroalkoxy, $NHSO_2C_{1-3}$ alkyl, $NHSO_2C_{1-3}$ fluoroalkyl, $(CO)C_{1-3}$ alkyl, $(CO)C_{1-3}$ fluoroalkyl, COOH, $(CO)C_{1-3}$ alkoxy, $(CO)C_{1-3}$ fluoroalkoxy, $(CO)NH_2$, $(CO)NHC_{1-3}$ alkyl, $(CO)NHC_{1-3}$ fluoroalkyl, $(CO)N(C_{1-3}$ alkyl$)_2$, $(CO)N(C_{1-3}$ fluoroalkyl$)_2$, $(CO)N(C_{1-3}$ alkyl$)C_{1-3}$ fluoroalkyl, $(CO)N(C_{4-6}$ alkylene), $(CO)N(C_{4-6}$ fluoroalkylene) and cyano;

R3 is selected from fluoro, bromo, iodo, C_{1-4} alkyl, C_{1-4} fluoroalkyl, trifluoromethyl, C_{1-3} alkyleneOC_{1-3} alkyl, C_{1-3} alkyleneOC_{1-3} fluoroalkyl, C_{1-3} alkyleneNH_2, C_{1-3} alkyleneNHC_{1-3} alkyl, C_{1-3} alkylene$N(C_{1-3}$ alkyl$)_2$, C_{1-3} alkyleneNHC_{1-3} fluoroalkyl, C_{1-3} alkylene$N(C_{1-3}$ fluoroalkyl$)_2$, C_{1-3} alkylene$N(C_{1-3}$ alkyl$)C_{1-3}$ fluoroalkyl, hydroxy, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, amino, NHC_{1-3} alkyl, NHC_{1-3} fluoroalkyl, $N(C_{1-3}$ alkyl$)_2$, $N(C_{1-3}$ fluoroalkyl$)_2$, $N(C_{1-3}$ alkyl$)C_{1-3}$ fluoroalkyl, $NH(C_{0-3}$ alkylene$)G2$, $N(C_{0-1}$ alkyl$)N(C_{0-1}$ alkyl$)_2$, $N(C_{0-1}$ alkyl$)OC_{0-1}$ alkyl, $NH(CO)C_{1-3}$ alkyl, $NH(CO)C_{1-3}$ fluoroalkyl, NH(CO)G2, $(CO)C_{1-3}$ alkyl, $(CO)C_{1-3}$ fluorolkyl, $(CO)C_{1-3}$ alkoxy, $(CO)C_{1-3}$ fluoroalkoxy, $(CO)NH_2$, $(CO)NHC_{1-3}$ alkyl, $(CO)NHC_{1-3}$ fluoroalkyl, $(CO)N(C_{1-3}$ alkyl$)_2$, $(CO)N(C_{1-3}$ fluoroalkyl$)_2$, $(CO)N(C_{1-3}$ alkyl$)C_{1-3}$ fluoroalkyl, $(CO)N(C_{4-6}$ alkylene), $(CO)N(C_{4-6}$ fluoroalkylene), $(CO)NH_2$G2, SO_2NH_2, SO_2NHC_{1-3} alkyl, SO_2NHC_{1-3} fluoroalkyl, $SO_2N(C_{1-3}$ alkyl$)_2$, $SO_2N(C_{1-3}$ fluoroalkyl$)_2$, $SO_2N(C_{1-3}$ alkyl$)C_{1-3}$ fluoroalkyl, cyano and G1, wherein G1 is;



G1

X_5 is selected from O, NH, NC_{1-3} alkyl and NC_{1-3} fluorolkyl;

G2 is phenyl or a 5- or 6-membered aromatic heterocycle, optionally substituted with a substituent seleeted from fluoro, bromo, iodo, methyl and methoxy;

Q is a 6-membered aromatic heterocycle containing either one or two N-atoms, wherein X_1, X_2, X_3 and X_4 are independently selected from N or C, and wherein one or two of X_1, X_2, X_3 and X_4 is N and the remaining is C;

as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof, with the proviso that when R1 and R2 both are H, R3 is not methyl, hydroxy, amino, aminophenyl, aminoacetyl or methoxy.

In another aspect of the invention, there is provided a compound according to formula I, wherein R1 is selected from hydrogen, halo, C_{1-5} alkyl, hydroxy, C_{1-6} alkoxy, amino, NHC_{1-3} alkyl, NHC_{1-3} fluoroalkyl, $N(C_{1-3}$ alkyl$)_2$, $NH(CO)C_{1-3}$ alkyl, $NH(CO)C_{1-3}$ fluoroalkyl, $(CO)NH_2$, $(CO)NHC_{1-3}$ alkyl and $(CO)NHC_{1-3}$ fluoroalkyl.

In another aspect of the invention, there is provided a compound according to formula I, whercin R2 is seleeted from hydrogen, halo, C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, amino, NHC_{1-3} alkyl, NHC_{1-3} fluoroalkyl, $N(C_{1-3}$ alkyl$)_2$, $NH(CO)C_{1-3}$ alkyl, $NH(CO)C_{1-3}$ fluoroalkyl, $(CO)NH_2$, $(CO)NHC_{1-3}$ alkyl and $(CO)NHC_{1-3}$ fluoroalkyl.

In another aspect of the invention, there is provided a compound according to formula I, wherein R3 is selected from fluoro, bromo, iodo, hydroxy, C_{1-4} alkoxy, trifluoromcthyl, C_{1-4} fluoroalkoxy, amino, NHC_{1-3} alkyl, NHC_{1-3} fluoroalkyl, $N(C_{1-3}$ alkyl$)_2$, $N(C_{1-3}$ fluoroalkyl$)_2$, $N(C_{1-3}$ alkyl$)C_{1-3}$ fluoroalkyl, $(CO)NH_2$, $NH(C_{0-3}$ alkylene$)$G2, $NH(CO)C_{1-3}$ alkyl and G1, whercin X_5 is selected from NH, O and NMe; G2 is phcnyl or pyridyl, said phenyl or pyridyl optioually substituted with a substituent selected from fluoro, methyl and methoxy.

6In another aspect of the invention, there is provided a compound aceording to formula I, wherein Q is a pyridine ring, wherein X_1 and X_2 are independently selected from N or C, and wherein one of X_1 and X_2 is N and the remaining of X_1, X_2, X_3 and X_4 are C.

In another aspect of the invention, there is provided a compound according to formula I, wherein Q is a pyrimidine ring, wherein X_1 and X_2 are independently seleeted from N or C, and wherein one of X_1 and X_2 is N; and wherein X_3 and X_4 are independently selected from N or C, and whcrein one of X_3 and X_4 is N.

In another aspect of the invention, there is provided a compound according to formula I, wherein R2 is selected from hydrogen, fluoro, hromo, iodo, amino, methyl, hydroxy, methoxy, NHMe and $(CO)NH_2$.

In another aspect of the invention, there is provided a compound according to formula I, wherein R2 is selected from hydrogen, methoxy and amino.

In another aspect of the invention, there is provided a compound according to formula I, wherein R1 is selected from hydrogen, fluoro, broino, iodo, amino, methyl, hydroxy, methoxy, NHMe and $(CO)NH_2$.

In another aspect of the invention, there is provided a compound according to formula I, wherein R3 is selected from fluoro, methoxy, ethoxy, trifluoromethyl, NHMe, amino, $N(C_{1-3}\text{ alkyl})_2$, $(CO)NH_2$, and G1, wherein X_5 is selected from NH, O and NMe.

In another aspect of the invention, there is provided a compound according to formula I, wherein Q is a pyridinc ring, wherein X_2 is N, and X_1, X_3 and X_4 are C.

In another aspect of the invention, there is provided a compound according to formula I, wherein Q is a pyridine ring, wherein X_4 is N, and X_1, X_2 and X_3 are C.

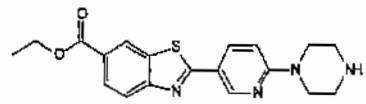
In another aspeet of the invention, there is provided a compound according to formula I, wherein Q is a pyrimidine ring, wherein X_2 and X_4 are N; and X_1 and X_3 are C.

In another aspect of the invention, there is provided a compound according to formula I, comprising one ^{11}C atom, wherein one of R1 and R2 is either hydroxy or [^{11}C]methoxy, and the other one of R1 and R2 is H;

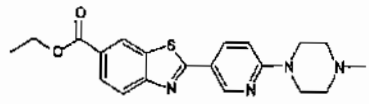
R3 is selected from amino, NHMe, $NH^{11}CH_3$ and $N(Me)^{11}CH_3$;

Q is a pyridine ring, wherein X_1 and X_2 are independently selected from N or C, and wherein one of X_1 and X_2 is N and the remaining of X_1, X_2, X_3 and X_4 are C.

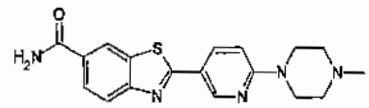
In another aspect of the invention, there is provided a compound according to formula I, said compound being:



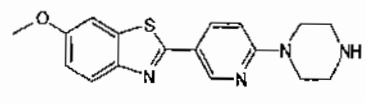
Ethyl 2-(6-Piperazin-1-ylpyridin-3-yl)-1,3-benzothiazole-6-carboxylate Trifluoroacetate



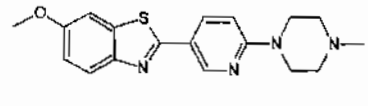
Ethyl 2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazole-6-carboxylate



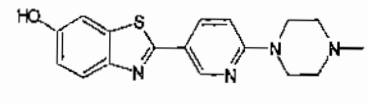
2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazole-6-carboxamide Acetate



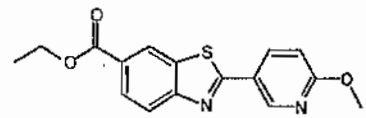
6-Methoxy-2-(6-piperazin-1-ylpyridin-3-yl)-1,3-benzothiazole



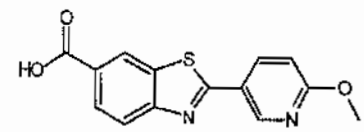
6-Methoxy-2-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazole



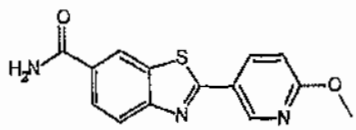
2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazol-6-ol Acetate



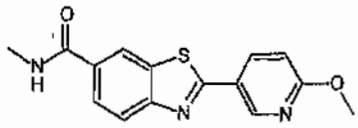
Ethyl 2-(6-Mathoxypyridin-3-yl)-1,3-benzothiazole-6-carboxylate



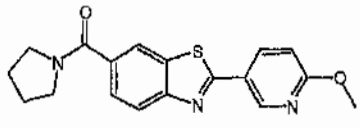
2-(6-Methoxypyridin-3-yl)-1,3-benzothiazole-6-carboxylic Acid



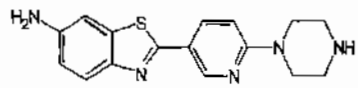
2-(6-Methoxypyridin-3-yl)-1,3-benzothiazole-6-carboxamide



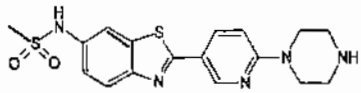
2-(6-Methoxypyridin-3-yl)-N-methyl-1,3-benzothiazole-6-carboxamide



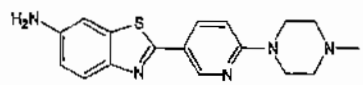
2-(6-Methoxypyridin-3-yl)-6-(pyrrolidin-1-ylcarbonyl)-1,3-benzothiazole



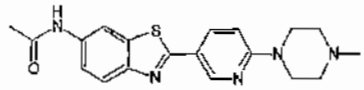
2-(6-Piperazin-1-ylpyridin-3-yl)-1,3-benzothiazol-6-amine



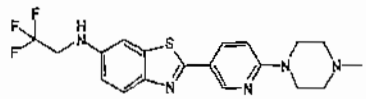
N-[2-(6-Piperazin-1-ylpyridin-3-yl)-1,3-benzothiazol-6-yl]methanesulfonamide



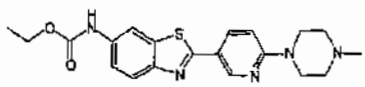
2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazol-6-amine Trifluoroacetate



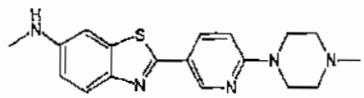
N-{2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazol-6-yl}acetamide



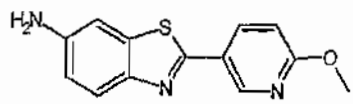
2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-N-(2,2,2-trifluoroethyl)-1,3-benzothiazol-6-amine



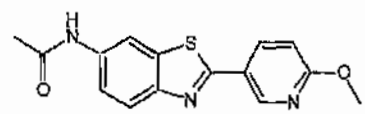
Ethyl {2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiezol-6-yl}carbamate



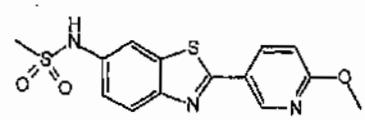
N-Methyl-2-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazol-6-amine



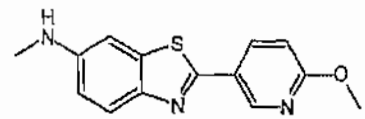
2-(6-Methoxypyridin-3-yl)-1,3-benzothiazol-6-amine



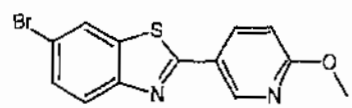
N-[2-(6-Methoxypyridin-3-yl)-1,3-benzothiazol-6-yl]acetamide



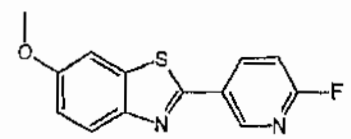
N-[2-(6-Methoxypyridin-3-yl)-1,3-benzothiazol-6-yl]methanesulfonamide



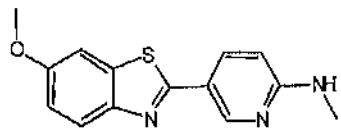
2-(6-Methoxypyridin-3-yl)-N-methyl-1,3-benzothiazol-6-amine



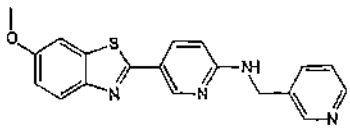
6-Bromo-2-(6-methoxypyridin-3-yl)-1,3-benzothiazole



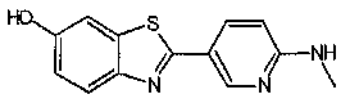
2-(6-Fluoropyridin-3-yl)-6-methoxy-1,3-benzothiazole



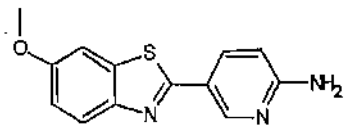
5-(6-Methoxy-1,3-benzothiazol-2-yl)-N-methylpyridin-2-amine



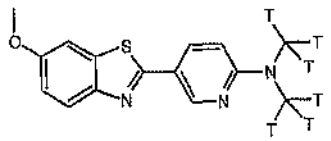
5-(6-Methoxy-1,3-benzothiazol-2-yl)-N-(pyridin-3-ylmethyl)pyridin-2-amine



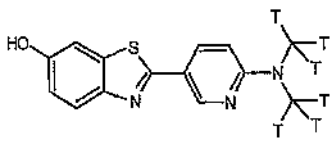
2-[6-(Methylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol



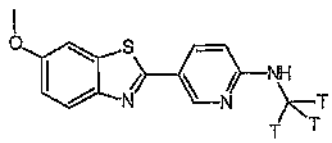
5-(6-Methoxy-1,3-benzothiazol-2-yl)pyridin-2-amine



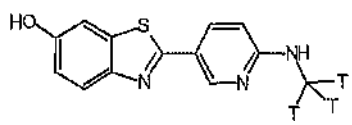
[N-Dimethyl-3H6]-[5-(6-Methoxy-benzothiazol-2-yl)-pyridin-2-yl]-dimethyl-amine



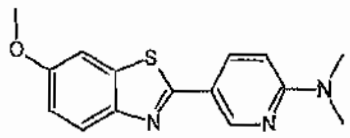
[N-Dimethyl-3H6]-2-(6-Dimethylamino-pyridin-3-yl)-benzothiazol-6-ol



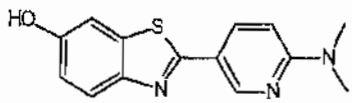
[N-Methyl-3H3]-[5-(6-Methoxy-benzothiazol-2-yl)-pyridin-2-yl]-methyl-amine



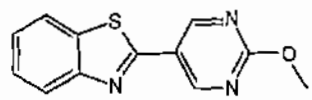
[N-Methyl-3H3]-2-(6-Methylamino-pyridin-3-yl)-benzothiazol-6-ol



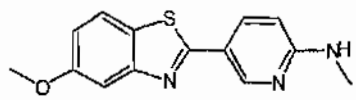
5-(6-methoxy-1,3-benzothiazol-2-yl)-N,N-dimethylpyridin-2-amine



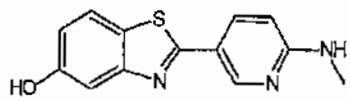
2-[6-(dimethylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol



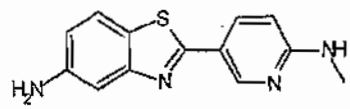
2-(2-methoxypyrimidin-5-yl)-1,3-benzothiazola



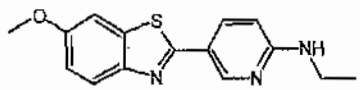
5-(5-methoxy-1,3-benzothiazol-2-yl)-N-methylpyridin-2-amine



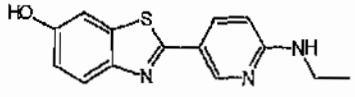
2-[6-(methylamino)pyridin-3-yl]-1,3-benzothiazol-5-ol



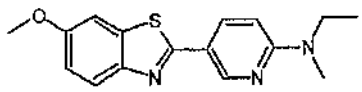
2-[6-(methylamino)pyridin-3-yl]-1,3-benzothiazol-5-amine



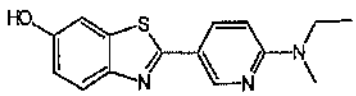
N-ethyl-5-(6-methoxy-1,3-benzothiazol-2-yl)pyridin-2-amine



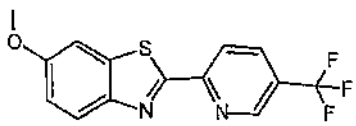
2-[6-(ethylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol



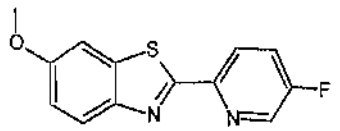
N-ethyl-5-(6-methoxy-1,3-benzothiazol-2-yl)-N-methylpyridin-2-amine



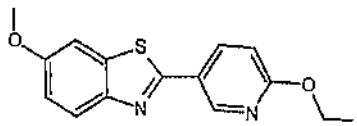
2-(6-[ethyl(methyl)amino]pyridin-3-yl)-1,3-benzothiazol-6-ol



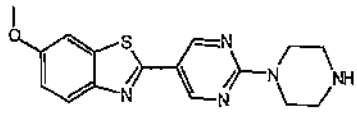
6-methoxy-2-[5-(trifluoromethyl)pyridin-2-yl]-1,3-benzothiazole



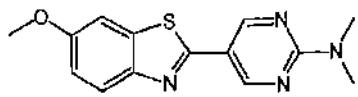
2-(5-fluoropyridin-2-yl)-6-methoxy-1,3-benzothiazole



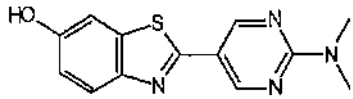
2-(6-ethoxypyridin-3-yl)-6-methoxy-1,3-benzothiezole



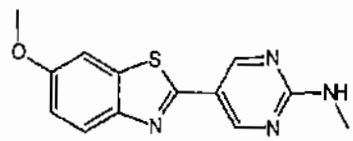
6-methoxy-2-(2-piperazin-1-ylpyrimidin-5-yl)-1,3-benzothiazole



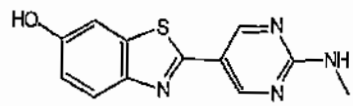
5-(6-methoxy-1,3-benzothiazol-2-yl)-N,N-dimethylpyrimidin-2-amine



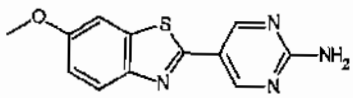
2-[2-(dimethylamino)pyrimidin-5-yl]-1,3-benzothiazol-6-ol



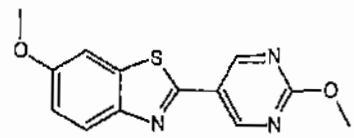
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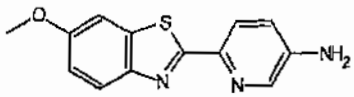
2-[2-(methylamino)pyrimidin-5-yl]-1,3-benzothiazol-6-ol



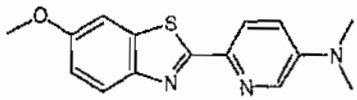
5-(6-methoxy-1,3-benzothiazol-2-yl)pyrimidin-2-amine



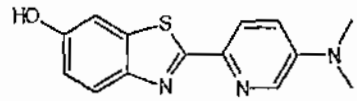
6-methoxy-2-(2-methoxypyrimidin-5-yl)-1,3-benzothiazole



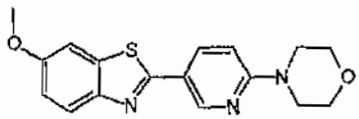
6-(6-methoxy-1,3-benzothiazol-2-yl)pyridin-3-amine



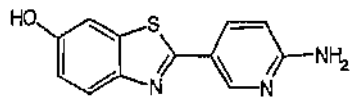
6-(6-methoxy-1,3-benzothiazol-2-yl)-N,N-dimethylpyridin-3-amine



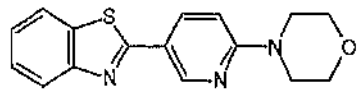
2-[5-(dimethylamino)pyridin-2-yl]-1,3-benzothiazol-6-ol



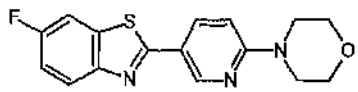
6-methoxy-2-(6-morpholin-4-ylpyridin-3-yl)-1,3-benzothiazole



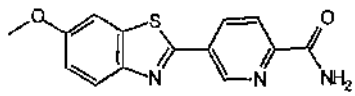
2-(6-aminopyridin-3-yl)-1,3-benzothiazol-6-ol



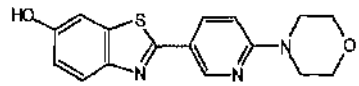
2-(6-morpholin-4-ylpyridin-3-yl)-1,3-benzothiazole



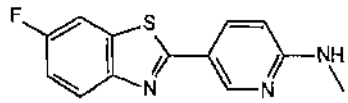
6-fluoro-2-(6-morpholin-4-ylpyridin-3-yl)-1,3-benzothiazole



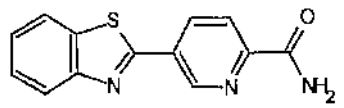
5-(6-methoxy-1,3-benzothiazol-2-yl)pyridine-2-carboxamide



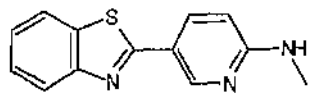
2-(6-morpholin-4-ylpyridin-3-yl)-1,3-benzothiazol-6-ol



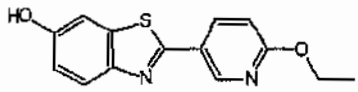
5-(6-fluoro-1,3-benzothiazol-2-yl)-N-methylpyridin-2-amine



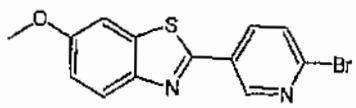
5-(1,3-benzothiazol-2-yl)pyridine-2-carboxamide



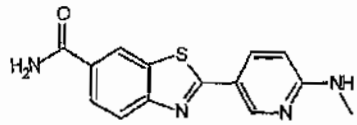
5-(1,3-benzothiazol-2-yl)-N-methylpyridin-2-amine



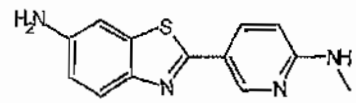
2-(6-ethoxypyridin-3-yl)-1,3-benzothiazol-6-ol



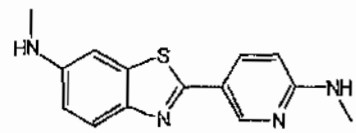
2-(6-bromopyridin-3-yl)-6-methoxy-1,3-benzothiazole



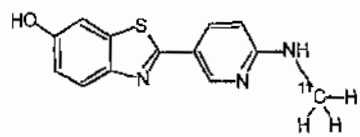
2-[6-(methylamino)pyridin-3-yl]-1,3-benzothiazole-6-carboxamide



2-[6-(methylamino)pyridin-3-yl]-1,3-benzothiazol-6-amine



N-methyl-2-[6-(methylamino)pyridin-3-yl]-1,3-benzothiazol-6-amine

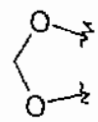


[N-Methyl-11C]-2-(6-Methylamino-pyridin-3-yl)-benzothiazol-6-ol

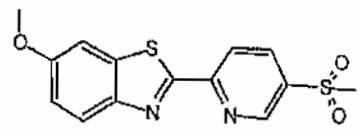
In another aspect of the invention, there is provided a compound according to formula I, wherein X_4 of formula I is a carbon atom substituted with fluoro or iodo.

In another aspect of the invention, there is provided a compound according to formula I, wherein R3 of formula I is selected from SO_2C_{1-6} alkyl, SC_{1-6} alkyl, SC_{1-6} fluoroalkyl and $N(C_{4-6}$ alkylene).

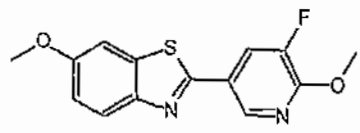
In another aspect of the invention, there is provided a compound according to formula I, wherein R1 and R2 together forms a ring;



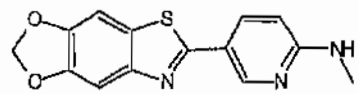
In another aspect of the invention, there is provided a compound according to formula I, said compound being:



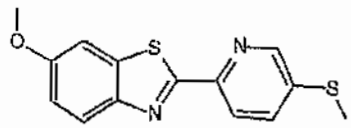
6-methoxy-2-[5-(methylsulfonyl)pyridin-2-yl]-1,3-benzothiazole



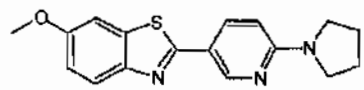
2-(5-fluoro-6-methoxypyridin-3-yl)-6-methoxy-1,3-benzothiazole



5-[1,3]dioxolo[4,5-f][1,3]benzothiazol-6-yl-N-methylpyridin-2-amine



6-methoxy-2-[5-(methylthio)pyridin-2-yl]-1,3-benzothiazole



6-methoxy-2-(6-pyrrolidin-1-ylpyridin-3-yl)-1,3-benzothiazole

In another aspect of the invention, there is provided a compound according to formula I, wherein one to three of the atoms represents a deteetable isotope selected from ^{3}H, ^{19}F and ^{13}C, or wherein one of the atoms is a detectable isotope selected from ^{18}F, ^{11}C and ^{14}C.

In another aspect of the invention, there is provided a compound according to formula I, wherein one or more of the, atoms of R1 is a radiolabeled atom.

In another aspect of the invention, there is provided a compound according to formula I, wherein one or more of the atoms of R2 is a radiolabeled atom.

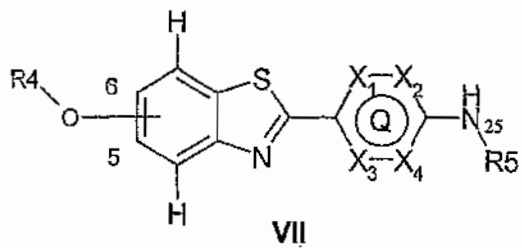
In another aspect of the invention, there is provided a compound according to formula I, wherein one or more of the atoms of R3 is a radiolabeled atom.

In another aspect of the invention, there is provided a compound according to formula I, wherein said radiolabeled atom is selected from ^{3}H, ^{18}F, ^{19}F, ^{11}C, ^{13}C, ^{14}C, ^{75}Br, ^{76}Br, ^{120}I, ^{123}I, ^{125}I and ^{131}I.

In another aspect of the invention, there is provided a compound according to formula I, wherein said radiolabeled atom is selected from ^{3}H, ^{18}F, ^{19}F, ^{11}C, ^{14}C and ^{123}I.

In another aspect of the invention, there is provided a compound according to formula I, wherein said radiolabeled atom is selected from ^{18}F and ^{11}C.

In another aspect of the invention, there is provided a compound according to formula VII



VII

wherein

O-R4 residue is attached to position 6, and a hydrogen atom is attached to position 5 of the benzothiazole ring;

R4 is selected from $Si(G3)_3$, CH_2G4, tetrahydropyranyl, 1-ethoxyethyl, phenacyl, 4-bromophenacyl, cyclohexyl, *t*-butyl, *t*-butoxycarbonyl, 2,2,2-trichloroethylcarbonyl and triphenylmethyl;

G3 is, independently of each other, selected from C_{1-4} alkyl and phenyl;

G4 is selected from 2-(trimethylsilyl)ethoxy, C_{1-3} alkoxy, 2-(C_{1-3} alkoxy)ethoxy, C_{1-3} alkylthio, cyclopropyl, vinyl, phenyl, *p*-methoxyphenyl, *o*-nitrophenyl, and 9-anthryl;

Q is a 6-membered aromatic heterocycle containing either one or two N-atoms, wherein X_1, X_2, X_3 and X_4 are independently selected from N or C, and wherein one or two of X_1, X_2, X_3 and X_4 is N and the remaining is C;

R5 is selected from C_{1-3} alkyl and hydrogen;
as a free base or a salt, solvate or solvate of a salt thereof.

In another aspect of the invention, there is provided a compound according to formula VII, wherein R4 is $Si(G3)_3$.

In another aspect of the invention, there is provided a compound according to formula VII, wherein R4 is selected from *t*-butyldimethylsilyl, 2-(trimethylsilyl)ethoxymethyl and ethoxymethyl.

In another aspect of the invention, there is provided a compound according to formula VII, wherein R4 is selected from *t*-butyldimethylsilyl and ethoxymethyl.

In another aspect of the invention, there is provided a compound according to formula VII, wherein R4 is *t*-butyldimethylsilyl.

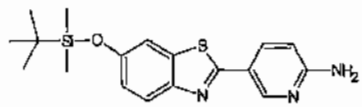
In another aspect of the invention, there is provided a compound according to formula VII, Q is a pyrimidine ring, wherein X_2 and X_4 are N, and X_1 and X_3 are C.

In another aspect of the invention, there is provided a compound according to formula VII, wherein Q is a pyridine ring, wherein X_2 is N, and X_1, X_3 and X_4 are C.

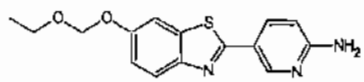
In another aspect of the invention, there is provided a compound according to formula VII, wherein Q is a pyridine ring, wherein X_4 is N, and X_1, X_2 and X_3 are C.

In another aspect of the invention, there is provided a compound according to formula VII, wherein R5 is hydrogen.

In another aspect of the invention, there is provided a compound according to formula VII, said compound being:

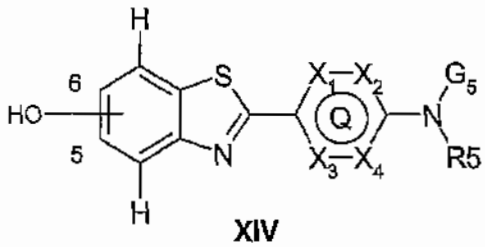


5-{6-{[*tert*-butyl(dimethyl)silyl]oxy}-1,3-benzothiazol-2-yl)pyridin-2-amine



5-[6-(ethoxymethoxy)-1,3-benzothiazol-2-yl]pyridin-2-amine

In another aspect of the invention, there is provided use of a compound according to formula VII as synthetic precursor in a process of preparation of a labeled compound of formula XIV



XIV

wherein

OH is attached to position 6, and a hydrogen atom is attached to position 5 of the benzothiazole ring;

Q is a 6-membered aromatic heterocycle containing either one or two N-atoms, wherein X_1, X_2, X_3 and X_4 are independently selected from N or C, and wherein one or two of X_1, X_2, X_3 and X_4 is N and the remaining is C;

R5 is seleeted from C_{1-3} alkyl and hydrogen;

G5 is selected from C_{1-3} alkyl and C_{1-3} fluoroalkyl, wherein one to three of the atoms of G5 is a deteetable isotope selected from ^{3}H, ^{19}F and ^{13}C, or wherein one of the atoms of G5 is detectable isotope selected from ^{18}F, ^{11}C and ^{14}C.

In another aspect of the invention, there is provided a pharmaceutical composition comprising a compound according to formula I, togcther with a pharmaceutically acceptable carrier.

In another aspect of the invention, there is provided a pharmaceutical composition for *in vivo* imaging of amyloid deposits, comprising a radio-labeled compound aecording to formula I, together with a pharmaceutically acceptable carrier.

In another aspect of the invention, there is provided an *in vivo* method for measuring amyloid deposits in a subject, comprising the steps of: (a) administering a detectable

quantity of a pharmaceutical composition comprising a radio-labeled compound of formula I, and detecting the binding of the compound to amyloid deposit in the subject. Said detection may be carried out by gamma imaging, magnetic resonance imaging or magnetic resonance spectroscopy. Said subject may be suspected of having a disease or syndrome selected from the group consisting of Alzheimer's Disease, familial Alzheimer's Disease, Down's Syndrome and homozygotes for the apolipoprotein E4 allele.

In another aspect of the invention, there is provided a compound of formula I for use in therapy.

In another aspect of the invention, there is provided use of a compound of formula I in the manufacture of a medicament for prevention and/or treatment of Alzheimer's Disease, familial Alzheimer's Disease, Cognitive Deficit in Schizophrenia (CDS), Down's Syndrome and homozygotes for the apolipoprotein E4 allele.

In another aspect of the invention, there is provided use of a compound of formula I in the manufacture of a medicament for prevention and/or treatment of Alzheimer's Disease.

In another aspect of the invention, there is provided use of a compound of formula I in the manufacture of a medicament for prevention and/or treatment of Cognitive Deficit in Schizophrenia (CDS).

In another aspect of the invention, there is provided a method of prevention and/or treatment of Alzheimer's Disease, familial Alzheimer's Disease, Down's Syndrome and homozygotes for the apolipoprotein E4 allele, comprising administrering to a mammal, including man in need of such prevention and/or treatment, a therapeutically effective amount of a compound of formula I.

In another aspect of the invention, there is provided a method of prevention and/or treatment of Alzheimer's Disease, comprising administrering to a mammal, including man

in need of sueh prevention and/or treatment, a therapeutically effective amount of a compound of formula I.

In another aspect of the invention, there is provided a method of prevention and/or treatment of Cognitive Deficit in Schizophrenia (CDS), comprising administrering to a mammal, including man in need of such prevention and/or treatment, a therapeutically effective amount of a compound of formula I.

Defimitions

As used herein, "alkyl", "alkylenyl" or "alkylene" used alone or as a suffix or prefix, is intended to include both branched and straight chain saturated aliphatic hydrocarbon groups having from 1 to 12 carbon atoms or if a specified number of carbon atoms is provided then that specific number would he intended. For example "C_{1-6} alkyl" denotes alkyl having 1, 2, 3, 4, 5 or 6 earbon atoms. When the specific number denoting the alkyl-group is the integer 0 (zero), a hydrogen-atom is intended as the substituent at the position of the alkyl-group. For example, "$N(C_0$ alkyl$)_2$" is equivalent to "NH_2" (amino). When the specific number denoting the alkylenyl or alkylene-group is the integer 0 (zero), a bond is intended to link the groups onto which the alkylenyl or alkylene-group is substituted. For example, "$NH(C_0$ alkylene$)NH_2$" is equivalent to "$NHNH_2$" (hydrazino). As used herein, the groups linked by an alkylene or alkylenyl-group are intended to be attached to the first and to the last carbon of the alkylene or alkylenyl-group. In the case of methylene, the first and the last carbon is the same. For example, "$N(C_4$ alkylene$)$", "$N(C_5$ alkylene$)$" and "$N(C_2$ alkylene$)_2NH$" is equivalent to pyrrolidinyl, piperidinyl and piperazinyl, repectively.

Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, and hexyl.

Examples of alkylene or alkylenyl include, but are not limited to, methylene, ethylene, propylene, and butylene.

As used herein, "alkoxy" or "alkyloxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy

include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, t-butoxy, n-pentoxy, isopentoxy, cyclopropylmethoxy, allyloxy and propargyloxy. Similarly, "alkylthio" or "thioalkoxy" represent an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge.

As used herein, "fluoroalkyl", "fluoroalkylene" and "fluoroalkoxy", used alone or as a suffix or prefix, refers to groups in which one, two, or three of the hydrogen(s) attached to the carbon(s) of the corresponding alkyl, alkylene and alkoxy-groups are replaced by fluoro. Examples of fluoroalkyl include, but are not limited to, trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 2-fluoroethyl and 3-fluoropropyl.

Examples of fluoroalkylene include, but are not limited to, difluoromethylene, fluoromethylene, 2,2-difluorobutylene and 2,2,3-trifluorobutylene.

Examples of fluoroalkoxy include, but are not limited to, trifluoromethoxy, 2,2,2-trifluoroethoxy, 3,3,3-trifluoropropoxy and 2,2-difluoropropoxy.

As used herein, "aromatic" refers to hydrocarbonyl groups having one or more unsaturated carbon ring(s) having aromatic characters, (e.g. 4n + 2 delocalized electrons) and comprising up to about 14 carbon atoms. In addition "heteroaromatic" refers to groups having one or more unsaturated rings containing carbon and one or more heteroatoms such as nitrogen, oxygen or sulphur having aromatic character (e.g. 4n + 2 delocalized electrons).

As used herein, the term "aryl" refers to an aromatic ring structure made up of from 5 to 14 carbon atoms. Ring structures containing 5, 6, 7 and 8 carbon atoms would be single-ring aromatic groups, for example, phenyl. Ring structures containing 8, 9, 10, 11, 12, 13, or 14 would be polycyclic, for example naphthyl. The aromatic ring can be substituted at one or more ring positions with such substituents as described above. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, for example, the other cyclic rings can be cycloalkyls,

cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls. The terms ortho, meta and para apply to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and ortho-dimethylbenzene are synonymous.

As used herein, the term "cycloalkyl" is intended to include saturated ring groups, having the specified number of carbon atoms. These may include fused or bridged polycyclic systems. Preferred cycloalkyls have from 3 to 10 carbon atoms in their ring structure, and more preferably have 3, 4, 5, and 6 carbons in the ring structure. For example, "C_{3-6} cycloalkyl" denotes such groups as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo, and iodo. "Counterion" is used, for example, to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, tosylate, benezensulfonate, and the like.

As used herein, the term "heteroeyclyl" or "heteroeyclie" or "heterocycle" refers to a saturated, unsaturated or partially saturated, monoeyclic, bicyclic or trieyclic ring (unless otherwise stated) eontaining 3 to 20 atoms of which 1, 2, 3, 4 or 5 ring atoms are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise speeified, be carbon or nitrogen linked, wherein a $-CH_2-$ group is optionally be replaced by a -C(O)-; and where unless stated to the contrary a ring nitrogen or sulphur atom is optionally oxidised to form the *N*-oxide or *S*-oxide(s) or a ring nitrogen is optionally quarternized; wherein a ring –NH is optionally substituted by acetyl, formyl, methyl or mesyl; and a ring is optionally substituted by one or more halo. It is understood that when the total number of S and O atoms in the heteroeyclyl exceeds 1, then these heteroatoms are not adjacent to one another. If the said heterocyclyl group is bi- or tricyclic then at least one of the rings may optionally be a heteroaromatic or aromatic ring provided that at least one of the rings is non-heteroaromatic. If the said beterocyclyl group is monocyclic then it must not be aromatic. Examples of heterocyclyls include, but are not limited to, piperidinyl, *N*-acetylpiperidinyl, *N*-methylpiperidinyl, *N*-formylpiperazinyl, *N*-mesylpiperazinyl, homopiperazinyl, piperazinyl, azetidinyl, oxetanyl, morpholinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, indolinyl, tetrahydropyranyl, dihydro-*2H*-pyranyl, tetrahydrofuranyl and 2,5-dioxoimidazolidinyl.

As used herein, "heteroaryl" refers to a heteroaromatic heterocycle having at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include monocyclic and polycyclic (e.g., having 2, 3 or 4 fused rings) systems. Examples of heteroaryl groups include without limitation, pyridyl (i.e., pyridinyl), pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl (i.e. furanyl), quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrryl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, benzothienyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, and the like. In some embodiments, the heteroaryl group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, the heteroaryl group contains 3 to about 14, 4 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heteroaryl group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms. In some embodiments, the heteroaryl group has 1 heteroatom.

As used herein, the phrase "protecting group" or "protective group" means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones respectively. A sub-group of protecting groups are those which protect a nucleophilic hydroxy group against alkylation and thus permit selective *N*-alkylation of an amino-group present in the same molecule under basic conditions. Examples of such protecting groups include, but is not limited to, methyl, 2-(trimethylsilyl)ethoxymethyl, alkoxymethyl and *t*-butyldimethylsilyl.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such

conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, phosphoric, and the like; and the salts prepared from organic acids such as lactic, maleic, citric, benzoic, methanesulfonic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used.

As used herein, "*in vivo* hydrolysable precursors" means an *in vivo* hydrolysable (or cleavable) ester of a compound of formula I that contains a carboxy or a hydroxy group. For example amino acid esters, C_{1-6} alkoxymethyl esters like methoxymethyl; C_{1-6}alkanoyloxymethyl esters like pivaloyloxymethyl; C_{3-8}cycloalkoxycarbonyloxy C_{1-6}alkyl esters like 1-cyclohexylcarbonyloxyethyl, acetoxymethoxy, or phosphoramidic cyclic esters.

As used herein, "tautomer" means other structural isomers that exist in equilibrium resulting from the migration of a hydrogen atom. For example, keto-enol tautomerism where the resulting compound has the properties of both a ketone and an unsaturated alcohol.

As used herein "stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic or diagnostic agent.

Compounds of the invention further include hydrates and solvates.

The present invention includes isotopically labeled compounds of the invention. An "isotopically-labeled", "radio-labeled", "labeled", "detectable" or "detectable amyloid binding" compound, or a "radioligand" is a compound of the invention where one or more

atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). Suitable radionuclides (i.e. "detectable isotopes") that may be incorporated in compounds of the present invention include but are not limited to ^{2}H (also written as D for deuterium), ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I and ^{131}I. It is to be understood that an isotopically labeled compound of the invention need only to be enriched with a detectable isotop to, or above, the degree which allows detection with a technique suitable for the particular application, e.g. in a detectable compound of the invention labeled with ^{11}C, the carbon-atom of the labeled group of the labeled compound may be constituted by ^{12}C or other carbon-isotopes in a fraction of the molecules. The radionuclide that is incorporated in the instant radiolabeled compounds will depend on the specific application of that radiolabeled compound. For example, for *in vitro* plaque or receptor labeling and competition assays, compounds that incorporate ^{3}H, ^{14}C, or ^{125}I will generally be most useful. For *in vivo* imaging applications ^{11}C, ^{13}C, ^{18}F, ^{19}F, ^{120}I, ^{123}I, ^{131}I, ^{75}Br, or ^{76}Br will generally be most useful.

In one embodiment of the invention the radionuclides are represented by ^{3}H, ^{18}F, ^{19}F, ^{11}C, ^{13}C, ^{14}C, ^{75}Br, ^{76}Br, ^{120}I, ^{123}I, ^{125}I or ^{131}I.

Examples of an "effective amount" include amounts that enable imaging of amyloid deposit(s) *in vivo*, that yield acceptable toxicity and bioavailability levels for pharmaceutical use, and/or prevent cell degeneration and toxicity associated with fibril formation.

This invention provides radiolabeled heteroaryl substituted benzothiazoles as amyloid imaging agents and synthetic precursor compounds from which such are prepared.

It is believed that the compounds of the present invention may be used for the treatment of Alzheimer disease. Hence, compounds of the present invention and their salts are expected to be active against age-related diseases such as Alzheimer, as well as other Aβ related pathologies such as Downs syndrome and β-amyloid angiopathy. It is expected that the

compounds of the present invention would most likely be used as single agents but could also be used in combination with a broad range of cognition deficit enhancement agents.

In one embodiment of the present invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, or a pharmaceutical composition or formulation comprising a compound of formula (I) is administered concurrently, simultaneously, sequentially or separately with another pharmaceutically active compound or compounds used in Alzheimer's therapies including for example donepezil, memantine, tacrine and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

Methods of use

The compounds of the present invention may be used to determine the presence, location and/or amount of one or more amyloid deposit(s) in an organ or body area, including the brain, of an animal. Amyloid deposit(s) include, without limitation, deposit(s) of Aβ. In allowing the temporal sequence of amyloid deposition to be followed, the inventive compounds may further be used to correlate amyloid deposition with the onset of clinical symptoms associated with a disease, disorder or condition. The inventive compounds may ultimately be used to treat, and to diagnose a disease, disorder or condition characterized by amyloid deposition, such as AD, familial AD, Down's syndrome, amyloidosis and homozygotes for the apolipoprotein E4 allele.

The method of this invention determines the presence and location of amyloid deposits in an organ or body area, preferably brain, of a patient. The present method comprises administration of a detectable quantity of a pharmaceutical composition containing an amyloid-binding compound of the present invention called a "detectable compound," or a pharmaceutically acceptable water-soluble salt thereof, to a patient. A "detectable quantity" means that the amount of the detectable compound that is administered is sufficient to enable detection of binding of the compound to amyloid. An "imaging effective quantity" means that the amount of the detectable compound that is administered is sufficient to enable imaging of binding of the compound to amyloid.

The invention employs amyloid probes which, in conjunction with non-invasive neuroimaging techniques such as magnetic resonance spectroscopy (MRS) or imaging (MINI), or gamma imaging such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT), are used to quantify amyloid deposition *in vivo*. The term "*in vivo* imaging" refers to any method which permits the detection of a labeled heteroaryl substituted benzothiazole derivative as described herein. For gamma imaging, the radiation emitted from the organ or area being examined is measured and expressed either as total binding or as a ratio in which total binding in one tissue is normalized to (for example, divided by) the total binding in another tissue of the same subject during the same *in vivo* imaging procedure. Total binding *in vivo* is defined as the entire signal detected in a tissue by an *in vivo* imaging technique without the need for correction by a second injection of an identical quantity of labeled compound along with a large excess of unlabeled, but otherwise chemically identical compound. A "subject" is a mammal, preferably a human, and most preferably a human suspected of having dementia.

For purposes of *in vivo* imaging, the type of detection instrument available is a major factor in selecting a given label. For instance, radioactive isotopes and ^{19}F are particularly suitable for *in vivo* imaging in the methods of the present invention. The type of instrument used will guide the selection of the radionuclide or stable isotope. For instance, the radionuclide chosen must have a type of decay detectable by a given type of instrument.

Another consideration relates to the half-life of the radionuclide. The half-life should be long enough so that it is still detectable at the time of maximum uptake by the target, but short enough so that the host does not sustain deleterious radiation. The radiolabeled compounds of the invention can be detected using gamma imaging wherein emitted gamma irradiation of the appropriate wavelength is detected. Methods of gamma imaging include, but are not limited to, SPECT and PET. Preferably, for SPECT detection, the chosen radiolabel will lack a particulate emission, but will produce a large number of photons in a 140-200 keV range.

For PET detection, the radiolabel will be a positron-emitting radionuclide such as ^{18}F which will annihilate to form two 511 keV gamma rays which will be detected by the PET camera.

In the present invention, amyloid binding compounds/probes are made which are useful for *in vivo* imaging and quantification of amyloid deposition. These compounds are to be used in conjunction with non-invasive neuroimaging techniques such as magnetic resonance spectroscopy (MRS) or imaging (MRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT). In aecordance with this invention, the heteroaryl substituted benzothiazole derivatives may be labeled with ^{19}F or ^{13}C for MRS/MRI by general organic chemistry techniques known in the art. The compounds may also be radiolabeled with ^{18}F, ^{11}C, ^{75}Br, ^{76}Br, or ^{120}I for PET by techniques well known in the art and are described by Fowler, J. and Wolf, A. in POSITRON EMISSION TOMOGRAPHY AND AUTORADIOGRAPHY 391-450 (Raven Press, 1986). The compounds also may be radiolabeled with ^{123}I and ^{131}I for SPECT by any of several techniques known to the art. See, e.g., Kulkarni, Int. J. Rad. Appl. &Inst. (Part B) 18: 647 (1991). The compounds may also be radiolabeled with known metal radiolabels, such as Technetium-99m (^{99m}Te). Modification of the substituents to introduce ligands that bind sueh metal ions can be effected without undue experimentation by one of ordinary skill in the radiolabeling art. The metal radiolabeled compound can then be used to detect amyloid deposits. Preparing radiolabeled derivatives of Tc-99m is well known in the art. See, for example, Zhuang *et al.* Nuclear Medieine & Biology 26(2):217-24, (1999); Oya *et al.* Nuclear Medicine &Biology 25(2) :135-40, (1998), and Hom *et al.* Nuclear Medicine &Biology 24(6):485-98, (1997). In addition, the compounds may be labeled with ^{3}H, ^{14}C and ^{125}I, by methods well known to the one skilled in the art, for detection of amyloid plaque in *in vitro* and post mortem samples.

The methods of the present invention may use isotopes detectable by nuclear magnetic resonance spectroseopy for purposes of *in vivo* imaging and spectroseopy. Elements particularly useful in magnetic resonance spectroseopy inelude ^{19}F and ^{13}C.

Suitable radioisotopes for purposes of this invention include beta-emitters, gamma-emitters, positron-emitters, and x-ray emitters. These radioisotopes include ^{120}I, ^{123}I, ^{131}I, ^{125}I, ^{18}F, ^{11}C, ^{75}Br, and ^{76}Br. Suitable stable isotopes for use in Magnetic Resonance Imaging (MRI) or Spectroscopy (MRS), according to this invention, include ^{19}F and ^{13}C. Suitable radioisotopes for *in vitro* quantification of amyloid in homogenates of biopsy or post-mortem tissue include ^{125}I, ^{14}C, and ^{3}H. Tlie preferred radiolabels are ^{11}C or ^{18}F for

use in PET *in vivo* imaging, ^{123}I for use in SPECT imaging, ^{19}F for MRS/MRI, and ^{3}H or ^{14}C for *in vitro* studies. However, any conventional method for visualizing diagnostic probes can be utilized in accordance with this invention.

The compounds of the present invention may be administered by any means known to one of ordinary skill in the art. For example, administration to the animal may be loeal or systemic and accomplished orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally, or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intraarterial, intramuscular, intraperitoneal, intrathecal, intraventricular, intrasternal, intracranial, and intraosseous injection and infusion techniques.

The exact administration protocol will vary depending upon various factors including the age, body weight, general health, sex and diet of the patient; the determination of specific administration procedures would be routine to an one of ordinary skill in the art.

Dose levels on the order of about 0.001 μg/kg/day to about 10,000 mg/kg/day of an inventive compound are useful for the inventive methods. In one embodiment, the dose level is about 0.001 μg/kg/day to about 10 g/kg/day. In another embodiment, the dose level is about 0.01 μg/kg/day to about 1.0 g/kg/day. In yet another embodiment, the dose level is about 0.1 mg/kg/day to about 100 mg/kg/day.

The specific dose level for any particular patient will vary depending upon various factors, including the activity and the possible toxicity of the specific compound employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the rate of excretion; the drug combination; and the form of administration. Typically, *in vitro* dosage-effect results provide useful guidance on the proper doses for patient administration. Studies in animal models are also helpful. The considerations for determining the proper dose levels are well known in the art and within the skills of an ordinary physician.

Any known administration regimen for regulating the timing and sequence of drug delivery may be used and repeated as necessary to effect treatment in the inventive methods.

The regimen may include pretreatment and/or co-administration with additional therapeutic agent(s).

In one embodiment, the inventive compounds are administered to a mammal, including man, that is suspected of having or that is at risk of developing a disease, disorder or condition characterized by amyloid deposition. For example, the animal may he an elderly human.

In another embodiment, compounds and methods for their preparation, useful as precursors, are provided. Such precursors may be used as synthetic starting materials for the incorporation of labeled molecular fragments leading to radiolabeled heteroaryl substituted benzothiazoles as amyloid imaging agents.

Method for Detecting Amyloid Deposits *In vitro*

This invention further provides a method for detecting amyloid deposit(s) *in vitro* comprising: (i) contacting a bodily tissue with an effective amount of an inventive compound, whcrein the compound would bind any amyloid deposit(s) in the tissue; and (ii) detecting binding of the compound to amyloid deposit(s) in the tissue.

The binding may be detected by any means known in the art. Examples of detection means include, without limitation, microscopic techniques, such as bright-field, fluorescence, laser-confocal and cross-polarization microscopy.

Pharmaceutical compositions

This invention further provides a pharmaceutical composition comprising: (i) an effective amount of at least one inventivc compound; and (ii) a pharmaeeutically aeceptable carrier.

The composition may comprise onc or more additional pharmaceutically acceptable ingredient(s), including without limitation one or more wetting agent(s), buffering agent(s), suspending agent(s), lubricating agent(s), emulsifier(s), disintegrant(s), absorbent(s),

preservative(s), surfaetant(s), eolorant(s), flavorant(s), sweetener(s) and therapeutic agent(s).

The composition may be formulated into solid, liquid, gel or suspension form for: (1) oral administration as, for example, a drench (aqueous or non-aqueous solution or suspension), tablet (for example, targeted for buceal, sublingual or systemic absorption), bolus, powder, gramule, paste for application to the tongue, hard gelatin capsule, soft gelatin capsule, mouth spray, emulsion and microemulsion; (2) parenteral administration by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution, suspension or sustained-relcase formulation; (3) topical application as, for example, a cream, ointment, controlled- release patch or spray applied to the skin; (4) intravaginal or intrarectal administration as, for example, a pessary, cream or foam; (5) sublingual administration; (6) oeular administration; (7) transdermal administration; or (8) nasal administration.

In one embodiment, the composition is formulated for intravenous administration and the carrier includes a fluid and/or a nutrient replenisher. In another embodiment, the composition is capable of binding specifically to amyloid *in vivo*, is capable of erossing the blood-brain barrier, is non-toxic at appropriate dose levels and/or has a satisfactory duration of effect. In yet another embodiment, the composition eomprises about 10 mg of human serum albumin and from about 0.0005 to 500 mg of a compound of the present invention per mL of phosphate buffer eontaining NaCl.

The present invention further provides compositions comprising a compound of formula I, and and at least one pharmaceutically acceptable carrier, diluent or excipient.

The present invention further provides methods of treating or preventing an Aβ-related pathology in a patient, comprising administering to the patient a therapeutically effective amount of a compound of formula I.

The present invention further provides a eompound of formula I for use as a medicament.

The present invention further provides a eompound of formula I for the manufacture of a medicament.

Some compounds of formula I may have stereogenic centres and/or geometric isomeric eentres (*E*- and *Z*- isomers), and it is to be understood that the invention encompasses all such optical isomers, enantiomers, diastereoisomers, atropisomers and geometric isomers.

The present invention relates to the use of compounds of formula I as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will bc pharmaceutically aceeptable salts, but other salts may be useful in the production of the compounds of formula I.

Compounds of the invention can be used as medicaments. In some embodiments, the present invention provides compounds of formula I, or pharmaceutieally acceptable salts, tautomers or *in vivo*-hydrolysable precursors thereof, for use as medicaments. In some embodiments, the present invention provides compounds described here in for use as as medicaments for treating or preventing an Aβ-related pathology. In some further embodiments, the Aβ-related pathology is Downs syndrome, a β-amyloid angiopathy, cerebral amyloid angiopathy, hereditary cerebral hemorrhage, a disorder associated with cognitive impairment, MCI ("mild cognitive impairment"), Alzheimer Disease, memory loss, attention deficit symptoms associated with Alzheimer disease, neurodegeneration associated with Alzheimer disease, dementia of mixed vascular origin, dementia of degencrative origin, pre-senile dementia, senile dementia, dementia associated with Parkinson's disease, progressive supranuclear palsy or eortical basal degeneration.

The invention further relates to therapies for the treatment of:
Neurodegenerative Disorder(s) including but not limited to Dementia, Cognitive Deficit in Schizophrenia (CDS), Mild Cognitive Impairment (MCI), Age-Associated Memory Impairment (AAMI), Age-Related Cognitive Decline (ARCD), Cognitive Impairement No Dementia (CIND), Multiple Sclerosis, Parkinson's Disease (PD), postencephalitic parkinsonism, Huntington's Disease, amyotrophic lateral sclerosis (ALS), motor neuron diseases (MND), Multiple System Atrophy (MSA), Corticobasal Degeneration,

Progressive Supranuclear Paresis, Guillain-Barré Syndrome (GBS), and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). Dementia includes, but is not limited to, Down syndrome, vascular dementia, , dementia with Lewy bodies, HIV dementia, Frontotemporal dementia Parkinson's Type (FTDP), Pick's Disease, Niemann-Pick's Disease, traumatic brain injury (TBI), dementia pugilistica, Creutzfeld-Jacob Disease and prion diseases.

Methods of preparation

The present invention also relates to processes for preparing the compound of formula I as a free base, acid, or pharmaceutically acceptable salts thereof. Throughout the following description of such processes it is to be understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in "Protective Groups in Organic Synthesis", T.W. Green, P.G.M. Wuts, Wiley-Interscience, New York, (1999). It is also to be understood that a transformation of a group or substituent into another group or substituent by chemical manipulation can be conducted on any intermediate or final product on the synthetic path toward the final product, in which the possible type of transformation is limited only by inherent incompatibility of other functionalities carried by the molecule at that stage to the conditions or reagents employed in the transformation. Such inherent incompatibilities, and ways to circumvent them by carrying out appropriate transformations and synthetic steps in a suitable order, will be readily understood to the one skilled in the art of organic synthesis. Examples of transformations are given below, and it is to be understood that the described transformations are not limited only to the generic groups or substituents for which the transformations are exemplified. References and descriptions on other suitable transformations are given in "Comprehensive Organic Transformations – A Guide to Functional Group Preparations" R. C. Larock, VHC Publishers, Inc. (1989). References and descriptions of other suitable reactions are described in textbooks of organic chemistry, for example, "Advanced Organic Chemistry", March 4th ed. McGraw Hill (1992) or, "Organic Synthesis", Smith, McGraw Hill, (1994). Techniques for purification of intermediates and final products include for example,

straight and reversed phase chromatography on column or rotating plate, recrystallisation, distillation and liquid-liquid or solid-liquid extraction, which will be readily understood by the one skilled in the art. The definitions of substituents and groups are as in formula I except where defined differently. The terms "room temperature" and "ambient temperature" shall mean, unless otherwise specified, a temperature between 16 and 25 °C. The term "reflux" shall mean, unless otherwise stated, in reference to an employed solvent using a temperature at or slightly above the boiling point of the named solvent. It is understood that microwaves can be nsed for the heating of reaction mixtures. The terms "flash chromatography" or "flash column chromatography" shall mean preparative chromatography on silica using an organic solvent, or mixtures thereof, as mobile phase.

Abbreviations

atm	atmosphere;
aq.	aqueous;
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphtyl
DBA	dibenzylideneacetone;
DCM	dichloromethane;
DME	1,2-dimethoxyethane;
DMF	dimethylformamide;
DMSO	dimethyl sulfoxide;
dppf	1,1'-bis(diphenylphosphino)ferrocene;
EA	ethyl acetate;
EtOAc	ethyl acetate;
EtOH	ethanol;
h	hour;
hep	heptane;
hex	hexane(s);
LAH	lithium aluminumhydride;
MeCN	acetonitrile;
McOH	methanol;
min	minutes;
NaHMDS	sodium hexamethyl disilazide;

o.n. or on over night;

$Pd(dppf)Cl_2*DCM$ or $Pd(dppf)Cl_2*CH_2Cl_2$:

(1,1'-bis(diphenylphosphino)ferrocene)palladium(II) chloride dichloromethane adduct;

prep. HPLC preparative HPLC;

r.t. or rt room temperature;

r.m. reaction mixture;

sat. saturated;

TBAF tetra-*N*-butylammonium fluoride

TBDMS *tert*-butyldimethylsilyl;

TFA trifluoroacetic acid;

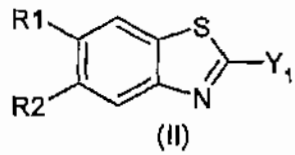
THF tetrahydrofurane;

NEt_3 triethylamine;

Otf thiomethyl.

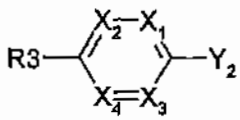
Preparation of Intermediates

Compounds of formula II, III, IV V and VI are useful intermediates in the preparation of compound of formula I. R1, R2, R3, and X1 to X4 are defined as in formula I. Compounds of formula II-VI are either commercially available, or can be prepared from either commercially available, or in the literature described compounds. For example, compounds in which one or more of Y1, Y2, Y3, Y4, R1, R2 and R3 does not correspond to the definitions of formula II –VI, can be used for the preparation of compounds of formula II-VI by transformations or introduction of substituents or groups. Such examples are given below:



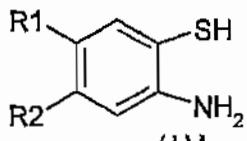
(II)

Y_1=H, F, Cl, Br, I, OTf, SMe, $B(OH)_2$, $B(Oalkyl)_2$, $Sn(n\text{-}Bu)_3$, MgX, ZnX

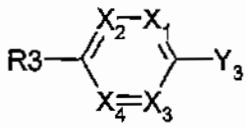


(III)

Y_2= F, Cl, Br, I, OTf, SMe, $B(OH)_2$, $B(Oalkyl)_2$, $Sn(n\text{-}Bu)_3$, MgX, ZnX

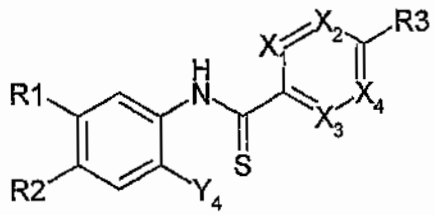


(IV)



(V)

Y_3= I, CHO, COOH, COCl, CN, COOalkyl, CONH2, CSNH2
, beta-chlorocinnamaldehyde
or equivalent carboxylic acid derivatives



(VI)

Y_4=H, Br

1) Preparation of compounds of formula II or III in which Y1 and Y2, respectively is $B(Oalkyl)_2$, $B(OH)_2$, MgX or ZnX:

a) From the corresponding chlorides, bromides, iodides or triflates through palladium catalysed borylation with for example bis(pinacolato)diboran using for example $PdCl_2(dppf)$, or $Pd(dba)_2$ with added tricyclohexylphosphine, as catalysts, together with

stochiometric amounts of a base such as KOAc and NEt_3 in solvents such as DMSO, DMF, DMA or dioxan at a temperature from r.t. to 80 °C, alternatively subsequently followed by acidic hydrolysis (Ishiyama *et al.* Tetrahedron 2001, 57, 9813; Murata *et al.* J. Org. Chem. 2000, 65, 164).

b) From the corresponding chlorides, bromides or iodides by initial conversion into an arylmagnesium (Y_1 or Y_2 = MgX) or lithium reagent by treatment with for example *n*BuLi, nBu$_3$MgLi or Mg, followed by trapping with for example triisopropyl borate or the like and alternatively subsequent acidic hydrolysis to give the corresponding borylated compounds, or with zinc dust to give the corresponding organic Zn-compounds.

2) Preparation of eompounds of formula II in which Y_1 is a halide:

a) From the corresponding unsubstituted benzothiazole (Y_1=H) via metallation with a lithium reagent such as *n*BuLi, followed by a metal-halogen exchange using halogen sources such as CCl_4, CBr_4 or I_2 (Boga *et al.* J. Organometallic Chem 2000, 601, 233)
b) From the corresponding amine via a Sandmeyer reaction initiated by converting the amine to a diazonium salt followed by treatment with cuprous chloride or cuprous bromide (Das *et al.* Bioorg. & Med. Chem. Lett. 2003, 13, 2587).

3) Preparation of compounds of formula II or III in which Y_1 and Y_2 respectively is a triflate:

From the corresponding alcohol by conversion into the triflate using $O(SO_2CF_3)_2$ and an base such as triethylamine and pyridine.

4) Preparation of compounds of formula II or III in which Y_1 and Y_2 respectively is a thioether, such as thiomethyl:

From the corresponding thiol by treatment with methyl iodide in a solvent such as DMF MeCN or DCM under basic conditions (Karlsson *et al.* Bioorg. & Med. Chem. 2004, 12, 2369).

5) Preparation of compounds of formula II or III in which Y_1 and Y_2 respectively is $Sn(nBu)_3$ or $Sn(Me)_3$, $Sn(Ph)_3$ or ZnX:

From the corresponding unsubstitutes benzothiazole (Y_1=H) via metallation with a lithium reagent, such as MeLi or *n*BuLi, followed by transmetallation using organotin chlorides such as Me_3SnCl or nBu_3SnCl, or a zinc salt (Molloy *et al.* J. Organometallic Chem 1989, 365, 61)

6) Preparation of Intermediate IV

a) From the corresponding 2-amino-benzothiazoles by base hydrolysis using a base such as aq. KOH, NaOH in a solvent such as ethylene glycol, ethanol and water under elevated temperatures. (Mathis *et al.* J. Med. Chem. 2003, 46, 2740; Inoue *et al.* Chem. Pharm. Bull. 1997, 45, 1008).

b) From the corresponding benzothiazole via hydrazinolysis using hydrazine in a solvent such as ethanol at elevated temperatures. (Tsuruoka *et al.* Chem. Pharm. Bull. 1998, 46, 623)

7) Preparation of Intermediate VI

A suitably substituted aniline is transformed into a benzoylamide by coupling with an appropriate acid chloride. The benzoylamide is subsequently converted into the corresponding benzoylthioamide using Lawesson's reagent in a solvent such as HMPA or chlorobenzene. (Shi *et al.* J. Med. Chem. 1996, 39, 3375; Mathis *et al.* J. Med. Chem. 2003, 46, 2740; Hutchinson *et al.* J. Med. Chem. 2001, 44, 1446).

Methods of Preparation of non-labeled compounds of formula I

Non-limiting examples of methods for the preparation of compounds of formula I are given below:

1) Preparation by Pd or Ni catalysed cross-coupling reactions of intermediates II and III:

a) Palladium catalysed Suzuki coupling of aryl halides, or pseudo-halides, of intermediates of formula II and III (e.g. Y_1,Y_2 = chloride, bromide, iodide or triflates) with boronic acids or esters of formula III or II (Y_1,Y_2 = $B(OH)_2$, $B(Oalkyl)_2$), respectively. A palladium catalyst, such as $Pd(dppf)Cl_2$*DCM, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$ or $Pd_2(dba)_3$, are used in combination with stochiometric amount of a base, such as K_2CO_3 (aq.), K_3PO_4, NaOH (aq.) or $NaHCO_3$ (aq.), in solvents, such as DME, DMF, THF, toluene or dioxane, at a temperature from r.t. to 120 °C (Kumar *et al.* J. Label Compd. Radiopharm. 2003, 46, 1055; Majo *et al.* Tetrahedron Lett. 2003, 44, 8535; Arterburn *et al.* Chem. Commun. 2003, 1890).

b) Palladium catalysed and copper(I) mediated cross coupling of thioethers of intermediates of formula II and III (eg. Y_1,Y_2 = SMe) with boronic acids or esters or stannanes of formula III or II (e.g. Y_1,Y_2 = $B(OH)_2$, $B(Oalkyl)_2$, $Sn(n\text{-}Bu)_3$), respectively. A palladium catalyst such as $Pd(dba)_2$, together with additives, such as tris(2-furyl)phosphine and ZnOAc, may be used in a solvent, such as THF, in the case of coupling of boronic acids or esters (Liebeskind *et al.* Org. Lett. 2002, 4, 979). In the case of coupling of stannanes, a palladium catalyst such as $Pd(PPh_3)_4$ or $PdCl(PPh_3)_2(CH_2Ph)$, may be used in a solvent, such as THF (Liebeskind *et al.* Org. Lett. 2003, 5, 801).

c) Palladium catalysed Stille coupling of aryl halides, or pseudo-halides, of intermediates of formula II and III (e.g. Y_1,Y_2 = chloride, bromide, iodide or triflates) with aryl stannanes of formula III or II (e.g. Y_1,Y_2 = $Sn(n\text{-}Bu)_3$), respectively. A palladium catalyst such as $Pd(PPh_3)Cl_2$, $Pd(PPh_3)_4$, or $Pd_2(dba)_3$ together with additives, such as CuI, tri-phenylarsine, tri-2-furylphosphine, may be used in solvents, such as DMF, THF, toluene or xylene, at a temperature from r.t. to 120°C (Benhida *et al.* Tetrahedron Lett. 1999, 40, 5701).

d) Nickel catalysed cross coupling of halides of intermediates of formula II and III (e.g. Y_1,Y_2 = Cl, Br, I) with Grignard reagents of formula III or II (e.g. Y_1,Y_2 = MgBr), respectively. A Nickel catalyst, such as $NiCl_2(PEt_3)_2$, $NiCl_2(PPh_3)_2$ or

$NiCl_2(Ph_2PCH_2CH_2CH_2PPh_2)$, may be used in solvents, such as THF, at elevated temp. (Babudri *et al.* Tetrahedron 1983, 39, 1515).

e) Palladium catalysed and copper(I) mediated eross coupling of benzothiazoles II (Y_1 = H) with bromides of formula III (Y_2 = Br). A palladium eatalyst, such as $Pd(OAc)_2$, together with a co-catalyst, such as CuBr, and additives, such as the ligand $P(t\text{-}Bu)_3$, and the base Cs_2CO_3, may be used in a solvent, such as DMF, at an elevated temperature (Yokooji *et al.* Tetrahedron 2003, 59, 5685 and Alagille *et al.* Tetrahedron Lett. 2005, 46, 1349).

2) Preparation by employment of compounds IV and V as starting materials:

(a) Condensation of the *ortho*-amino thiophenol IV with intermediate V in which Y_3 is aldehyde, carboxylie acid, acid ehloride, nitrile, phenolic ester, anhydride, amide, thioamide or equivalent carboxylic acid derivatives in solvents, such as DMSO, EtOH, toluene, $CHCl_3$, pyridine or in ionic liquids, at a temperature from r.t. to 220 °C by conventional heating, or with microwave irradiation. An additive, sueh as polyphosporic acid, scandium triflate, cerie ammonium nitrate or silica, is used to facilitate the reaction (Mathis *et al.* J. Med. Chem. 2003, 46, 2740; Kodomari *et al.* Synth. Commun. 2004, 34, 3029; Hein *et al.* J. Am. Chem. Soc. 1957, 79, 427; Karlsson *et al.* Bioorg. & Med. Chem. 2004, 12, 2369; Tale Org. Lett. 2002, 4, 1641; Chakraborti *et al.* Synlett 2004, 1533; Matsushita *et al.* Tetrahedron Lett. 2004, 45, 313; Dyes and Pigments 1990, 12, 243-8; Archiv der Pharmazie 1991, 324, 185).

(b) Reacting *ortho*-amino thiophenols IV with intermediates V in which Y_3 is a halide through palladium-catalyzed carbonylation under high pressure in the presence of 2,6-lutidine in solvents sueh as dimethyl acetamide. (Perry *et al.* Organometallics 1994, 13, 3346).

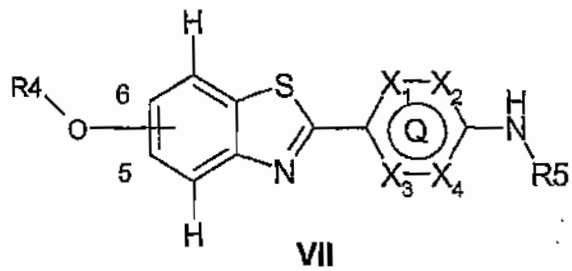
(c) Microwave mediated reaction of *o*-amino thiophenols IV with intermediate V in which Y_3 is a β-chlorocinnamaldehyde in the presence of *p*-TsOH (Paul *et al.* Synth. Commun 2002, 32, 3541).

3. The following other routes may be used for the synthesis of compounds of formula I starting from intermediates of formula VI:

a) By the Jacobson method through oxidative radical cyclization of thioanilides VI (Y_3=H) by treatment with excess of potassium ferricyanide at elevated temperature under basic conditions (Mathis *et al.* J. Med. Chem. 2003, 46, 2740; Hutchinson *et al.* J. Med. Chem. 2001, 44, 1446; Shi *et al.* J. Med. Chem. 1996, 39, 3375; Zeitschrift fuer Chemie 1985, 25, 23).

b) Through intramolecular cyclization of *o*-bromo substituted thioanilides VI (Y_4 = Br) under basic conditions, e.g. with NaH as base in NMP as solvent (Hutchinson *et al.* Tetrahedron Lett 2000, 41, 425; Hutchinson *et al.* J. Med. Chem. 2001, 44, 1446), or via palladium catalysis (Benedi *et al.* Tetrahedron Lett 2003, 44, 6073).

Methods of preparation of precursors of formula VII



VII

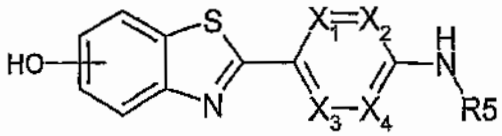
Non-limiting examples of methods for preparation of precursors of formula VII are given below. Compounds of formula VII are useful precursors for preparation of [^{11}C]methyl labeled compounds of formula I.

Preparation of intermediates useful for the preparation of precursors VII

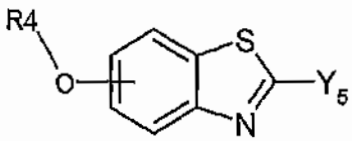
Compounds of formula VIII, IX, X, XI, XII and XIII are useful intermediates in the preparation of precursors of formula VII. R4, R5 and X_1 to X_4 are defined as in formula VII. Compounds of formula VIII–XIII are either commercially available, or can be prepared from commercially available samples, or non-limiting methods for their

preparation are described herein, or in the literature. For example, compounds in which one or more of Y_3, Y_4, Y_5, Y_6, R4 or R5 does not correspond to the definitions of formula VIII–XIII, can be used for the preparation of compounds of formula VIII–XIII by transformations or introduction of substituents or groups. Such examples are given below:

5

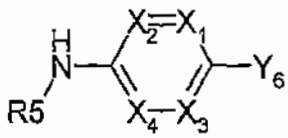


VIII



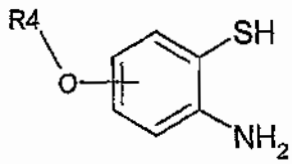
Y_5 = Cl, Br, I, OTf, $B(OH)_2$, $B(Oalkyl)_2$, $Sn(n\text{-}Bu)_3$, MgX

IX

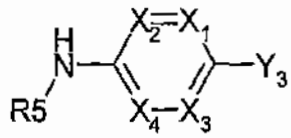


Y_6 = Cl, Br, I, OTf, B(OH)2, B(Oalkyl)2, Sn(n-Bu)3, MgX

X

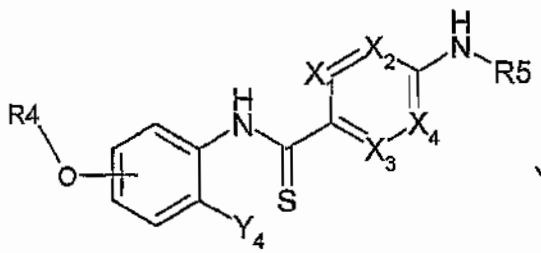


XI



Y_3= I, CHO, COOH, COCl, CN, COOalkyl,CONH2, CSNH2
, beta-chlorocinnamaldehyde
or equivalent carboxylic acid derivatives

XII



Y_4=H Br

XIII

1) Preparation of compounds of formula VIII:

a) Palladium-catalyzed Suzuki coupling of aryl halides, or pseudo-halides, of intermediates of formula II (R1 or R2 = OH) and X (e.g. Y_5, Y_6 = chloride, bromide, iodide or triflates) with boronic acids or esters of formula X or II (R1 or R2 = OH, Y_5, Y_6 = $B(OH)_2$ or $B(Oalkyl)_2$), respectively, according to the procedure described for the preparation of compounds I. When R1 or R2 of formula II is a protected hydroxy-group, and the protective group employed is not stable under standard aqueous basic Suzuki conditions, as in the case of for example *t*-butyldimethylsilyl protected hydroxy-groups, it will normally be cleaved of during the reaction to generate a product in which the former proteeted hydroxy-group is found as the free hydroxy.

b) Palladium-eatalyzed Stille coupling of aryl halides, or pseudo-halides, of intermediates of formula II (R1 or R2 = OH) and X (e.g. Y_5, Y_6 = chloride, bromide, iodide or triflates) with aryl stannanes of formula X or II (R1 or R2 = OH, Y_5, Y_6 = e.g. $Sn(n\text{-}Bu)_3$), respectively, according to thc procedure described in the preparation of eompounds I.

c) By employment of compounds XI and XII as starting materials in analogy to the methods described for the preparation of compounds I starting from IV and V.

d) Starting from intermediates XIII in analogy to the synthesis of I from VI.

2) Preparation of IX and X, in which Y_5 and Y_6 is an halide, a triflate, $B(Oalkyl)_2$, $B(OH)_2$, $Sn(n\text{-}Bu)_3$ or MgX, may be done by the same procedures as described for the preparation of the corresponding compounds II, in which R1 or R2 is O-R4, where R4 is a suitable protective group compatible with the respective reaction conditions employed as well known to the one skilled in the art.

3) Compounds XI and XIII may be prepared according to the synthesis of intermediates IV and VI.

Methods of preparation of precursors of formula VII

In the synthesis of precursors VII, the protective group R4 may be introduced either on a benzothiazole derivative before coupling of the hence produced intermediates IX with

intermediates X, or after the fusion of benzothiazole derivatives with heterocycles X, i.e. on structures VIII. All protective groups that represent R4 may be introduced by conventional procedures. Non-limiting examples of methods for the preparation of precursors of formula VII are given below:

1) Reacting intermediates VIII with a silylating agent, such as *t*-butyldimethylsilylchloride, in the presence of a base, such as imidazole or triethylamine, in a solvent, such as DMF or DCM, at a temperature from 0 °C to rt.

2) Intermediates VIII may be treated with 2-(trimethylsilyl)ethoxymethylchloride and a base, for example $(i\text{-Pr})_2NEt$, NaH or Et_3N in the presence of DMAP, in a solvent, such as DCM, DMF or benzene, at rt or elevated temperature.

3) By treatment of VIII with *p*-methoxybenzylbromide and a base such as $(i\text{-Pr})_2NEt$ in DCM at ambient temperature.

4) Transition metal-catalyzed cross couplings of intermediates IX and X:

Precursors VII may be prepared from intermediates IX and X by the metal-catalyzed cross coupling reactions described for the preparation of compounds I by coupling II (R1 or R2 = OH) and III provided that the R4-moiety is stable under the conditions employed.

5) Preparation of precursors of formula VII may be done through intermolecular reactions between intermediates XI and XII, or alternatively, through intramolecular reactions of XIII, in accordane to methods **1c** and **1d**, respectively, as described for the syntheses of VIII.

Methods of Preparation of labeled compounds of formula I

In general, the same synthetic reactions used for the assembly of non-labeled compounds of formula I from non-labeled reagents or intermediates, can be employed for the

analogous incorporation of a detectable isotope by use of the corresponding labeled reagents or intermediates.

It is preferred to introduce the label at a late stage of the synthesis toward compounds of formula I, especially if the label is an isotope with relatively short half-life, such as ^{11}C. Most preferred is to do this introduction as the last synthetic step.
Several useful reagents, synthons or intermediates labeled with long-lived or non-radioactive isotopes, including for example $[^{2/3}H]H_2$, $[^{2/3}H]CH_3I$, $[^{13/14}C]CH_3I$, $[^{13/14}C]CN^-$, $[^{13/14}C]CO_2$ are commercially available and can, if needed, be further synthetically transformed by conventional synthetic methods. Reagents labeled with more short-lived isotopes, such as ^{11}C and ^{18}F, are generated by a cyclotron, followed by suitable trapping and optionally further synthetic manipulations to provide the desired reagent. The generation and the synthetic manipulations of labeled reagents and intermediates, and the use and chemistries of these precursors for the synthesis of more complex labeled molecules, is well known to the one skilled in the art of radio-synthesis and labeling and reviewed in the literature (Långström *et al.* Acta Chem. Seand. 1999, 53, 651). For additional references see for example: Ali *et al.* Synthesis 1996, 423 for labeling with halogens; Antoni G., Kihlberg T., and Långström B. (2003) Handbook of nuclear chemistry, edited by Vertes A., Nagy S., and Klenscar Z., Vol. 4, 119-165 for labeling for PET-applications; Saljoughian *et al.* Synthesis 2002, 1781 for labeling with ^3H; McCarthy *et al.* Curr. Pharm. Des. 2000, 6, 1057 for labeling with ^{14}C.

Detectable isotopes, useful for the labeling of compounds of formula I as defined herein inelude, for use in PET: ^{11}C, ^{18}F, ^{75}Br, ^{76}Br and ^{120}I, for use in SPECT: ^{123}I and ^{131}I, for MRI-applications: ^{19}F and ^{13}C, for detection in *in-vitro* and *post-mortem* samples: ^3H, ^{14}C and ^{125}I. The most useful isotopes for labeling are ^{11}C, ^{18}F, ^{123}I, ^{19}F, ^3H and ^{14}C.

Below follow non-limiting descriptions on proeesses for the preparation of labeled compounds of formula I:

Compounds of formula I, in which either R1, R2, or R3 is hydroxy, amino or aminoalkyl are useful precursors for *O*- and *N*-alkylation, respectively, with a labcled alkylating agent, such as [^{11}C]methyl iodide or triflate, as described in for example Solbach *et al.* Applied Radiation and Isotopes 2005, 62, 591 and Mathis *et al.* J. Med. Chem. 2003, 46, 2740, [^{3}H]-methyl iodide, or [^{14}C]-methyl iodide.

For example, the compounds of formula I in which R1 or R2 is hydroxy (the other is hydrogen), X1 or X2 is nitrogen (the other is earbon), X3 and X4 is earbon, and R3 is amino or aminomethyl, constitute suitable precursors for labeling. Treatment of an excess of either of these precursors with ^{11}C-methyl triflate, in a solvent such as acetone without added base, results in seléctive *N*-alkylation and thus in the formation of the corresponding ^{11}C labelled compounds of formula I in which R3 is transformed into NH[^{11}C]CH_3 (from amino) and NCH_3[^{11}C]CH_3 (from aminomethyl), respeetively. When the same before mentioned precursors, however, is treated with [^{11}C]methyl iodide under basic condition, sueh as in the presence of potassium carbonate, in a solvent such as DMSO, selective *O*-alkylation occurs because of relatively higher reactivity of the oxygen-atom after deprotonation, and thus in the formation of compounds of formula I in which the OH-group (R1 or R2) is transformed into the O[^{11}C]CH_3-group.

The most suitable and preferred precursors for labeling by selective introduction of a ^{11}C-methyl group by *N*-alkylation, are compounds in which the reactivity to alkylation, of a present competing nucleophilic functional group, such as hydroxy, is lowered or blocked by a suitable protective group. The function of the protective group is in this eontext to protect the nueleophilie functional group against alkylation and should preferrably be stable under non-aqueous basic eonditions, under which the desired *N*-alkylation is facilitated, but readily removed by other means after fulfilment of its duty. Such protective groups, and methods for their introduction and removal, are well known to the one skilled in the art. Examples of proteetive groups useful for protection of aromatic hydroxy-groups against competing alkylation include, but is not limited to, methyl, 2-(trimethylsilyl)ethoxymethyl, alkoxymethyl and *t*-butyldimethylsilyl. Removal of such a protective group after the alkylation is well known to the one skilled in the art and include,

in the case of silyl-based protective groups such as *t*-butyldimethylsilyl, for example treatment with a fluoride ion source, such as TBAF, or treatment with water under basic conditions in a suitable solvent, such as DMSO in the presence of KOH at rt.

Compounds of formula I, in which either R1, R2, or R3 is amino, are useful precursor for labeling by initial diazotation, when appropriate followed by conversion into the corresponding triazine derivative, before subsequent treatment with labeled nucleophilic reagents according to standard reactions. Detectable isotopes that may be introduced this way include, but is not limited to ^{18}F, ^{75}Br, ^{123}I, ^{125}I and ^{131}I as described in for example Zhu *et al.* J. Org. Chem. 2002, 67, 943; Maeda *et al.* J. Label Compd Radiopharm 1985, 22, 487; Berridge et al. J. Label Compd Radiopharm 1985, 22, 687; Suehiro *et al.* J. Label Compd Radiopharm 1987, 24, 1143; Strouphauer *et al.* Int. J. Appl. Radiat. Isot. 1984, 35, 787; Kortylevicz *et al.* J. Label Compd Radiopharm 1994, 34, 1129; Khalaj *et al.* J. Label Compd Radiopharm 2001, 44, 235 and Rzeczotarski *et al.* J. Med. Chem. 1984, 27, 156. In compounds of formula I, where R1, R2, or R3 is a trialkyltin-group, halogenation with labeled reagents results in displacement of the trialkyltin-group as described in for example Staelens *et al.* J. Label Compd Radiopharm 2005, 48, 101; Hocke *et al.* Bioorg. Med. Chem. Lett. 2004, 14, 3963; Zhuang *et al.* J. Med. Chem. 2003, 46, 237; Füchtner *et al.* Appl. Rad. Isot. 2003, 58, 575 and Kao *et al.* J. Label Compd Radiopharm 2001, 44, 889. The same precursors are also useful for palladium-catalyzed conversion into the corresponding ^{11}C-labeled ketones and methyl-derivatives as described in for example Lidström *et al.* J. Chem. Soc. Perkin Trans. 1 1997, 2701 and Tarkiainen *et al.* J. Label Compd Radiopharm 2001, 44, 1013. The trialkyltin substituted compounds, in turn, are preferably prepared from the corresponding halides or pseudo-halides, such as the triflates, by well known methods employing palladium as catalyst in reaction with the corresponding distannane. When this methodology is used, the trialkyltin-group is preferably trimethyltin or tributyltin.

When R1, R2, or R3, in a compound of formula I, is a leaving group suitable for nucleophilic aromatic substitution, a labeled nucleophile, such as a halogenide or cyanide,

can be introduced by such a displacement, resulting in a labeled compound of formula I as described in for example Zhang *et al.* Appl. Rad. Isot. 2002, 57, 145. The aromatic ring on which the displacement takes place is preferably relatively electron-poor for a facile reaction, and might therefore need to be substituted with an electron-withdrawing activating group such as cyano, carbaldehyde or nitro. Useful reactions, closely related to nucleophilic aromatic substitutions and well known to the one skilled in the art, include the employment of stoehiometric amounts of copper-salts for the introduetion of a labeled iodo-atom, and the use of palladium-catalysis for the introduction of a ^{11}C-labelled cyano-group, as described in for example Musacio *et al.* J. Label Compd Radiopharm 1997, 34, 39 and Andersson *et al.* J. Label Compd Radiopharm 1998, 41, 567 respectively.
If the aromatic ring onto which the leaving group is positioned is more electron-defieient as compared to benzene, sueh as Q of formula I as defined herein, it is generally not needed to employ activating groups for electrophilic aromatic substitution to take place. Compounds of formula I, where R3 is either of the leaving-groups fluoro, chloro, bromo, iodo, or a sulphonate ester, and either or both of X2 and X4 is nitrogen, are suitable precursors for labeling via nucleophilic aromatic substitution of R3. It is furthermore generally preferable to use a leaving group that is chemically diverse from the group introdueed by the reaction with the labeled nucleophile, in order to facilitate ehromatographic separation of the labeled reaction produet from the unconsumed precursor.

Additional useful methods, well known to the one skilled in the art, for prcparation of labeled compounds of formula I by funetional group transformations of suitable precursors include *N*-acylation of amines with [^{11}C], [^{14}C], or [^{3}H]acyl chlorides, palladium-catalyzed [^{11}C] or [^{14}C] eyanation of aromatic chlorides, bromides or iodides, transition-metal catalyzed substitution of suitable halides for ^{3}H in the presence of [^{3}H]H_2, and palladium-eatalyzed carbonylations with [$^{11/14}$C]CO (Perry *et al.* Organometallics 1994, 13, 3346).

Compound examples

Below follows a number of non-limiting examples of compounds of the invention. All of the below examplified compounds under the paragraph "compound examples", or their corresponding non-labeled analogs, display an IC_{50} of less than 20 μM in the competition binding assay described herein.

General Methods

All solvents used were analytical grade and commercially available anhydrous solvents were routinely used for reactions. Reactions were typically run under an inert atmosphere of nitrogen or argon.

^1H spectra were recorded on a Bruker av400 NMR spectrometer, operating at 400 MHz for proton, equipped with a 3mm flow injection SEI $^1H/D$-^{13}C probehead with Z-gradients, using a BEST 215 liquid handler for sample injection, or on a Bruker DPX400 NMR speetrometer, operating at 400 MHz for proton, equipped with a 5 mm 4-nucleus probehead cquipped with Z-gradients.

Unless specifically noted in the examples, ^1H spectra were recorded at 400 MHz in DMSO-d_6 as solvent. The residual solvent signal was used as reference. The following reference signals were used: the middle line of DMSO-d_6 δ 2.50; the middle line of CD_3OD δ 3.31; $CDCl_3$ δ 7.26. In those instanees where spectra were run in a mixture of $CDCl_3$ and CD_3OD, the reference was set to 3.31 ppm. All chemical shifts are in ppm on the delta-scale (δ) and the fine splitting of the signals as appearing in the recordings (s: singlet, br. s: broad singlet, d: doublet, t: triplet, q: quartet, m: multiplet).

^3H spectra were recorded on a Bruker DRX600 NMR Spectrometer, operating at 640 MHz for tritium and at 600 MHz for proton, equipped with a 5mm $^3H/^1H$ SEX probehead with Z-gradients. ^1H decoupled ^3H spectra were recorded on samples dissolved in CD_3OD. For ^3H NMR spectra referencing, a ghost reference frequency was used, as calculated by multiplying the frequency of internal TMS in a ^1H spectrum with the Larmor frequency ratio between ^3H and ^1H (1.06663975), according to the description in Al-Rawi *et al.* **J. Chem. Soc. Perkin Trans. II** 1974, 1635.

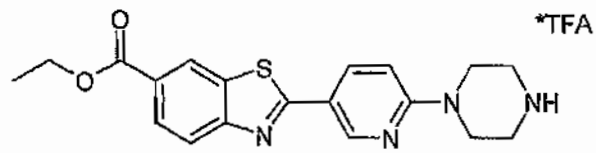
Mass spectra were recorded on a Waters LCMS consisting of an Alliance 2795 (LC), Waters PDA 2996, and ELS detector (Sedex 75) and a ZMD single quadrupole mass spectrometer. The mass spectrometer was equipped with an electrospray ion source (ES) operated in a positive or negative ion mode. The capillary voltage was 3 kV and cone voltage was 30 V. The mass spectrometer was scanned between *m/z* 100-600 with a scan time of 0.7s. The column temperature was set to 40 °C. A linear gradient was applied starting at 100% A (A: 10 mM NH_4OAc in 5% MeCN) and ending at 100% B (B: MeCN). The column used was a X-Terra MS C8, 3.0 x 50; 3.5 µm (Waters) run at 1.0 mL/min.

Preparative chromatography (prep. HPLC) was run on a Waters autopurification HPLC with a diode array detector. Column: XTerra MS C8, 19 x 300 mm, 10 µm. Narrow gradients with MeCN/(95:5 0.1M NH_4OAc:MeCN) were used at a flow rate of 20 ml/min.

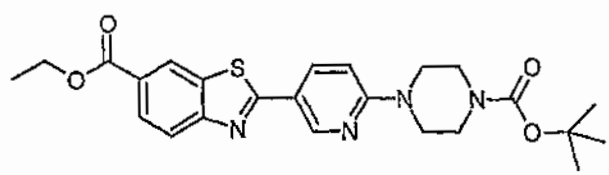
Microwave heating was performed in a Creator, Initiator or Smith Synthesizer Single-mode microwave cavity producing continuous irradiation at 2450 MHz.

Example 1

Ethyl 2-(6-Piperazin-1-ylpyridin-3-yl)-1,3-benzothiazole-6-carboxylate Trifluoroacetate



(a) 2-[6-[4-[(1,1-Dimethylethoxy)carbonyl]-1-piperazinyl]-3-pyridinyl]- 6-benzothiazolecarboxylic Acid Ethyl Ester



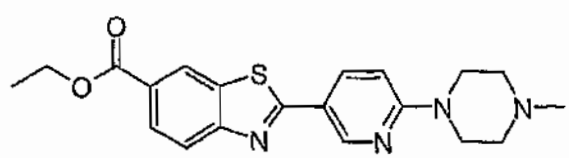
A mixture of 2-bromo-1,3-benzothiazole-6-carboxylic acid ethyl ester (See WO 95/25108) (0.74 g, 2.57 mmol), 4-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl-piperazine-1-carboxylic acid tert-butyl ester (1.0 g, 2.57 mmol), sodium carbonate (0.820 g, 7.71 mmol) and $Pd(dppf)Cl_2$*DCM (0.094 g, 0.13 mmol) in THF/water (9:1, 15 mL) was stirred at reflux o.n. Additional $Pd(dppf)Cl_2$*DCM (20 mg) was added and the reaction was refluxed for one more day. The r.m. was concentrated *in vacuo* and to the residue was added DCM and water. The aqueous layer was extracted three times with DCM, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The product was purified by flash column chromatography (35% ethyl acetate in hexane), giving the title compound (0.85 g) as a solid. ^{1}H NMR δ 8.83 (d, 1 H) 8.73 (s, 1 H) 8.19 (dd, 1 H) 8.04 (s, 2 H) 7.00 (d, 1 H) 4.36 (q, 2 H) 3.65 - 3.72 (m, 4 H) 3.42 - 3.50 (m, 4 H) 1.43 (s, 9 H) 1.36 (t, 3 H); MS m/z (M+H) 469.

(b) Ethyl 2-(6-Piperazin-1-ylpyridin-3-yl)-1,3-benzothiazole-6-carboxylate Trifluoroacetate (title compound)

2-[6-[4-[(1,1-Dimethylethoxy)carbonyl]-1-piperazinyl]-3-pyridinyl]- 6-benzothiazoleearboxylic acid ethyl ester (0.42 g, 0.90 mmol) was dissolved in DCM (35 mL) and TFA (2 mL) was added. The reaction was stirred at r.t. for 3 days. Sat. sodium hydrogencarbonate was added to the mixture. The precipitate was collected, followed by washing with DCM and water, before drying *in vacuo* over P_2O_5 to give the title compound (0.34 g) as a yellow solid. ^{1}H NMR δ 8.82 - 8.93 (m, 3 H) 8.76 (s, 1 H) 8.27 (dd, 1 H) 8.07 (d, 2 H) 7.11 (d, 1 H) 4.37 (q, 2 H) 3.84 - 3.95 (m, 4 H) 3.23 (br. s., 4 H) 1.36 (t, 3 H); MS m/z (M+H) 369.

Example 2

Ethyl 2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazole-6-carboxylate

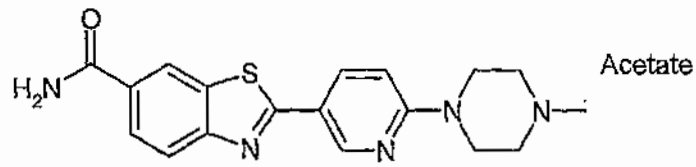


Formaldehyde (37% aq., 0.212 mL, 2.61 mmol) was added to a suspension of ethyl 2-(6-piperazin-1-ylpyridin-3-yl)-1,3-benzothiazole-6-carboxylate trifluoroacetate (0.315 g, 0.65

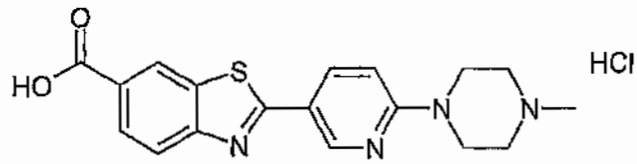
mmol) in methanol (10 mL). Sodium cyanoborohydride (74 mg, 1.17 mmol) was added and the resulting mixture was stirred at r.t. for 1h. The r.m. was then kept at –10 °C o.n. The formed solid was collected, washed with cold methanol and dried to give the title compound. The mother liquor was evaporated *in vacuo* and the residue was partitioned between DCM and sat. sodium hydrogencarbonate. The aqueous layer was extraetcd twiee with DCM, dried (Na_2SO_4), filtered, and evaporated *in vacuo*, giving together with the filtrated solid the title compound (0.20 g) as a yellow solid. ^{1}H NMR δ ppm 8.83 (d, 1 H) 8.73 (s, 1 H) 8.17 (dd, 1 H) 8.05 (s, 2 H) 7.01 (d, 1 H) 4.36 (q, 2 H) 3.70 (br. s., 4 H) 3.32 (s, 4 H) 2.29 (s, 3 H) 1.36 (t, 3 H); MS m/z (M+H) 383.

Example 3

2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazole-6-carboxamide Acetate



(a) 2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazole-6-carboxylic Acid Hydrochloride



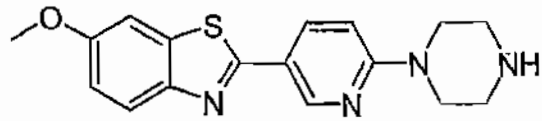
Ethyl 2-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazole-6-carboxylate (46 mg, 0.12 mmol) was heated at 110 °C in 6 M HCl (2 mL) for 3h. The solvent was evaporated *in vacuo*, before co-evaporation with toluene three times, to give the title compound (46 mg) as a yellow solid. ^{1}H NMR δ 10.90 (br. s., 1 H) 8.88 (d, 1 H) 8.73 (s, 1 H) 8.28 (dd, 1 H) 8.05 (s, 2 H) 6.97 - 7.40 (m, 2 H) 4.59 (d, 2 H) 3.51 (d, 2 H) 3.33 - 3.45 (m, 2 H) 3.02 - 3.16 (m, 2 H) 2.80 (d, 3 H); MS m/z (M+H) 355, (M-H) 353.

(b) 2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazole-6-carboxamide Acetate (title compound)

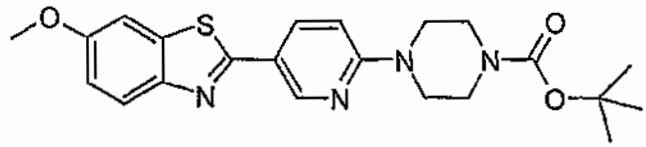
2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazole-6-carboxylic acid hydrochloride acid (46 mg, 0.12 mmol) was added to thionyl chloride (3 mL), followed by 3 drops DMF, before heating at 70 °C o.n. The solvent was thereafter evaporated *in vacuo* and once with toluene to give crude 2-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazole-6-carbonyl chloride. Ammonium hydroxide (conc., 3 mL) was added dropwise to this crude product and the mixture was thereafter stirred for 1h at r.t. The r.m. was extracted twice with DCM, dried (Na_2SO_4), and evaporated *in vacuo*. The obtained residue was purified by prep. HPLC to give the title compound (7 mg) as a light yellow solid. ^{1}H NMR δ 8.81 (d, 1 H) 8.58 (s, 1 H) 8.16 (dd, 1 H) 8.07 (br. s., 1 H) 7.99 (s, 2 H) 7.45 (br. s., 1 H) 7.00 (d, 1 H) 3.61 - 3.71 (m, 4 H) 2.37 - 2.46 (m, 4 H) 2.23 (s, 3 H) 1.89 (s, 3 H);); MS m/z (M+H) 354.

Example 4

6-Methoxy-2-(6-piperazin-1-ylpyridin-3-yl)-1,3-benzothiazole



(a) Tert-butyl 4-[5-(6-Methoxy-1,3-benzothiazol-2-yl)pyridin-2-yl]piperazine-1-carboxylate



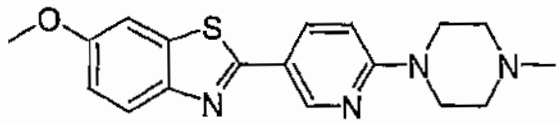
Tert-butyl 4-[5-(6-Methoxy-1,3-benzothiazol-2-yl)pyridin-2-yl]piperazine-1-carboxylate was prepared aceording to the method used for the preparation of 2-[6-[4-[(1,1-dimethylethoxy)carbonyl]-1-piperazinyl]-3-pyridinyl]- 6-benzothiazolecarboxylic aeid ethyl ester, from 2-bromo-6-methoxybenzothiazole (Yang *et al.* J. Biological Chem. 1989, 2, 891-898) (0.20 g), and obtained as a solid (0.23 g). ^{1}H NMR δ 8.74 (s, 1 H) 8.12 (d, 1 H) 7.87 (d, 1 H) 7.67 (s, 1 H) 7.09 (dd, 1 H) 6.98 (d, 1 H) 3.84 (s, 3 H) 3.64 (br. s., 4 H) 3.45 (br. s., 4 H) 1.43 (s, 9 H); MS m/z M+H 427.

(b) 6-Methoxy-2-(6-piperazin-1-ylpyridin-3-yl)-1,3-benzothiazole (title compound)

6-Methoxy-2-(6-piperazin-1-ylpyridin-3-yl)-1,3-benzothiazole was prepared according to the method used for the preparation of ethyl 2-(6-piperazin-1-ylpyridin-3-yl)-1,3-benzothiazole-6-carboxylate trifluoroacetate, from tert-butyl 4-[5-(6-methoxy-1,3-benzothiazol-2-yl)pyridin-2-yl]piperazine-1-carboxylate (0.22 g), with the exception that sodium hydroxide was used instead of sat. sodium hydrogencarbonate after completion of the reaction, and that the product was taken up in DCM thereafter. The title compound was obtained as a solid (0.15 g) after drying and concentration. ^{1}H NMR δ 8.71 (d, 1 H) 8.07 (dd, 1 H) 7.85 (d, 1 H) 7.66 (d, 1 H) 7.09 (dd, 1 H) 6.93 (d, 1 H) 3.84 (s, 3 H) 3.47 - 3.64 (m, 4 H) 2.65 - 2.89 (m, 4 H); MS m/z (M+H) 327.

Example 5

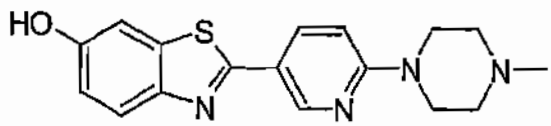
6-Methoxy-2-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazole



The title compound was obtained as a solid (70 mg) after preparation in accordance with the method used for the preparation of ethyl 2-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazole-6-carboxylate, from 6-methoxy-2-(6-piperazin-1-ylpyridin-3-yl)-1,3-benzothiazole (0.13 g), with the following exceptions: Three drops of acetic acid was added to the reaction mixture and the reaction was stirred at r.t. o.n. The product was filtered and washed with methanol. ^{1}H NMR δ 8.72 (d, 1 H) 8.08 (dd, 1 H) 7.86 (d, 1 H) 7.67 (d, 1 H) 7.09 (dd, 1 H) 6.97 (d, 1 H) 3.84 (s, 3 H) 3.53 - 3.69 (m, 4 H) 2.36 - 2.45 (m, 4 H) 2.22 (s, 3 H); MS m/z (M+H) 341.

Example 6

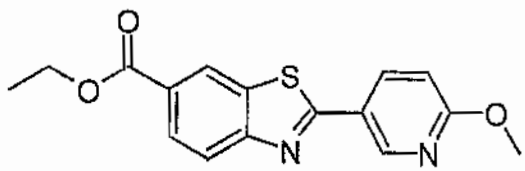
2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazol-6-ol Acetate



6-Methoxy-2-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazole (0.050 g, 0.15 mmol) was dissolved in DCM (20 mL). The mixture was made acidic by addition of HCl in diethyl ether. The solvent was removed by concentration *in vacuo* and the residue was suspended in DCM (5 mL). Boron tribromide (0.05 mL, 0.54 mmol) in DCM (1 mL) was thereafter added dropwise at 0 °C, followed by stirring at r.t. o.n. Additional DCM (5 mL) and boron tribromide (0.05 mL) was added and the reaction was continued stirring at r.t. for 3 days. The r.m. was then partitioned between DCM and sat. sodium hydrogencarbonate. The aqueous layer was extracted twice with DCM, and the combined organics dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude produet was purified by prep. HPLC to give the title compound (11 mg) as a white solid. ^{1}H NMR δ 9.94 (br. s., 1 H) 8.69 (d, 1 H) 8.06 (dd, 1 H) 7.76 (d, 1 H) 7.37 (d, 1 H) 6.84 - 7.06 (m, 2 H) 3.50 - 3.73 (m, 4 H) 2.35 - 2.45 (m, 4 H) 2.22 (s, 3 H) 1.90 (s, 3 H); MS m/z (M+H) 327, (M-H) 325.

Example 7

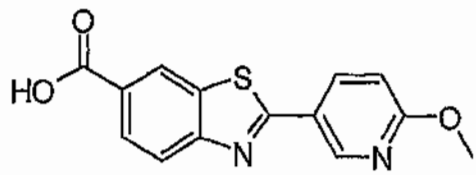
Ethyl 2-(6-Methoxypyridin-3-yl)-1,3-benzothiazole-6-carboxylate



The title compound was prepared according to the method used for the preparation of 2-[6-[4-[(1,1-dimethylethoxy)carbonyl]-1-piperazinyl]-3-pyridinyl]- 6-benzothiazolecarboxylic acid ethyl ester, from 2-methoxy-5-pyridineboronic acid (0.48 g, 3.14 mmol), and obtained as a solid (0.29 g) after purification by flash column chromatography using 15% ethyl acetate in hexane. ^{1}H NMR δ 8.94 (d, 1 H) 8.81 (s, 1 H) 8.40 (dd, 1 H) 8.00 - 8.19 (m, 2 H) 7.04 (d, 1 H) 4.37 (q, 2 H) 3.97 (s, 3 H) 1.36 (t, 3 H); MS m/z (M+H) 315.

Example 8

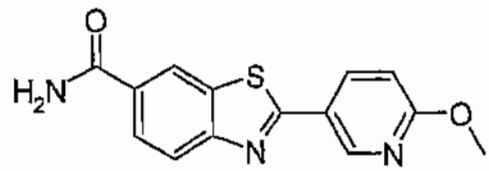
2-(6-Methoxypyridin-3-yl)-1,3-benzothiazole-6-carboxylic Acid



Ethyl 2-(6-methoxypyridin-3-yl)-1,3-benzothiazole-6-carboxylate (0.28 g, 0.89 mmol) was suspended in a mixture of ethanol (6 mL) and THF (2 mL). 2M NaOH (1.3 mL) was thereafter added and the reaction was stirred at r.t. for 6 h, before heating for 5 minutes with a heating gun to give a clear solution. The solution was evaporated *in vacuo*, water was added and the mixture was filtrated. The filtrate was made aeidie with 3M HCl. The precipitated solid was collected, washed with water, dried (*in vacuo* over P_2O_5) to give the title compound (0.23 g) as a white solid. ^{1}H NMR δ 13.13 (s, 1 H) 8.93 (d, 1 H) 8.77 (s, 1 H) 8.40 (dd, 1 H) 7.95 - 8.21 (m, 2 H) 7.04 (d, 1 H) 3.97 (s, 3 H); MS m/z (M+H) 287, (M-H) 285.

Example 9

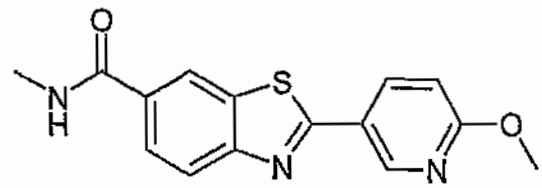
2-(6-Methoxypyridin-3-yl)-1,3-benzothiazole-6-carboxamide



2-(6-Methoxypyridin-3-yl)-1,3-benzothiazole-6-carboxylic acid (30 mg, 0.10 mmol) was mixed with thionyl chloride (0.8 mL) and stirred at r.t. for 3 h, then heated to 50 °C for 1h. The solvent was evaporated *in vacuo* to give the intermediate 2-(6-methoxypyridin-3-yl)-1,3-benzothiazole-6-carbonyl chloride as a crude product. This aeid chloride was dissolved in DCM (3 mL) and added to ammonium hydroxide (conc., 2 mL). The reaction was stirred at r.t. without stopper overnight. The formed solid was colleeted by filtration, washed with water and dried (*in vacuo* over P_2O_5) to give the title compound (23 mg) as a yellow solid. ^{1}H NMR δ 8.93 (d, 1 H) 8.64 (s, 1 H) 8.39 (dd, 1 H) 7.95 - 8.19 (m, 3 H) 7.50 (s, 1 H) 7.04 (d, 1 H) 3.97 (s, 3 H); MS m/z (M+H) 286, (M-H) 284.

Example 10

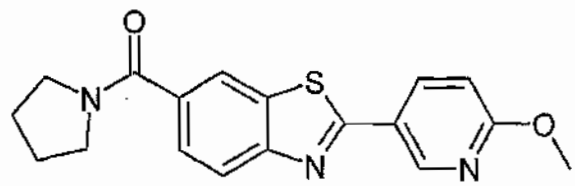
2-(6-Methoxypyridin-3-yl)-*N*-methyl-1,3-benzothiazole-6-carboxamide



2-(6-Methoxypyridin-3-yl)-1,3-benzothiazole-6-carboxylic acid (40 mg, 0.14 mmol) was mixed with thionyl chloride (1 mL) and stirred at r.t. for 3 h, then heated to 50 °C for 1h. The solvent was evaporated *in vacuo* to give the intermediate 2-(6-methoxypyridin-3-yl)-1,3-benzothiazole-6-carbonyl chloride as a crude product. This acid chloride was dissolved in DCM (3 mL) and added to methylamine (40% in methanol, 2 mL). The reaction was stirred at r.t. without stopper overnight. The formed solid was collected by filtration, washed with water and dried (*in vacuo* over P_2O_5) to give the title compound (35 mg) as a light yellow solid. ^{1}H NMR δ 8.92 (d, 1 H) 8.51 - 8.68 (m, 2 H) 8.39 (dd, 1 H) 8.09 (d, 1 H) 7.98 (d, 1 H) 7.04 (d, 1 H) 3.97 (s, 3 H) 2.83 (d, 3 H); MS m/z (M+H) 300, (M-H) 298.

Example 11

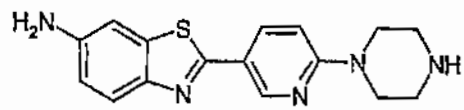
2-(6-Methoxypyridin-3-yl)-6-(pyrrolidin-1-ylcarbonyl)-1,3-benzothiazole



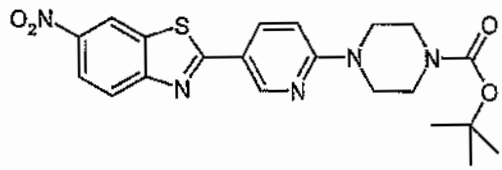
2-(6-Methoxypyridin-3-yl)-1,3-benzothiazole-6-carboxylic acid (40 mg, 0.14 mmol) was mixed with thionyl chloride (1 mL) and stirred at r.t. for 3 h, then heated to 50 °C for 1h. The solvent was evaporated *in vacuo* to give the intermediate, 2-(6-methoxypyridin-3-yl)-1,3-benzothiazole-6-carbonyl chloride as a crude product. This acid chloride was dissolved in DCM (3 mL) and added to pyrrolidine (0.5 mL) in CH_2Cl_2 (1.5 mL). The reaction was stirred at r.t. for 1h. Water was added and the reaction mixture was extracted, twice, with DCM, dried ($MgSO_4$), filtered and the solvent was evaporated. The solid was dried (*in vacuo* over P_2O_5) to give the title compound (45 mg) as an off-white solid. ^{1}H NMR δ 8.92 (d, 1 H) 8.39 (dd, 1 H) 8.35 (s, 1 H) 8.07 (d, 1 H) 7.67 (d, 1 H) 7.04 (d, 1 H) 3.97 (s, 3 H) 3.51 (t, 2 H) 3.45 (t, 2 H) 1.78 - 1.95 (m, 4 H); MS m/z (M+H) 340.

Example 12

2-(6-Piperazin-1-ylpyridin-3-yl)-1,3-benzothiazol-6-amine

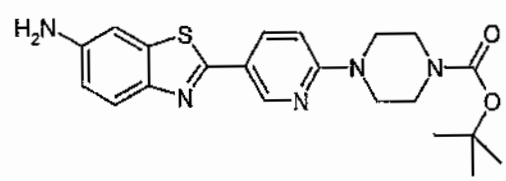


(a) tert-*Butyl 4-[5-(6-nitro-1,3-benzothiazol-2-yl)pyridin-2-yl]piperazine-1-carboxylate*



The compound *tert*-butyl 4-[5-(6-nitro-1,3-benzothiazol-2-yl)pyridin-2-yl]piperazine-1-carboxylate was prepared in accordance with the method used for preparation of 2-[6-[4-[(1,1-dimethylethoxy)carbonyl]-1-piperazinyl]-3-pyridinyl]- 6-benzothiazolecarboxylic acid ethyl ester, from 2-bromo-6-nitrobenzothiazole (0.55 g, 2.14 mmol), with the following modifications: In the workup the solid was filtered off and washed with THF/water (9:1), followed by water. The solid product was dried (*in vacuo* over P_2O_5). The filtrate was extracted three times with DCM. The combined organic phases was washed with brine, dried (Na_2SO_4), filtrated and evaporated *in vacuo*. The combined crude solid was purified by flash column chromatography (heptane:ethyl acetate; 80:20 to 60:40) to give the title compound
(0.47 g) as a solid. MS m/z (M+H) 442.

(b) 4-[5-(6-Amino-benzothiazol-2-yl)-pyridin-2-yl]-piperazine-1-carboxylic acid tert-butyl ester



tert-Butyl 4-[5-(6-nitro-1,3-benzothiazol-2-yl)pyridin-2-yl]piperazine-1-carboxylate (90 mg, 0.2 mmol) was dissolved in methanol (8 mL). After addition of 7M NH_3 in methanol (2 mL), palladium on carbon (10%, 10 mg) was added and the flask was evacuated and

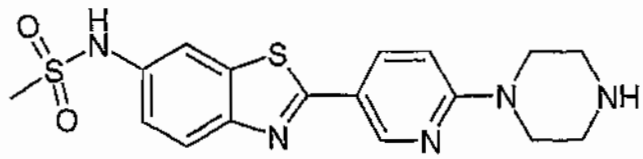
filled with hydrogen gas. The reaction mixture was shaken under an atmosphere of hydrogen overnight. The mixture was thereafter filtered through diatomaceous earth and evaporated *in vacuo*. The crude product was purified by flash column chromatography (heptane:ethyl acetate; 70:30 to 35:65), to give the title compound (38 mg) as a solid. MS m/z (M+H) 412.

(c) 2-(6-Piperazin-1-ylpyridin-3-yl)-1,3-benzothiazol-6-amine (title compound)

4-[5-(6-Amino-benzothiazol-2-yl)-pyridin-2-yl]-piperazine-1-carboxylic acid tert-butyl ester (13 mg, 0.032 mmol) was dissolved in DCM (1 mL), followed by addition of TFA (70 µL). The r.m. was thereafter stirred for 4 hrs at r.t. After addition of HCl (1 M; 1 mL), the two layers were separated. The organic layer was extracted with HCl (1M). The combined aqueous layers were made basic (pH 9-10) with NaOH (2 M) and extracted with DCM. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and the solvent was evaporated to give the title compound (10 mg) as an opac colored solid. ^1H NMR δ 8.70 (d, 1 H) 8.07 (dd, 1 H) 7.67 (d, 1 H) 7.13 (d, 1 H) 6.97 (d, 1 H) 6.81 (dd, 1 H) 5.45 (s, 2 H) 3.53 - 3.66 (m, 4 H) 2.77 - 2.92 (m, 4 H); MS m/z (M+H) 311.

Example 13

N-[2-(6-Piperazin-1-ylpyridin-3-yl)-1,3-benzothiazol-6-yl]methanesulfonamide

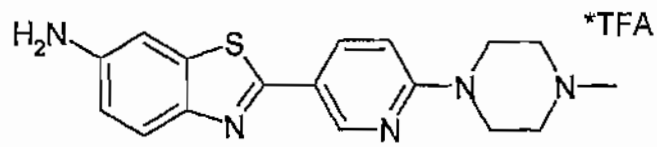


To 4-[5-(6-amino-benzothiazol-2-yl)-pyridin-2-yl]-piperazine-1-carboxylic acid tert-butyl ester (12.7 mg, 0.031 mmol) in DCM (1 mL) was added methanesulfonyl chloride (3 µL, 0.034 mmol) followed by pyridine (3 µL, 0.034 mmol). The r.m. was stirred o.n. at r.t. The crude mixture was purified by flash column chromatography (heptane:ethyl acetate; 50:50 to 40:60), to give intermediate *tert*-butyl 4-(5-{6-[(methylsulfonyl)amino]-1,3-benzothiazol-2-yl}pyridin-2-yl)piperazine-1-carboxylate (7.4 mg) as a solid. MS m/z (M+H) 490, (M-H) 488. This intermediate was dissolved in DCM (1 mL) and TFA (300 µL) was added. The reaction mixture was thereafter stirred for three hours at r.t. The

solvent was removed in a stream of nitrogen and the residue was dissolved in DMF (400 µL) and purified by prep. HPLC, to give the title compound (3 mg) as a white solid. ^{1}H NMR δ 8.71 (d, 1 H) 8.09 (dd, 1 H) 7.72 - 7.86 (m, 2 H) 7.27 (dd, 1 H) 6.88 (d, 1 H) 3.63 - 3.77 (m, 4 H) 2.95 - 3.08 (m, 4 H) 2.90 (s, 3 H); MS m/z M+H 390, M-H 388.

Example 14

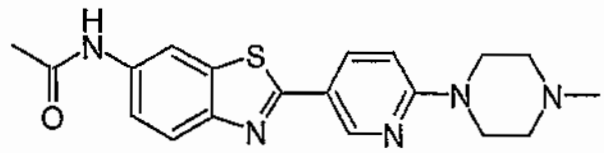
2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazol-6-amine Trifluoroacetate



To *tert*-butyl 4-[5-(6-nitro-1,3-benzothiazol-2-yl)pyridin-2-yl]piperazine-1-carboxylate (0.29 g) in DCM (15 mL) was added TFA (1.5 mL) before stirring o.n. at r.t. The solvent was thereafter removed by blowing with nitrogen and the residue, crude 6-nitro-2-(6-piperazin-1-ylpyridin-3-yl)-1,3-benzothiazole (MS m/z [M+H] 342.), was used directly in the next step. To this residue in methanol (3 mL), was added formaldehyde (37% aq., 0.25 mL) and sodium cyanoborohydride (74 mg), followed by heating at 70 °C for 5 minutes. A thick solid formed and additional methanol (3 mL) was added. The mixture was stirred at r.t. for 1 h, then filtered. The solid was washed with ice-cold methanol and was then dried under vacuum over P_2O_5, to give intermediate 2-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-6-nitro-1,3-benzothiazole trifluoroacetate (0.26 g) as a solid. MS m/z (M+H) 356. This intermediate (0.26 g) was dissolved in methanol (8 mL) and ammonia (7M in methanol, 2 mL) was added. The flask was evacuated and flushed with argon. Palladium (10% on carbon, 30 mg) was added and the flask was evacuated and filled with hydrogen gas. The reaction mixture was shaken under an atmosphere of hydrogen o.n. at r.t. The mixture was thereafter filtered through diatomaceous earth and evaporated *in vacuo*, to give the title compound (0.22 g) as a white solid. ^{1}H NMR (CHLOROFORM-*d*) δ 8.67 (d, 1 H) 8.05 (dd, 1 H) 7.70 (d, 1 H) 7.04 (d, 1 H) 6.74 (dd, 1 H) 6.63 (d, 1 H) 3.33 - 4.01 (m, 6 H) 2.42 - 2.55 (m, 4 H) 2.30 (s, 3 H); MS m/z (M+H) 326.

Example 15

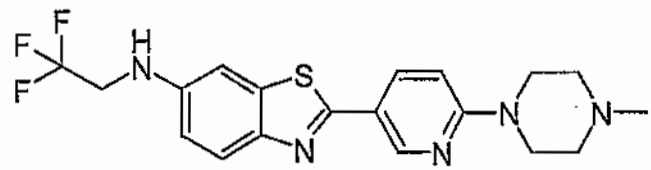
N-{2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazol-6-yl}acetamide



2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazol-6-amine trifluoroacetate (40 mg, 0.09 mmol) was partitioned between DCM and sat. sodium hydrogencarbonate and the aqueous layer was extracted twice with DCM. The combined organic layers were dried (Na_2SO_4), filtered and evaporated *in vacuo*, giving the free amine. To the free amine in DCM (2 mL) was added acetyl chloride (0.01 mL) and pyridine (0.01 mL) and the mixture was stirred at r.t. for 1 h. The solvent was evaporated *in vacuo* and the residue was purified by prep. HPLC, giving the title compound (20 mg) as a pale yellow solid. ^{1}H NMR (CHLOROFORM-*d*) δ 8.72 (d, 1 H) 8.34 (s, 1 H) 8.07 (dd, 1 H) 7.82 (d, 1 H) 7.27 (s, 1 H) 7.13 - 7.23 (m, 1 H) 6.63 (d, 1 H) 3.57 - 3.71 (m, 4 H) 2.43 - 2.54 (m, 4 H) 2.30 (s, 3 H) 2.16 (s, 3 H); MS m/z (M+H) 368, (M-H) 366.

Example 16

2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-*N*-(2,2,2-trifluoroethyl)-1,3-benzothiazol-6-amine

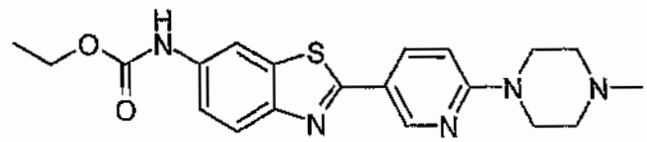


A mixture of 2-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazol-6-amine trifluoroacetate (0.12 g, 0.27 mmol), ethyl chloroformiate (36 µL, 0.38 mmol) and diisopropylethylamine (0.238 mL, 1.44 mmol) in DCM/THF (1:1, 7 mL) was stirred at r.t. overnight. Additional DCM was added before washing the sol. with sat. sodium hydrogencarbonate and then brine. The sol. was then dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by prep. HPLC, to give intermediate 2,2,2-trifluoro-N-{2-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazol-6-yl}acetamide (43 mg). MS m/z (M+H) 422, (M-H) 420. To this intermediate (43 mg) in THF (5 mL) was

added lithium aluminium hydride (12 mg, 0.3 mmol). The r.m. was refluxed for 1.5 h then allowed to come to r.t. Two drops of sat. Na_2SO_4, followed by ethyl acetate was added and the mixture was stirred for a few minutes. The organic layer was washed with brine, dried (Na_2SO_4), filtered and evaporated in vacuo. The residue was purified by prep. HPLC to yield the title compound (25 mg) as a pale yellow solid. ^{1}H NMR (MeOH-D4) δ 8.59 (d, 1 H) 7.97 (dd, 1 H) 7.60 (d, 1 H) 7.11 (d, 1 H) 6.75 - 6.87 (m, 2 H) 3.80 (q, 2 H) 3.55 - 3.70 (m, 4 H) 2.50 - 2.61 (m, 4 H) 2.33 (s, 3 H); MS m/z (M+H) 408, (M-H) 406.

Example 17

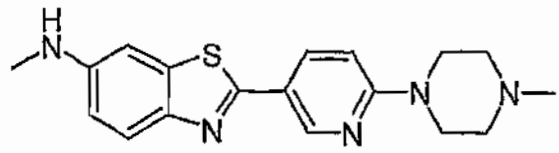
Ethyl {2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazol-6-yl}carbamate



2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazol-6-amine trifluoroacetate (40 mg, 0.09 mmol) was partitioned between DCM and sat. sodium hydrogencarbonate and the aqueous layer was extracted twice with DCM. The combined organic layers were dried (Na_2SO_4), filtered and evaporated *in vacuo*, giving the free amine. To the free aminen in CH_2Cl_2/THF (1:1, 4 mL) was added ethyl chloroformiate (15 µL, 0.15 mmol) and diisopropylethylamine (97 µL, 0.59 mmol) before stirring the r.m. at r.t. overnight. Additional DCM was then added and the organic layer was washed with sat. sodium hydrogencarbonatc and brine, then dried (Na_2SO_4), filtered and evaporated *in vacuo*, to give the title compound (37 mg) as an off-white solid. ^{1}H NMR δ 9.81 (s, 1 H) 8.67 (d, 1 H) 8.15 (d, 1 H) 8.02 (dd, 1 H) 7.80 (d, 1 H) 7.42 (dd, 1 H) 6.91 (d, 1 H) 4.09 (q, 2 H) 3.50 - 3.64 (m, 4 H) 2.30 - 2.38 (m, 4 H) 2.16 (s, 3 H) 1.20 (t, 3 H); MS m/z (M+H) 398, (M-H) 396.

Example 18

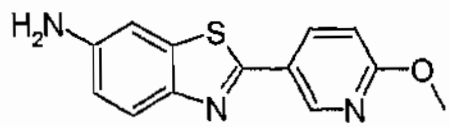
***N*-Methyl-2-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazol-6-amine**



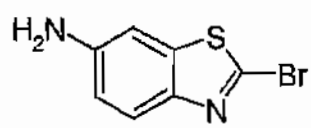
The title compound (11 mg, 38%) was prepared by reduction according to the method described for the preparation of 2-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-*N*-(2,2,2-trifluoroethyl)-1,3-benzothiazol-6-amine by the use of ethyl {2-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazol-6-yl}carbamate (37 mg, 0.088 mmol) as starting material, and lithium aluminiumhydride (10 mg, 0.26 mmol) as reagent, with the following modification: The reaction mixture was stirred at reflux for 1 h then at r.t. o.n. The crude was purified by prep. HPLC, to give the title compound (11 mg) as a pale yellow solid. ^{1}H NMR (MeOH-D4) δ 8.59 (d, 1 H) 7.98 (dd, 1 H) 7.56 (d, 1 H) 6.93 (d, 1 H) 6.82 (d, 1 H) 6.73 (dd, 1 H) 3.55 - 3.69 (m, 4 H) 2.74 (s, 3 H) 2.48 - 2.60 (m, 4 H) 2.32 (s, 3 H); MS m/z (M+H) 340.

Example 19

2-(6-Methoxypyridin-3-yl)-1,3-benzothiazol-6-amine



(a) 2-Bromo-1,3-benzothiazol-6-amine



Iron (0.53 g, 9.45 mmol) was added to a sol. of 2-bromo-6-nitrobenzothiazole (0.5 g, 1.93 mmol) in acetic acid (10 mL) at r.t. After vigorous stirring for 1.5 h, additional iron (0.3 g) and acetic acid (6 mL) was added. After 5 h, the mixture was filtered and washed with ethyl acetate. The organic layer was washed with water, brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash column chromatography (20 to 50% ethyl acetate in heptane), to give the title compound (0.12 g) as a pale pink solid. ^{1}H NMR

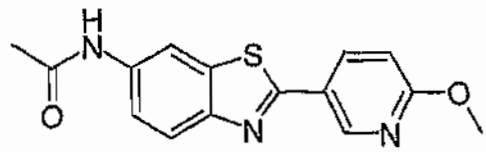
(CHLOROFORM-*d*) δ 7.74 (d, 1 H) 7.02 (d, 1 H) 6.80 (dd, 1 H) 3.85 (s, 2 H); MS m/z (M+H) 229, 231.

(b) 2-(6-Methoxypyridin-3-yl)-1,3-benzothiazol-6-amine (title compound)

A mixture of 2-bromo-1,3-benzothiazol-6-amine (53 mg, 0.23 mmol), 2-methoxy-5-pyridineboronic acid (50 mg, 0.327 mmol), $Pd(dppf)Cl_2$*DCM (8 mg, 0.01 mmol) and sodium carbonate (0.1 g, 1 mmol) in THF/water (9:1, 3 mL) was heated at 140 °C for 10 minutes in a microwave reactor under argon atmosphere. The mixture was filtered and washed with THF/water (9:1). After having added DCM to the filtrate, the organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash column chromatography (20 to 70% ethyl acetate in heptane), to yield the title compound (57 mg) as an off-white solid. ^{1}H NMR (CHLOROFORM-*d*) δ 8.68 (d, 1 H) 8.16 (dd, 1 H) 7.74 (d, 1 H) 7.06 (d, 1 H) 6.70 - 6.81 (m, 2 H) 3.94 (s, 3 H) 3.77 (s, 2 H); MS m/z (M+H) 258.

Example 20

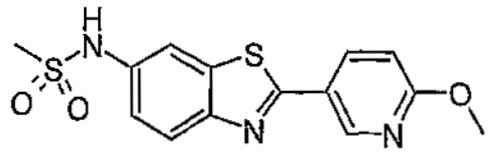
N-[2-(6-Methoxypyridin-3-yl)-1,3-benzothiazol-6-yl]acetamide



Acetylchloride (3 µL, 0.037 mmol) and pyridine (3 µL, 0.037 mmol) was added to a sol. of 2-(6-methoxypyridin-3-yl)-1,3-benzothiazol-6-amine (9 mg, 0.034 mmol) in DCM (1 mL). The r.m. was stirred at r.t. o.n. Half of the solvent was distilled of *in vacuo* and a few drops of hexane were added. The precipitated solid was collected and dried *in vacuo*, to give the title compound (4 mg) as a white solid. ^{1}H NMR δ 10.30 (s, 1 H) 8.91 (d, 1 H) 8.57 (d, 1 H) 8.39 (dd, 1 H) 8.03 (d, 1 H) 7.63 (dd, 1 H) 7.08 (d, 1 H) 4.02 (s, 3 H) 2.16 (s, 3 H); MS m/z (M+H) 300, (M-H) 298.

Example 21

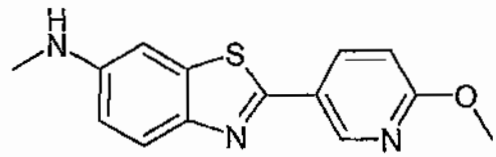
N-[2-(6-Methoxypyridin-3-yl)-1,3-benzothiazol-6-yl]methanesulfonamide



Mesylchloride (3 µL, 0.037 mmol) and pyridine (3 µL, 0.037 mmol) was added to a sol. 2-(6-methoxypyridin-3-yl)-1,3-benzothiazol-6-amine (9 mg, 0.034 mmol) in DCM (1 mL). The r.m. was stirred at r.t. for 6 days. A few drops of hexane was added and the precipitated solid was collected and dried *in vacuo*. The crude product was purified by flash column chromatography (20 to 100% ethyl acetate in heptane), to give the title compound (8 mg) as an off-white solid. ^{1}H NMR δ 9.84 (s, 1 H) 8.63 (d, 1 H) 8.11 (dd, 1 H) 7.77 (d, 1 H) 7.71 (d, 1 H) 7.14 (dd, 1 H) 6.79 (d, 1 H) 3.73 (s, 3 H) 2.82 (s, 3 H); MS m/z (M+H) 336, (M-H) 334.

Example 22

2-(6-Methoxypyridin-3-yl)-N-methyl-1,3-benzothiazol-6-amine

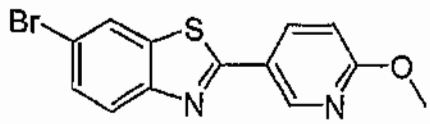


To 2-(6-methoxypyridin-3-yl)-1,3-benzothiazol-6-amine (57 mg, 0.22 mmol) in DCM/THF (1:1, 5 mL), was added ethyl chloroformiate (22.5 µL, 0.24 mmol) and diisopropylethylamine (0.147 mL, 0.89 mmol), before stirring the r.m. at r.t. o.n. Additional DCM was then added and the organic layer was washed with sat. sodium hydrogencarbonate and brine, then dried (Na_2SO_4), filtered and evaporated *in vacuo*, to give intermediate ethyl [2-(6-methoxypyridin-3-yl)-1,3-benzothiazol-6-yl]carbamate (70 mg) as a solid. MS m/z (M+H) 330, (M-H) 328. This intermediate (70 mg) was reacted with lithium aluminiumhydride (24 mg, 0.63 mmol) according to the procedure described for the preparation of 2-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-*N*-(2,2,2-trifluoroethyl)-1,3-benzothiazol-6-amine. The crude product obtained was purified by prep. HPLC to give

the title compound (2 mg) as a pale yellow solid. ^{1}H NMR (CHLOROFORM-*d*) δ 8.60 (d, 1 H) 8.08 (dd, 1 H) 7.66 (d, 1 H) 6.85 (d, 1 H) 6.69 (d, 1 H) 6.63 (dd, 1 H) 3.86 (s, 3 H) 2.77 (s, 3 H); MS m/z (M+H) 272.

Example 23

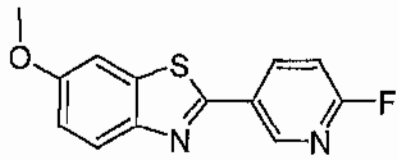
6-Bromo-2-(6-methoxypyridin-3-yl)-1,3-benzothiazole



A mixture of 2,6-dibromo-benzothiazole (0.29 g, 1.0 mmol), 2-methoxy-5-pyridineboronic acid (0.17 g, 1.1 mmol), Pd(dppf)Cl_2*DCM (41 mg, 0.05 mmol) and sodium carbonate (0.382 g, 3.6 mmol) in THF/water (9:1, 4 mL) was heated at 140 °C for 10 minutes in a microwave reactor. The reaction mixture was thereafter filtered through a plug of silica nsing DCM as eluent. The filtrate was concentrated and the crude product was purified by flash column chromatography (10% ethyl acetate in heptane), followed by recrystallization from ethyl acetate, to give the title compound (61 mg) as a solid. ^{1}H NMR (CHLOROFORM-*d*) δ 8.83 (d, 2 H) 8.27 (dd, 1 H) 8.03 (d, 1 H) 7.90 (d, 1 H) 7.60 (dd, 1 H) 6.87 (d, 1 H) 4.03 (s, 3 H); MS m/z (M+H) 321.

Example 24

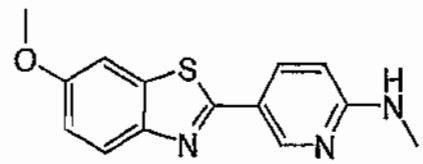
2-(6-Fluoropyridin-3-yl)-6-methoxy-1,3-benzothiazole



The title compound was prepared according the method described for the preparation of 6-bromo-2-(6-methoxypyridin-3-yl)-1,3-benzothiazole, by reacting 2-bromo-6-methoxy-benzothiazole (1.09 g, 4.46 mmol) with 2-fluropyridine-5-boronie acid (0.692 g, 4.9 mmol). The crude product was purified by flash column chromatography (0 to 2% methanol in DCM), to give the title compound (0.57 g). ^{1}H NMR δ 8.88 (d, 1 H) 8.58 (td, 1 H) 7.98 (d, 1 H) 7.76 (d, 1 H) 7.38 (dd, 1 H) 7.16 (dd, 1 H) 3.86 (s, 3 H); MS m/z (M+H) 261.

Example 25

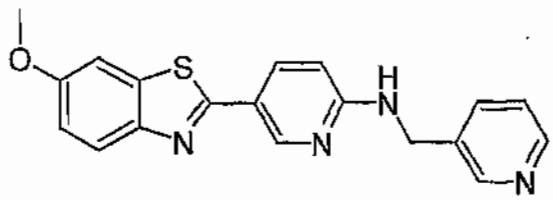
5-(6-Methoxy-1,3-benzothiazol-2-yl)-*N*-methylpyridin-2-amine



A mixture of 2-(6-fluoropyridin-3-yl)-6-methoxy-1,3-benzothiazole (0.20 g, 0.77 mmol) in methylamine (8M in ethanol, 5 mL) was heated at 100 °C for 5 minutes in a microwave reactor. The mixture was diluted with water and the solid product was collected by filtration and dried *in vacuo*, to yield the title compound (0.17 g) as a solid. ^{1}H NMR δ 8.64 (d, 1 H) 7.97 (dd, 1 H) 7.83 (d, 1 H) 7.64 (d, 1 H) 7.21 (d, 1 H) 7.07 (dd, 1 H) 6.58 (d, 1 H) 3.83 (s, 3 H) 2.85 (d, 3 H); MS m/z (M+H) 271.9.

Example 26

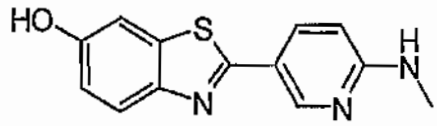
5-(6-Methoxy-1,3-benzothiazol-2-yl)-*N*-(pyridin-3-ylmethyl)pyridin-2-amine



A mixture of 2-(6-fluoropyridin-3-yl)-6-methoxy-1,3-benzothiazole (0.10 g, 0.38 mmol) and 3-(aminomethyl)pyridine (1.0 mL, 9.5 mmol) in ethanol (4 mL) was heated at 100 °C for 9 minutes in a microwave reactor. The mixture was diluted with water, then cooled to r.t. and the formed precipitate was collected by filtration and dried. The crude product was purified by prep. HPLC to give the title compound (71 mg) as a solid. ^{1}H NMR (CHLOROFORM-*d*) δ 8.75 (d, 1 H) 8.66 (d, 1 H) 8.56 (dd, 1 H) 8.11 (dd, 1 H) 7.89 (d, 1 H) 7.66 - 7.76 (m, 1 H) 7.34 (d, 1 H) 7.26 - 7.31 (m, 2 H) 7.07 (dd, 1 H) 6.50 (d, 1 H) 5.18 (t, 1 H) 4.67 (d, 2 H) 3.90 (s, 3 H); MS m/z (M+H) 348.9.

Example 27

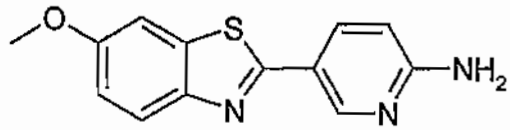
2-[6-(Methylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol



A mixture of 5-(6-methoxy-1,3-benzothiazol-2-yl)-*N*-methylpyridin-2-amine (50 mg, 0.18 mmol) and tetrabutylammonium bromide (catalytical amount) in hydrogen bromide (48% aq., 2 mL) was heated at 120 °C for 10 minutes in a microwave reactor. The solution was neutralized with sodium hydrogencarbonate and the aqueous layer was extracted twice with chloroform. The combined organic layers were evaporated *in vacuo*, and the crude product was purified by prep. HPLC to give the title compound (22 mg) as a solid. ^{1}H NMR δ 9.78 (s, 1 H) 8.60 (d, 1 H) 7.94 (dd, 1 H) 7.73 (d, 1 H) 7.35 (d, 1 H) 7.17 (q, 1 H) 6.93 (dd, 1 H) 6.57 (d, 1 H) 2.85 (d, 3 H); MS m/z (M+H) 357.9.

Example 28

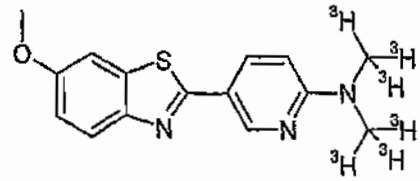
5-(6-Methoxy-1,3-benzothiazol-2-yl)pyridin-2-amine



A mixture of 2-bromo-6-methoxy-benzothiazole (1.14 g), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (1.23g, 1.2 eq.), Pd(dppf)Cl_2*DCM (170 mg, 0.05 eq.) and 2.0 M aq. K_2CO_3 (10 ml, 4 eq.) in DMF(20 ml) was heated at 80 °C for 2 h under argon while stirring. Ethyl acetate (200 ml) was subsequently added before concentrating the sol. onto diatomaceous earth *in vacuo*. Purification by flash chromatography (DCM:methanol, 99:1 to 95:5) provided the title compound (730 mg) as a yellow solid. ^{1}H NMR δ 8.56 (d, 1 H) 7.96 (dd, 1 H) 7.82 (d, 1 H) 7.64 (d, 1 H) 7.07 (dd, 1 H) 6.67 (br. s, 2 H) 6.55 (d, 1 H) 3.83 (s, 3 H); MS m/z (M+H) 258.1.

Example 29

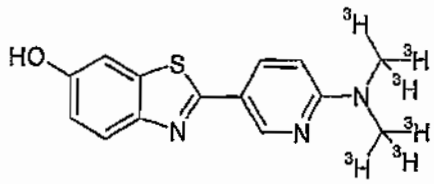
[*N-Dimethyl*-$^3H_6$]-[5-(6-Methoxy-benzothiazol-2-yl)-pyridin-2-yl]-dimethyl-amine



5-(6-Methoxy-benzothiazol-2-yl)-pyridin-2-ylamine (0.7 mg, 2.7 μmol) was mixed with [^{3}H]methyl iodide (100 mCi, 1.2 μmol) in DMF (0.4 mL) with sodium hydride (4 mg) as base and heated to 50°C for 1h. The reaction mixture was purified by reversed phase HPLC to afford the title compound (8.4 mCi, 8%). MS m/z (M+H) 298.

Example 30

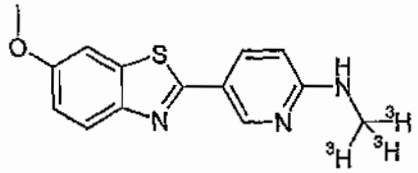
[*N-Dimethyl*-^{3}H$_6$]-2-(6-Dimetbylamino-pyridin-3-yl)-benzothiazol-6-ol



[*N-Dimethyl*-^{3}H$_6$]-[5-(6-Methoxy-benzothiazol-2-yl)-pyridin-2-yl]-dimethyl-amine (5 mCi, 0.06 μmol) was mixed with sodium thiophenoxide (4 mg) in *N*-methyl pyrrolidinone (0.4 mL) and heated to 250°C for 10 min by means of a microwave reactor. The reaction mixture was purified by reversed phase HPLC to afford the title compound (4.6 mCi, 92%). MS m/z M+H 284; ^{3}H NMR (proton decoupled in CD_3OD) δ 2.90 (s, $CH\underline{T}_2$) 2.88 (s, $C\underline{T}_3$) with the relative intensities 1:9.1.

Example 31

[*N-Methyl*-^{3}H$_3$]-[5-(6-Methoxy-benzothiazol-2-yl)-pyridin-2-yl]-methyl-amine

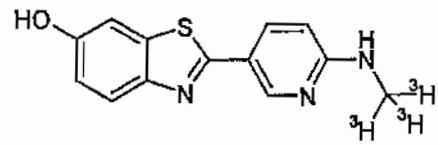


5-(6-Methoxy-benzothiazol-2-yl)-pyridin-2-ylamine (3.6 mg, 14 μmol) was mixed with [^{3}H]methyl iodide (30 mCi, 0.35 μmol) in dimethylformamide (0.4 mL) with sodium

hydride (24 mg) as base and heated to 60°C for 30 min. The reaetion mixture was purified by reversed phase HPLC to afford the title compound (17 mCi, 57%). MS m/z M+H 278.

Example 32

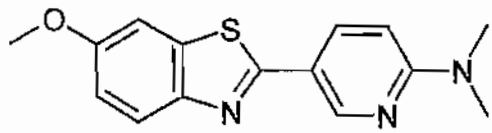
[*N-Methyl*-$^3H_3$]-2-(6-Methylamino-pyridin-3-yl)-benzothiazol-6-ol



[*N-Methyl*-$^3H_3$]-[5-(6-Methoxy-benzothiazol-2-yl)-pyridin-2-yl]-methyl-amine (12.7 mCi, 0.15 µmol) was mixed with sodium thiophenoxide (4.4 mg) in *N*-methyl pyrrolidinone (0.4 mL) and heated to 250°C for 20 min by means of a microwave reactor. The reaction mixture was purified by reversed phase HPLC to afford the title compound (11 mCi, 87%). MS m/z M+H 264; ^3H NMR (proton decoupled in CD_3OD) δ 3.14 (s, $CH\underline{T}_2$) 3.11 (s, $C\underline{T}_3$) with the relative intensities 1:9.6.

Example 33

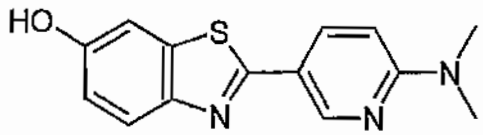
5-(6-Methoxy-1,3-benzothiazol-2-yl)-*N,N*-dimethylpyridin-2-amine



2-(6-Fluoropyridin-3-yl)-6-methoxy-1,3-benzothiazole (0.201 g) and 2 M dimethylamine in THF (5 mL) were heated in a microwave oven at 100°C for 5 min. Water was added and the precipitated product was filtered off, washed with water and dried in a desicator over P_2O_5 to yield 0.193 g of the product as a pale beige solid. ^1H NMR δ ppm 8.71 (d, 1 H) 8.07 (dd, 1 H) 7.84 (d, 1 H) 7.65 (d, 1 H) 7.08 (dd, 1 H) 6.77 (d, 1 H) 3.84 (s, 3 H) 3.12 (s, 6 H); MS m/z (M+H) 286.

Example 34

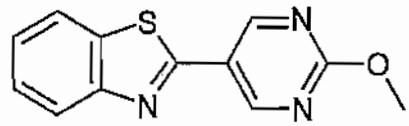
2-[6-(Dimethylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol



5-(6-Methoxy-1,3-benzothiazol-2-yl)-*N*,*N*-dimethylpyridin-2-amine (131 mg) was subjected to the procedure used for the preparation of 2-[6-(methylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol. After neutralization, the aq. phase was extracted with dichloromethane (3x), dried ($MgSO_4$), filtered and the solvent removed in vacuo. Recrystallization from methanol gave the title compound (75 mg) as a pale beige solid. ^{1}H NMR δ ppm 9.75 (s, 1 H) 8.68 (d, 1 H) 8.04 (dd, 1 H) 7.75 (d, 1 H) 7.36 (d, 1 H) 6.93 (dd, 1 H) 6.77 (d, 1 H) 3.12 (s, 6 H); MS m/z (M+H) 272.

Example 35

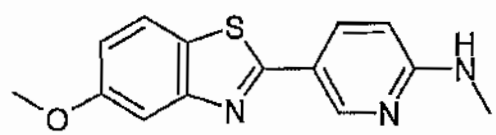
2-(2-Methoxypyrimidin-5-yl)-1,3-benzothiazole



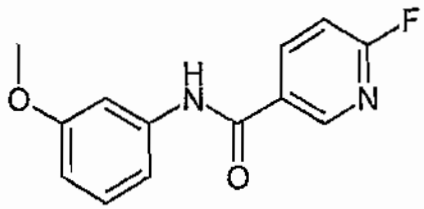
To 1,3-benzothiazole (0.100 g, 0.74 mmol) in dry DMF (3.5 mL) were added 5-bromo-2-methoxypyrimidinc (0.168 g, 0.89 mmol), Cu(I)Br (23 mg, 0.16 mmol), eesium carbonate (0.242 g, 0.74 mmol) and bis(tri-*t*-butylphosphine) palladium (0) (38 mg, 0.075 mmol) and the reaction was heated in a sealed tube under argon at 150°C for 1h. Water and dichloromethane were added and the layers separated. The aqueous layer was extracted with dichloromethane (3x). The combined organie phases were washed with water and brine, dried ($MgSO_4$), filtered and the solvent was removed in vacuo. The crude material was purified by flash chromatography (Heptane/EtOAc 1:1) to give the title compound (71 mg) as a pale brown solid. ^{1}H NMR δ ppm 9.26 (s, 2 H) 8.20 (d, 1 H) 8.09 (d, 1 H) 7.55–7.61 (m, 1 H) 7.46–7.53 (m, 1 H) 4.04 (s, 3 H); MS m/z (M+H) 244.

Example 36

5-(5-Methoxy-1,3-benzothiazol-2-yl)-*N*-methylpyridin-2-amine

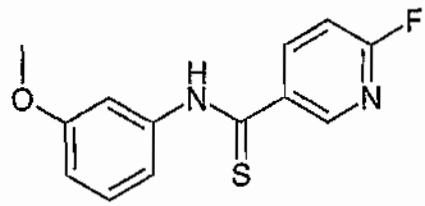


(a) 6-Fluoro-N-(3-methoxyphenyl)nicotinamide



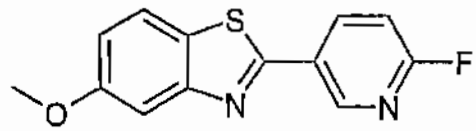
To a solution of 3-methoxyaniline (3.00 g, 24.4 mmol), 6-fluoronicotinic acid (4.41 g, 31.3 mmol) and 4-dimethylaminopyridine (DMAP) (0.298 g, 2.44 mmol) in dichloromethane (210 mL) was added, under an atmosphere of nitrogen, a solution of *N,N'*-dicyclohexylcarbodiimide (6.48 g, 31.4 mmol) in DCM (60 mL) dropwise at 0°C. The solution was then allowed to warm to rt and stirred for 1 h. The reaction mixture was filtered and the organic phase was washed with sat. aq. $NaHCO_3$, water and brine. The organic phase was dried ($MgSO_4$), filtered and the solvent removed in vacuo to give the title compound (quant.) as an orange solid that was taken to the next step without further purification. MS m/z (M+H) 247.

(b) 6-Fluoro-N-(3-methoxyphenyl)pyridine-3-carbothioamide



6-Fluoro-*N*-(3-methoxyphenyl)nicotinamide (1.00 g, 4.07 mmol) was dispersed in toluene (20 mL), and hexamethyldisiloxane (1.65 mL, 7.73 mmol) was added with stirring under argon. The reaction mixture was heated to 60°C and phosphorus pentasulfide (2.23 g) was added with further toluene (7 mL) and the reaction mixture was heated at 100°C for 3.5 h. After cooling to rt, toluene was removed in vacuo and water and DCM were added and the layers separated. The aqueous phase was extracted with DCM (3x). The combined organic phases were washed with water, dried ($MgSO_4$), filtered and the solvent removed in vacuo. The crude material was purified by column chromatography (heptane/EtOAc 60:40) to give the title compound (0.337 g) as a yellow oil. ^{1}H NMR δ ppm 11.98 (s, 1 H) 8.64 (d, 1 H) 8.31–8.46 (m, 1 H) 7.58 (t, 1 H) 7.23–7.49 (m, 3 H) 6.89 (dd, 1 H) 3.78 (s, 3 H); MS m/z (M+H) 263.

(c) 2-(6-Fluoropyridin-3-yl)-5-methoxy-1,3-benzothiazole



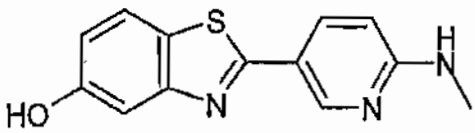
6-Fluoro-*N*-(3-methoxyphenyl)pyridine-3-carbothioamide (0.317 g, 1.21 mmol) was first wetted with ethanol, and NaOH (30% aq, 0.30 mL) was added. The mixture was diluted with water to provide a final suspension of 10% NaOH. Aliquots of this mixture were added at 1 min intervals to a stirred solution of potassium hexacyanoferrate(III) (1.59 g, 4.84 mmol) in water (3.2 mL) at 85°C. The reaction mixture was then heated at 85°C for another 45 minutes. After cooled to rt, water and DCM were added and the layers separated. The aqueous phase was extracted with DCM (3x). The combined organic phases were dried ($MgSO_4$), filtered and the solvent removed in vacuo. The crude material was purified by column chromatography (DCM) to give the title compound (61 mg) as a pale yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.89 (d, 1 H) 8.44–8.52 (m, 1 H) 7.77 (d, 1 H) 7.57 (d, 1 H) 7.04–7.12 (m, 2 H) 3.92 (s, 3 H); MS m/z (M+H) 261.

(d) 5-(5-Methoxy-1,3-benzothiazol-2-yl)-N-methylpyridin-2-amine (title compound)

To 2-(6-fluoropyridin-3-yl)-5-methoxy-1,3-benzothiazole (59.2 mg, 0.227 mmol) was added methylamine in ethanol (8 M, 2 mL) and the reaction mixture was heated in a microwave oven at 100°C for 5 min. Water and dichloromethane were added and the layers separated. The aqueous phase was extracted with dichloromethane (3x). The combined organic phases were washed with water, dried ($MgSO_4$), filtered and the solvent removed in vacuo. The crude material was purified by column chromatography (heptane/EtOAc 60:40 to 50:50) to give the title compound (39 mg) as a pale yellow solid. ^{1}H NMR δ ppm 8.68 (d, 1 H) 7.98 (dd, 1 H) 7.91 (d, 1 H) 7.50 (d, 1 H) 7.27 (q, 1 H) 7.01 (dd, 1 H) 6.59 (d, 1 H) 3.85 (s, 3 H) 2.86 (d, 3 H); MS m/z (M+H) 272.

Example 37

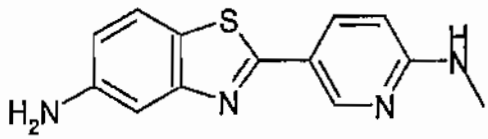
2-[6-(Methylamino)pyridin-3-yl]-1,3-benzothiazol-5-ol



5-(5-Methoxy-1,3-benzothiazol-2-yl)-*N*-methylpyridin-2-amine (29.6 mg, 0.109 mmol) was subjected to the procedure used for the preparation of 2-[6-(methylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol. After neutralization, the precipitated product was filtered off, washed with water and EtOAc and dried under vacuum to afford the title compound (23 mg) as a yellow solid. ^{1}H NMR δ ppm 9.57 (br s, 1 H) 8.45 (d, 1 H) 7.78 (dd, 1 H) 7.59 (d, 1 H) 6.98–7.16 (m, 2 H) 6.67 (dd, 1 H) 6.38 (d, 1 H) 2.66 (d, 3 H); MS m/z (M+H) 258.

Example 38

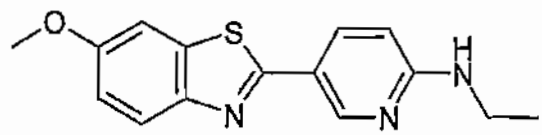
2-[6-(Methylamino)pyridin-3-yl]-1,3-benzothiazol-5-amine



The title compound was prepared according to the method used for the preparation of 2-(2-methoxypyrimidin-5-yl)-1,3-benzothiazole, now starting from 1,3-benzothiazol-5-amine (50 mg, 0.33 mmol) and 5-bromo-*N*-methylpyridin-2-amine (75 mg, 0.40 mmol). The crude material was purified on a preparative HPLC to give the title eompound (12 mg) as a pale beige solid. ^{1}H NMR δ ppm 8.62 (d, 1 H) 7.95 (dd, 1 H) 7.61 (d, 1 H) 7.19 (q, 1 H) 7.07 (d, 1 H) 6.69 (dd, 1 H) 6.56 (d, 1 H) 5.24 (s, 2 H) 2.85 (d, 3 H); MS m/z (M+H) 257.

Example 39

***N*-Ethyl-5-(6-methoxy-1,3-benzothiazol-2-yl)pyridin-2-amine**

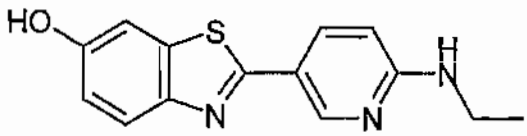


In a microwave vial were added 2-(6-fluoropyridin-3-yl)-6-methoxy-1,3-benzothiazole (75 mg, 0.289 mmol), water (1.2 mL) and ethylamine in water (70%, 1.2 mL) and the reaction was heated in a microwave oven at 100°C for 5 min. The precipitated product was filtered off, washed with water and dried in a desicator over P_2O_5 to yield the product (67 mg) as a white solid. ^{1}H NMR δ ppm 8.62 (d, 1 H) 7.95 (dd, 1 H) 7.82 (d, 1 H) 7.64 (d, 1 H) 7.23 (t,

1 H) 7.07 (dd, 1 H) 6.57 (d, 1 H) 3.83 (s, 3 H) 3.33–3.40 (m, 2 H) 1.16 (t, 3 H); MS m/z (M+H) 286.

Example 40

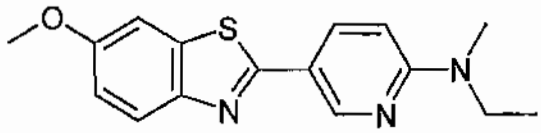
2-[6-(Ethylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol



To *N*-ethyl-5-(6-methoxy-1,3-benzothiazol-2-yl)pyridin-2-amine (52.8 mg, 0.185 mmol) in dichloromethane (2 mL) was added BBr_3 in dichloromethane (1 M, 925 µL) at 0°C under an argon atmosphere. The reaction was then stirred at 0°C for 3h before it was neutralized with $NaHCO_3$ (sat aq). The precipitated product was filtered off, washed with water and DCM and dried. Recrystallization from (MeOH/toluene) gave the title compound (11 mg) as a white solid. ^{1}H NMR δ ppm 9.75 (br s, 1 H) 8.58 (d, 1 H) 7.93 (dd, 1 H) 7.73 (d, 1 H) 7.34 (d, 1 H) 7.19 (t, 1 H) 6.92 (dd, 1 H) 6.56 (d, 1 H) 3.32–3.38 (m, 2 H) 1.16 (t, 3 H); MS m/z (M+H) 272.

Example 41

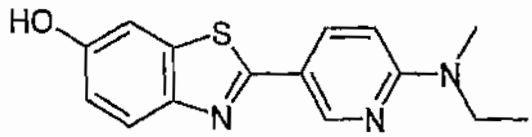
***N*-Ethyl-5-(6-methoxy-1,3-benzothiazol-2-yl)-*N*-methylpyridin-2-amine**



In a microwave vial were added 2-(6-fluoropyridin-3-yl)-6-methoxy-1,3-benzothiazole (75 mg, 0.289 mmol), water (2.0 mL) and ethylmethylamine (0.50 mL) and the reaction was heated in a microwave oven at 100°C for 5 min. The preeipitated product was filtered off, washed with water and dried in a desicator over P_2O_5 to yield the product (70 mg) as a beige solid. ^{1}H NMR δ ppm 8.71 (d, 1 H) 8.06 (dd, 2.53 Hz, 1 H) 7.85 (d, 1 H) 7.66 (d, 1 H) 7.08 (dd, 1 H) 6.76 (d, 1 H) 3.84 (s, 3 H) 3.64 (q, 2 H) 3.08 (s, 3 H) 1.12 (t, 3 H); MS m/z (M+H) 300.

Example 42

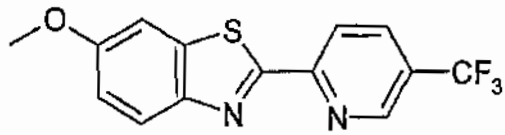
2-{6-[Ethyl(methyl)amino]pyridin-3-yl}-1,3-benzothiazol-6-ol



N-Ethyl-5-(6-methoxy-1,3-benzothiazol-2-yl)-*N*-methylpyridin-2-amine (55.4 mg, 0.185 mmol) was subjected to the procedure described for 2-[6-(ethylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol. Recrystallization from methanol gave 23.7 mg of the title compound as a pale yellow solid. ^{1}H NMR δ ppm 9.75 (s, 1 H) 8.67 (d, 1 H) 8.03 (dd, 1 H) 7.75 (d, 1 H) 7.35 (d, 1 H) 6.93 (dd, 1 H) 6.75 (d, 1 H) 3.63 (q, 2 H) 3.07 (s, 3 H) 1.11 (t, 3 H); MS m/z (M+H) 286.

Example 43

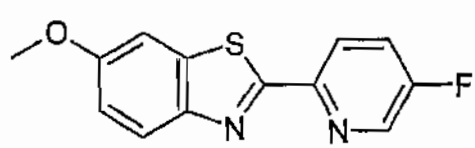
6-Methoxy-2-[5-(trifluoromethyl)pyridin-2-yl]-1,3-benzothiazole



6-Methoxy-1,3-benzothiazole (35 mg, 0.21 mmol) and 2-bromo-5-(trifluoromethyl)pyridine (1.1 equiv) were dissolved in dry, degassed DMF (1.5 mL). Cesium carbonate (72.5 mg, 0.22 mmol) and bis(tri-*t*-butylphosphine) palladium (0) (5.5 mg, 0.011 mmol) were added and the reaction was heated under argon at 150°C for 3h. After cooling to about 40°C, the reaction mixture was filtered, and the filter was washed with DMF. The filtrate was concentrated in a centrifuge, and the residue was taken up in DMSO and purified by preparative HPLC to give the title compound (11 mg) as a yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.88–8.95 (m, 1 H) 8.44 (d, 1 H) 8.06 (dd, 1 H) 8.00 (d, 1 H) 7.42 (d, 1 H) 7.15 (dd, 1 H) 3.93 (s, 3 H); MS m/z (M+H) 311.

Example 44

2-(5-Fluoropyridin-2-yl)-6-methoxy-1,3-benzothiazole

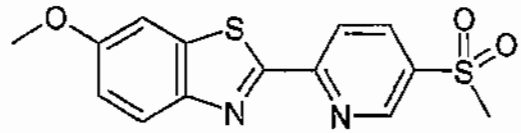


6-Methoxy-1,3-benzothiazole (35 mg, 0.21 mmol) and 2-bromo-5-fluoropyridine (1.1 equiv) were reacted according to the procedure used for the preparation of 6-methoxy-2-

[5-(trifluoromethyl)pyridin-2-yl]-1,3-benzothiazole. This gave the title compound (6 mg) as a yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.52 (d, 1 H) 8.35 (dd, 1 H) 7.96 (d, 1 H) 7.51–7.59 (m, 1 H) 7.40 (d, 1 H) 7.12 (dd, 1 H) 3.92 (s, 3 H); MS m/z (M+H) 261.

Example 45

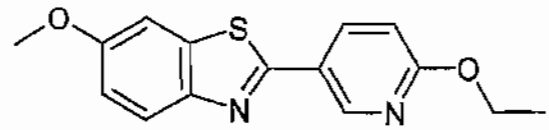
6-Methoxy-2-[5-(methylsulfonyl)pyridin-2-yl]-1,3-benzothiazole



6-Methoxy-1,3-benzothiazole (35 mg, 0.21 mmol) and 2-bromo-5-(methylsulfonyl)pyridine (1.1 equiv) were reacted according to the procedure used for the preparation of 6-methoxy-2-[5-(trifluoromethyl)pyridin-2-yl]-1,3-benzothiazole. This gave the title compound (3 mg) as a brown solid. ^{1}H NMR (400 MHz, MeOH) δ ppm 9.11 (d, 1 H) 8.46 (d, 1 H) 8.34 (dd, 1 H) 7.96 (d, 1 H) 7.41 (d, 1 H) 7.13 (dd, 1 H) 3.89 (s, 3 H) 3.17 (s, 3 H); MS m/z (M+H) 321.

Example 46

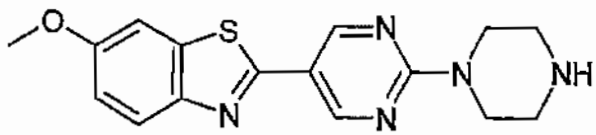
2-(6-Ethoxypyridin-3-yl)-6-methoxy-1,3-benzothiazole



6-Methoxy-1,3-benzothiazole (35 mg, 0.21 mmol) and 2-bromo-5-ethoxypyridine (1.1 equiv) were reacted according to the procedure used for the preparation of 6-methoxy-2-[5-(trifluoromethyl)pyridin-2-yl]-1,3-benzothiazole. This gave the title eompound (17 mg) as a pale beige solid. ^{1}H NMR δ ppm 8.81 (d, 1 H) 8.30 (dd, 1 H) 7.93 (d, 1 H) 7.72 (d, 1 H) 7.13 (dd, 1 H) 6.97 (d, 1 H) 4.40 (q, 2 H) 3.85 (s, 3 H) 1.36 (t, 3 H); MS m/z (M+H) 287.

Example 47

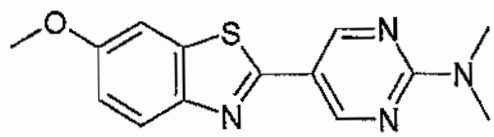
6-Methoxy-2-(2-piperazin-1-ylpyrimidin-5-yl)-1,3-benzothiazole



6-Methoxy-1,3-benzothiazole (35 mg, 0.21 mmol) and 5-bromo-2-piperazin-1-ylpyrimidine (1.1 equiv) were reacted according to the procedure used for the preparation of 6-methoxy-2-[5-(trifluoromethyl)pyridin-2-yl]-1,3-benzothiazole. This gave the title compound (3 mg) as a yellow solid. ^{1}H NMR (400 MHz, MeOH) δ ppm 8.84 (s, 2 H) 7.83 (d, 1 H) 7.30 (d, 1 H) 7.04 (dd, 1 H) 3.87–3.94 (m, 4 H) 3.84 (s, 3 H) 2.90–2.99 (m, 4 H); MS m/z (M+H) 328.

Example 48

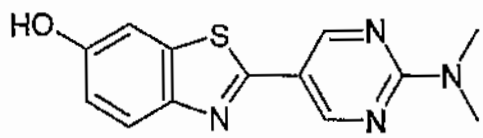
5-(6-Methoxy-1,3-benzothiazol-2-yl)-*N*,*N*-dimethylpyrimidin-2-amine



6-Methoxy-1,3-benzothiazole (0.165 g, 1.00 mmol) and 5-bromo-*N*,*N*-dimethylpyrimidin-2-amine (0.242 g, 1.20 mmol) were reacted according to the procedure used for the preparation of 2-(2-methoxypyrimidin-5-yl)-1,3-benzothiazole with the exception that the reaction was heated at 170°C in a microwave reaetor for 3 h. Purification by flash chromatography (Heptane/EtOAc gradient) followed by reerystallization from acetonitrile gave the title compound (10 mg) as colorless needle crystals. ^{1}H NMR (CHLOROFORM-*d*) δ 8.92 (s, 2 H) 7.90 (d, 1 H) 7.34 (d, 1 H) 7.08 (dd, 1 H) 3.90 (s, 3 H) 3.29 (s, 6 H); MS m/z (M+H) 287.

Example 49

2-[2-(Dimethylamino)pyrimidin-5-yl]-1,3-benzothiazol-6-ol

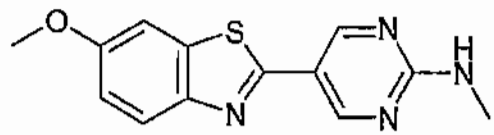


To a stirred slurry of 5-(6-methoxy-1,3-benzothiazol-2-yl)-*N*,*N*-dimethylpyrimidin-2-amine (0.196 mg, 0.68 mmol) in DCM (2 mL) at 0 °C under argon, was added BBr_3 (1 M in DCM, 4.1 mL) from a syringe. After 5 min of stirring, the reaction mixture was allowed

to reach rt over 6.5 h, while being stirred under a drying tube ($CaCl_2$). Then sat. aq. $NaHCO_3$ was carefully added and the mixture was vigorously stirred at rt on before it was concentrated under vacuum. The residue was dissolved in MeOH, concentrated on and filtered through silica (EtOAc/MeOH 10:1). Purification by HPLC gave the title compound (12 mg) as yellow solid. ^{1}H NMR δ 8.89 (s, 2H) 7.79 (d, 1H) 7.39 (d, 1H) 6.96 (dd, 1H) 3.22 (s, 6H); MS m/z (M+H) 273.

Example 50

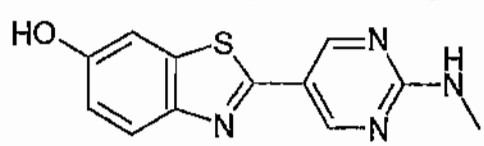
5-(6-Methoxy-1,3-benzothiazol-2-yl)-*N*-methylpyrimidin-2-amine



6-Methoxy-1,3-benzothiazole (0.100 g, 0.61 mmol) and 5-bromo-*N*-methylpyrimidin-2-amine (0.171 g, 0.91 mmol) were reacted according to the procedure used for the preparation of 2-(2-methoxypyrimidin-5-yl)-1,3-benzothiazole with the exception that the reaction was heated at 170°C in a microwave reactor for 1.5 h. The reaction mixture was diluted with EtOAc and water and the mixture was filtered. The phases were separated and the aqueous layer was extracted with EtOAc (3×). The organic phase was washed with brine (2×), dried ($MgSO_4$) and concentrated under vacuum. Flash chromatography (Heptane/EtOAc gradient) gave the title compound (54 mg) as a yellow solid. ^{1}H NMR (CHLOROFORM-*d*) δ 8.93 (s, 2 H) 7.91 (d, 1 H) 7.35 (d, 1 H) 7.10 (dd, 1 H) 5.53 (br s, 1 H) 3.90 (s, 3 H) 3.11 (d, 3 H); MS m/z (M+H) 273.

Example 51

2-[2-(Methylamino)pyrimidin-5-yl]-1,3-benzothiazol-6-ol

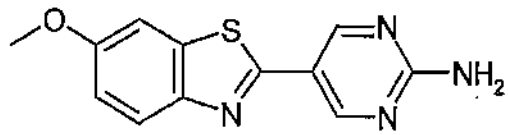


5-(6-Methoxy-1,3-benzothiazol-2-yl)-*N*-methylpyrimidin-2-amine (0.146 g, 0.54 mmol) was reacted according to the procedure used for the preparation of 2-[2-(dimethylamino)pyrimidin-5-yl]-1,3-benzothiazol-6-ol. The residue obtained after evaporation was purified by HPLC to afford the title compound (11 mg). ^{1}H NMR δ 8.96

(br s, 1H) 8.86 (s, 1H) 8.82 (s, 1H) 7.81–7.76 (m, 2H) 7.39 (d, 1H) 6.95 (dd, 1H) 2.88 (d, 3H); MS m/z (M+H) 259.

Example 52

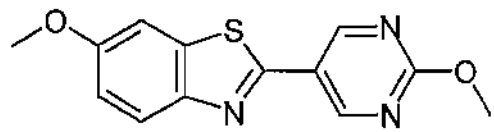
5-(6-Methoxy-1,3-benzothiazol-2-yl)pyrimidin-2-amine



A mixture of 2-bromo-6-methoxy-1,3-benzothiazole (0.300 g, 1.23 mmol), 5-(4,4,5-trimethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine (0.326 g, 1.47 mmol), $Pd(dppf)Cl_2$*DCM (50 mg, 0.061 mmol) and 2 M aq. K_2CO_3 (3 mL) in DMF (7 mL) was stirred under argon at 80 °C for 1 h. The reaction mixture was allowed to reach rt and was filtered through silica. The filter cake was washed with DCM and DMF. The filtrate was concentrated under vacuum. Flash chromatography (Heptane/EtOAc gradient) of the residue gave the title compound (0.171 g) as a yellow solid. ^{1}H NMR δ ppm 8.83 (s, 2 H) 7.87 (d, 1 H) 7.70 (d, 1 H) 7.35 (br s, 2 H) 7.11 (dd, 1 H) 3.84 (s, 3 H); MS m/z (M+H) 259.

Example 53

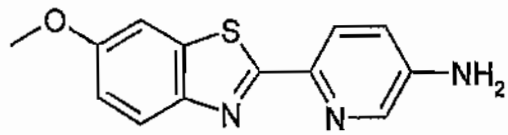
6-Methoxy-2-(2-methoxypyrimidin-5-yl)-1,3-benzothiazole



6-Methoxy-1,3-benzothiazole (30 mg, 0.18 mmol) and 5-bromo-2-methoxypyrimidine (41 mg, 0.22 mmol) were reacted according to the procedure used for the preparation of 2-(2-methoxypyrimidin-5-yl)-1,3-benzothiazole with the exception that the reaction was heated at 150°C in a microwave reactor for 15 min. Purification by flash chromatography (Heptane/EtOAc 3:1) gave the title compound (13 mg) as a white solid. ^{1}H NMR (CHLOROFORM-*d*) δ 9.13 (s, 2 H) 7.97 (d, 1 H) 7.38 (d, 1 H) 7.13 (dd, 1 H) 4.12 (s, 3 H) 3.92 (s, 3 H); MS m/z (M+H) 274.

Example 54

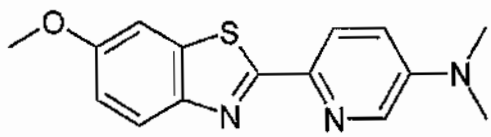
6-(6-Methoxy-1,3-benzothiazol-2-yl)pyridin-3-amine



6-Methoxy-1,3-benzothiazole (60 mg, 0.36 mmol) and 6-bromopyridin-3-amine (76 mg, 0.44 mmol) were reaeted according to the procedure used for the preparation of 2-(2-methoxypyrimidin-5-yl)-1,3-benzothiazole with the exception that the reaction was heated at 170 °C in a microwave reactor for 1.5 h. Water and EtOAc were added and the mixture was filtered. The phases of the filtrate were separated and the aqueous layer was extracted with EtOAc (3×). The organic phase was washed with brine, dried ($MgSO_4$) and concentrated under vacuum. Purification by flash chromatography (Heptan/EtOAc) followed by preparative HPLC gave the title compound (22 mg) as an off-white solid. ^{1}H NMR (CHLOROFORM-*d*) δ 8.16–8.11 (m, 2H) 7.91 (d, 1H) 7.38 (d, 1H) 7.11–7.05 (m, 2H) 4.01 (br s, 2H) 3.91 (s, 3H); MS m/z (M+H) 258.

Example 55

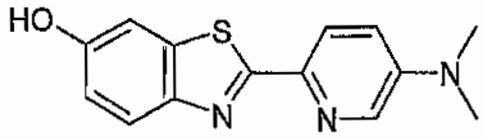
6-(6-Methoxy-1,3-benzothiazol-2-yl)-*N*,*N*-dimethylpyridin-3-amine



6-Methoxy-1,3-benzothiazole (0.136 g, 0.82 mmol; M. A. Matulenko et al. *Bioorg. Med. Chem.* **2005**, *13*, 3705.) and 6-bromo-*N*,*N*-dimethylpyridin-3-amine (0.199 g, 0.99 mmol) were reacted according to the procedure used for the preparation of 6-methoxy-2-[5-(trifluoromethyl)pyridin-2-yl]-1,3-benzothiazole, with the following exceptions: 10 mol% bis(tri-*t*-butylphosphine) palladium (0) was nsed, the amount of DMF was reduced (2 mL) and the reaction mixture was heated at 150 °C for 4.5 h before it was filtered through a short plug of silica that was rinsed by DCM and DMF. The solvents were evsporated under reduced pressure and the residue was subjected to flash chromatogaphy (Heptane/EtOAc gradient). The title compound (0.100 g) was isolated as a yellow solid. ^{1}H NMR (CHLOROFORM-*d*) δ 8.19–8.15 (m, 2H) 7.90 (d, 1H) 7.38 (d, 1H) 7.09–7.04 (m, 2H) 3.90 (s, 3H) 3.10 (s, 6H); MS m/z (M+H) 286.

Example 56

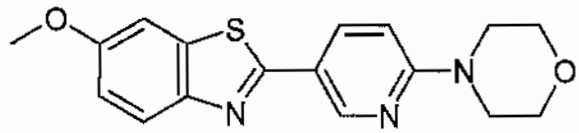
2-[5-(Dimethylamino)pyridin-2-yl]-1,3-benzothiazol-6-ol



To a stirred solution of 6-(6-methoxy-1,3-benzothiazol-2-yl)-*N*,*N*-dimethylpyridin-3-amine (61 mg, 0.21 mmol) in DCM (1 mL) at 0 °C under argon, was added BBr_3 (1 M in DCM, 1.1 mL) from a syringe. After 5 min of stirring, the reaction mixture was allowed to reach rt on while being stirred under a drying tube ($CaCl_2$). Then sat. aq. $NaHCO_3$ was carefully added and the mixture was vigorously stirred for another 4 h at rt. DCM was evaporated under reduced pressure and the aqueous phase was continuously extracted with EtOAc on. The organic layer was concentrated to give the title compound (15 mg) as a yellow solid. ^{1}H NMR δ ppm 9.74 (s, 1 H) 8.16 (d, 1 H) 8.01 (d, 1 H) 7.76 (d, 1 H) 7.33 (d, 1 H) 7.21 (dd, 1 H) 6.93 (dd, 1 H) 3.04 (s, 6 H); MS m/z (M+H) 272.

Example 57

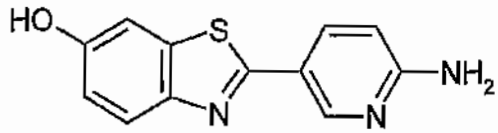
6-Methoxy-2-(6-morpholin-4-ylpyridin-3-yl)-1,3-benzothiazole



2-Bromo-6-methoxy-1,3-benzothiazole (49 mg, 0.20 mmol), 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]morpholine (70 mg, 0.24 mmol) were reacted according to the procedure used for the preparation of 5-(6-methoxy-1,3-benzothiazol-2-yl)pyrimidin-2-amine, with the following exceptions: The reaction was heated for 4 h before the solvent was evaporated under reduced pressure. The residue was dissolved in MeOH/DCM 1:1 and filtered through silica. The filtrate was concentrated and the crude product was purified by preparative HPLC to give the title compound (0.6 mg). ^{1}H NMR (CHLOROFORM-*d*) δ 8.79 (d, 1 H) 8.18 (dd, 1 H) 7.90 (d, 1 H) 7.35 (d, 1 H) 7.08 (dd, 1 H) 6.71 (d, 1 H) 3.90 (s, 3 H) 3.87–3.83 (m, 4H) 3.67–3.63 (m, 4H); MS m/z (M+H) 328.

Example 58

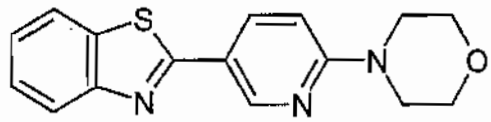
2-(6-Aminopyridin-3-yl)-1,3-benzothiazol-6-ol



5-(6-Methoxy-1,3-benzothiazol-2-yl)pyridin-2-amine (190 mg, 0.74 mmol) was exposed to the procedure used for the preparation of 2-[6-(methylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol. After neutralization, the precipitate was filtered off and washed with water. The crude solid was slurred in hot EtOAc/MeOH 95:5 and filtered. The filtrate was concentrated under reduced pressure and the residue was subjected to flash chromatography (EtOAc/MeOH 95:5) to give a product that was chromatographed once more (DCM/MeOH 95:5) to yield the title compound (65 mg). ^{1}H NMR δ 9.74 (s, 1 H) 8.53 (d, 1 H) 7.93 (dd, 1 H) 7.73 (d, 1 H) 7.35 (d, 1 H) 6.93 (dd, 1 H) 6.61 (br s, 2 H) 6.55 (d, 1 H); MS m/z (M+H) 244.

Example 59

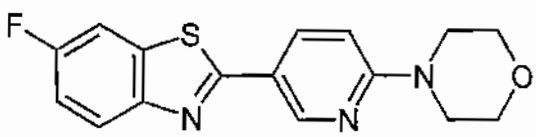
2-(6-Morpholin-4-ylpyridin-3-yl)-1,3-benzothiazole



2-Bromo-1,3-benzothiazole (100 mg, 0.47 mmol) and 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]morpholine (163 mg, 0.56 mmol) were reacted according to the procedure used for the preparation of 5-(6-methoxy-1,3-benzothiazol-2-yl)pyrimidin-2-amine. Flash chromatography (Heptane/EtOAc 1:1) furnished the title compound (73 mg) as an off-white solid. ^{1}H NMR δ 8.81 (d, 1 H) 8.18 (dd, 1 H) 8.10 (d, 1 H) 7.98 (d, 1 H) 7.54–7.48 (m, 1 H) 7.44–7.38 (m, 1 H) 7.00 (d, 1 H) 3.74–3.70 (m, 4 H) 3.65–3.60 (m, 4 H); MS m/z (M+H) 298.

Example 60

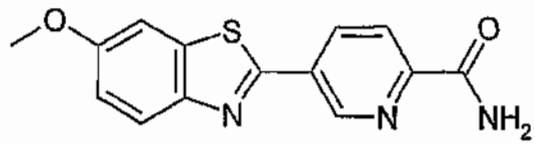
6-Fluoro-2-(6-morpholin-4-ylpyridin-3-yl)-1,3-benzothiazole



2-Bromo-6-fluoro-1,3-benzothiazole (100 mg, 0.43 mmol) and 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]morpholine (150 mg, 0.52 mmol) were reacted according to the procedure used for the preparation of 5-(6-methoxy-1,3-benzothiazol-2-yl)pyrimidin-2-amine. Flash chromatography (Heptane/EtOAc 1:1) furnished the title compound (126 mg) as an off-white solid. ^{1}H NMR δ 8.79 (d, 1 H) 8.15 (dd, 1 H) 8.05–7.97 (m, 2 H) 7.40–7.34 (m, 1 H) 6.99 (d, 1 H) 3.73–3.69 (m, 4 H) 3.64–3.60 (m, 4 H); MS m/z (M+H) 316.

Example 61

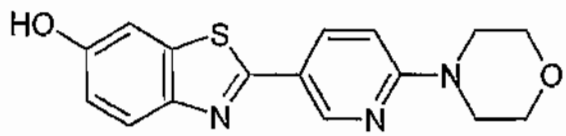
5-(6-Methoxy-1,3-benzothiazol-2-yl)pyridine-2-carboxamide



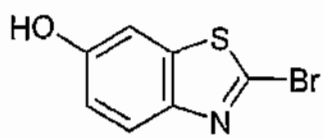
6-Methoxy-1,3-benzothiazole (0.100 g, 0.61 mmol) and 5-bromopyridine-2-carboxamide (0.146 g, 0.73 mmol) were reacted according to the procedure used for the preparation of 6-methoxy-2-[5-(trifluoromethyl)pyridin-2-yl]-1,3-benzothiazole, with the following exceptions: 10 mol% bis(tri-*t*-butylphosphine) palladium (0) was used and the amount of DMF was reduced (3 mL). The reaction mixture was coneentrated and flash chromatography of the residue gave the title compound (10 mg) as an off-white solid. ^{1}H NMR δ 9.25 (dd, 1 H) 8.56 (dd, 1 H) 8.23 (br s, 1 H) 8.19 (dd, 1 H) 8.04 (d, 1 H) 7.81 (d, 1 H) 7.78 (br s, 1 H) 7.20 (dd, 1 H) 3.88 (s, 3 H); MS m/z (M+H) 286.

Example 62

2-(6-Morpholin-4-ylpyridin-3-yl)-1,3-benzothiazol-6-ol



(a) 2-Bromo-1,3-benzothiazol-6-ol



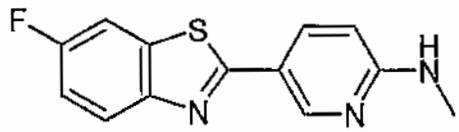
2-Bromo-6-methoxy-1,3-benzothiazole (0.832 g, 3.41 mmol) was subjected to the procedure used for the preparation of 2-[2-(dimethylamino)pyrimidin-5-yl]-1,3-benzothiazol-6-ol, with the following exceptions: 4.4 equiv BBr_3-solution was used, and after being stirred on, the mixture was poured into MeOH and then concentrated under reduced pressure. A slurry of this residue in EtOAc was filtered through silica and eluted with EtOAc/DCM/MeOH 10:10:1 and DCM/MeOH 9:1. The crude product was recrystallized from EtOAc to give 2-bromo-1,3-benzothiazol-6-ol (0.602 g). ^{1}H NMR δ 10.00 (br s, 1H) 7.77 (d, 1H) 7.39 (d, 1H) 6.97 (dd, 1H).

(b) 2-(6-Morpholin-4-ylpyridin-3-yl)-1,3-benzothiazol-6-ol (title compound)

2-Bromo-1,3-benzothiazol-6-ol (40 mg, 0.17 mmol) and 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]morpholine (61 mg, 0.21 mmol) were reacted according to the procedure used for the preparation of 5-(6-methoxy-1,3-benzothiazol-2-yl)pyrimidin-2-amine. The reaction mixture was cooled to rt and concentrated. Flash chromatography (Heptane/EtOAc 1:1) gave the title compound (21 mg) as an off-white solid. ^{1}H NMR δ 9.80 (br s, 1 H) 8.71 (d, 1 H) 8.09 (dd, 1 H) 7.77 (d, 1 H) 7.37 (d, 1 H) 6.98–6.93 (m, 2 H) 3.73–3.69 (m, 4 H) 3.61–3.56 (m, 4 H); MS m/z (M+H) 314.

Example 63

5-(6-Fluoro-1,3-benzothiazol-2-yl)-*N*-methylpyridin-2-amine

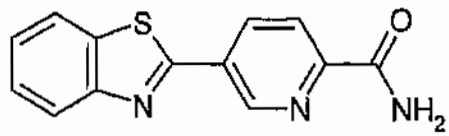


A mixture of 5-bromo-*N*-methylpyridin-2-amine (50 mg, 0.27 mmol), bis(pinacolato)diboron (75 mg, 0.30 mmol), Pd(dppf)Cl_2*DCM (6.5 mg, 0.008 mmol) and KOAc (79 mg, 0.80 mmol) in DMF (2 mL) was heated at 150 °C for 10 minutes in a microwave reactor. Then 2-bromo-6-fluoro-1,3-benzothiazole (93 mg, 0.40 mmol), another batch of Pd(dppf)Cl_2*DCM (6.5 mg, 0.008 mmol) and 2 M aq. K_2CO_3 (0.5 mL) were added and the reaction mixture was heated at 100 °C for 5 minutes in a microwave reactor. The mixture was allowed to cool and was partitioned between EtOAc and H_2O. The organic phase was washed with water and brine and was dried (Na_2SO_4). Concentration

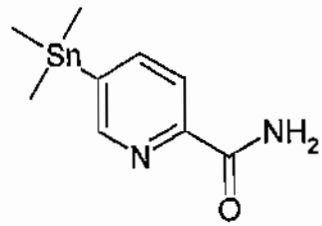
under vacuum and purification by HPLC gave the title compound (8 mg). ^{1}H NMR (CHLOROFORM-*d*: CD_3OD) δ 8.61 (d, 1 H) 8.02 (dd, 1 H) 7.87 (dd, 1 H) 7.57 (dd, 1 H) 7.22–7.15 (m, 1 H) 6.55 (d, 1 H) 2.94 (s, 3 H); MS m/z (M+H) 260, (M-H) 258.

Example 64

5-(1,3-Benzothiazol-2-yl)pyridine-2-carboxamide



(a) 5-(Trimethylstannyl)pyridine-2-carboxamide



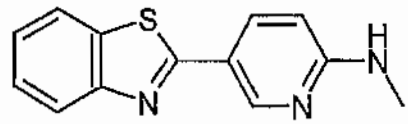
A mixture of 5-bromo-2-pyridinecarboxamide (0.100 g, 0.50 mmol), hexamethylditin (0.21 mL, 1.0 mmol) and tetrakis(triphenylphosphine)palladium (0) (57 mg, 0.05 mmol) in dioxane (2 mL) was heated in a microwave reactor at a power of 300 W for 10 min. The reaction mixture was filtered and eoncetrated under reduced pressure. Flash chromatography (Heptane/EtOAc gradient) gave 5-(trimethylstannyl)pyridine-2-carboxamide (98 mg) as a white solid. MS m/z (M+H) 287.

(b) 5-(1,3-Benzothiazol-2-yl)pyridine-2-carboxamide (title compound)

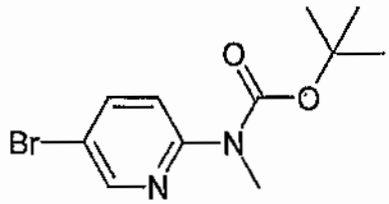
A mixture of 2-chloro-1,3-benzothiazole (38 µL, 0.31 mmol), 5-(trimethylstannyl)pyridine-2-carboxamide (97 mg, 0.34 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) in dry dioxane (2 mL) was heated under argon to 160 °C for 30 min in a microwave reactor. The precipitate was filtered off. Flash chromatography (DCM/MeOH 99:1 → DCM/Acetone 1:1) gave the title compound (23 mg) as a white solid. ^{1}H NMR δ 9.31 (dd, 1 H) 8.63 (dd, 1 H) 8.27 (br s, 1 H) 8.26–8.19 (m, 2 H) 8.16 (d, 1 H) 7.83 (br s, 1 H) 7.64–7.59 (m, 1 H) 7.57–7.52 (m, 1 H); MS m/z (M+H) 256.

Example 65

5-(1,3-Benzothiazol-2-yl)-*N*-methylpyridin-2-amine

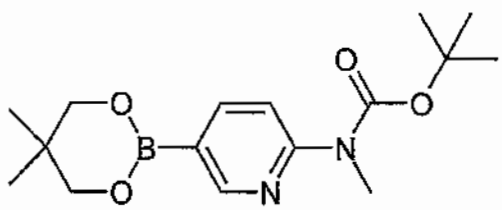


(a) tert-Butyl (5-bromopyridin-2-yl)methylcarbamate



NaHMDS (88 mL, 1 M in THF) was added dropwise to 5-bromo-*N*-methylpyridin-2-amine (15.0 g, 80.2 mmol) and di-*tert*-butyl dicarbonate (21.0 g, 96.2 mmol) in THF (50 mL) at °C. The reaction mixture was allowed to reach rt and was stirred for 3 h before it was concentrated under reduced pressure. The residue was partitioned between EtOAc and sat. aq. $NaHCO_3$. The layers were separated and the aqueous phase was extracted with EtOAe.The combined organic layers were dried (Na_2SO_4) and concentrated. Filtration through silica, eluting with Heptane/EtOAc 9:1, gave *tert*-butyl (5-bromopyridin-2-yl)methylcarbamate (22.7 g) as a pale yellow oil. ^{1}H NMR δ 8.48 (d, 1 H) 7.96 (dd, 1 H) 7.64 (d, 1 H) 3.27 (s, 3 H) 1.46 (s, 9 H).

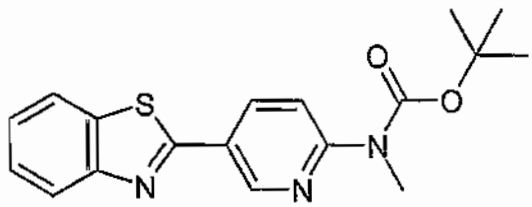
(b) tert-Butyl [5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)pyridin-2-yl]methylcarbamate



n-BuLi (27 mL, 2.5 M) was slowly added to a stirred solution of *tert*-butyl (5-bromopyridin-2-yl)methylcarbamate (17.7 g, 61.6 mmol) in THF (280 mL) at –78 °C under an argon atmosphere. After 5 min at –78 °C, triisopropylborate (28.5 mL, 123 mmol) was added and the mixture was stirred at –78 °C for 1 h. Neopentyl glycol (6.4 g, 61.4 mmol) was added and the reaction mixture was allowed to reach rt and was stirred for 2.5

d. The reaction was quenched with water (300 mL). The phases were separated and the aqueous phase was extracted with DCM. The organic layer was concentrated and the residue was purified by two successive flash chromatographies (Heptane/EtOAc 9:1 → 1:4 and DCM/MeOH 24:1 respectively) to give the product (2.23 g) as a white solid. ^{1}H NMR δ 8.57 (dd, 1 H) 7.94 (dd, 1 H) 7.65 (dd, 1 H) 3.76 (s, 4 H) 3.30 (s, 3 H) 1.47 (s, 9 H) 0.96 (s, 6 H).

(c) tert-Butyl [5-(1,3-benzothiazol-2-yl)pyridin-2-yl]methylcarbamate



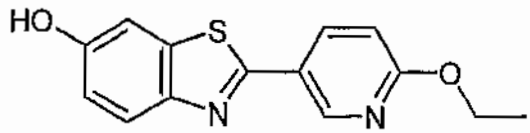
2-Chlorobenzothiazole (31 µL, 0.25 mmol) and *tert*-butyl [5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)pyridin-2-yl]methylcarbamate (80 mg, 0.25 mmol) were reacted according to the procedure used for the preparation of 5-(6-methoxy-1,3-benzothiazol-2-yl)pyrimidin-2-amine. After 1 h at 80 °C, the mixture was concentrated under reduced pressure and the residue was partitioned between DCM and H_2O. The organic phase was eoneentrated. Flash chromatography (Heptane/EtOAc gradient) gave the product (53 mg) as a white solid. MS m/z (M+H) 342.

(d) 5-(1,3-Benzothiazol-2-yl)-N-methylpyridin-2-amine (title compound)

tert-Butyl [5-(1,3-benzothiazol-2-yl)pyridin-2-yl]methylearbamate (40 mg, 0.12 mmol) was dissolved in DCM (5 mL). TFA (0.5 mL) was added and the reaction mixture was stirred at rt for 4 h. The mixture was concentrated and the residue was partitioned between EtOAc and sat. aq. $NaHCO_3$. The organic phase was washed with brine, dried (Na_2SO_4) and eoncentrated under reduced pressure. Purification by HPLC gave the title compound (18 mg) as a white solid. ^{1}H NMR δ 8.70 (d, 1 H) 8.06 (m, 1 H) 8.02 (dd, 1 H) 7.94 (dd, 1 H) 7.46–7.51 (m, 1 H) 7.40–7.35 (m, 1 H) 7.29 (br q, 1 H) 6.59 (d, 1 H) 2.86 (d, 3 H); MS m/z (M+H) 242, (M-H) 240.

Example 66

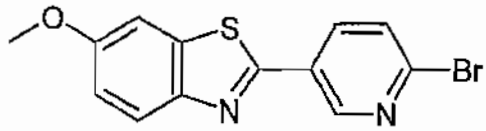
2-(6-Ethoxypyridin-3-yl)-1,3-benzothiazol-6-ol



2-(6-Ethoxypyridin-3-yl)-6-methoxy-1,3-benzothiazole (23 mg, 80 μmol) was reacted according to the procedure used for the preparation of 2-[2-(dimethylamino)pyrimidin-5-yl]-1,3-benzothiazol-6-ol, with the following exceptions: The reaction mixture was allowed to reach rt on. sat. aq. $NaHCO_3$ was added and the mixture was extracted with EtOAc. The organic phase was dried and concentrated under reduced pressure. Preparative HPLC of the residue gave the title compound (4 mg). ^{1}H NMR (CHLOROFORM-*d*: CD_3OD) δ 8.69 (d, 1 H) 8.20 (dd, 1 H) 7.79 (d, 1 H) 7.29 (d, 1 H) 6.99 (dd, 1 H) 6.86 (d, 1 H) 4.39 (q, 2 H) 1.41 (t, 3 H); MS m/z (M+H) 273.

Example 67

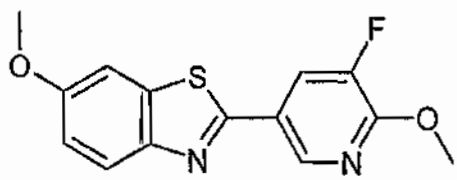
2-(6-Bromopyridin-3-yl)-6-methoxy-1,3-benzothiazole



2-Bromo-6-methoxy-1,3-benzothiazole (49 mg, 0.20 mmol) and 2-bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (68 mg, 0.24 mmol) were reacted according to the procedure used for the preparation of 5-(6-methoxy-1,3-benzothiazol-2-yl)pyrimidin-2-amine, with the following exceptions: The reaction was stirred for 2 h and was then allowed to reach rt on. The mixture was filtered through a plug of silica and Na_2SO_4, eluting with DCM. The volume of the filtrate was reduced in a centrifuge and the remainder was purified by HPLC to give the title compound (4.2 mg). ^{1}H NMR (CHLOROFORM-*d*: CD_3OD) δ 8.93 (d, 1 H) 8.21 (dd, 1 H) 7.92 (d, 1 H) 7.68 (d, 1 H) 7.43 (d, 1 H) 7.12 (dd, 1 H) 3.89 (s, 3 H).

Example 68

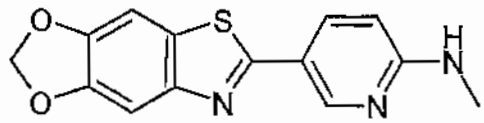
2-(5-Fluoro-6-methoxy-pyridin-3-yl)-6-methoxy-benzothiazole



2-Bromo-6-methoxy-1,3-benzothiazole (49 mg, 0.20 mmol) and (5-chloro-6-methoxypyridin-3-yl)boronic acid (45 mg, 0.24 mmol) were reacted according to the procedure used for the preparation of 2-(6-bromopyridin-3-yl)-6-methoxy-1,3-benzothiazole to give the title compound (0.2 mg). ^{1}H NMR (CHLOROFORM-*d*: CD_3OD) δ 8.51 (d, 1 H) 8.03 (dd, 1 H) 7.87 (d, 1 H) 7.43 (d, 1 H) 7.10 (dd, 1 H) 4.08 (s, 3 H) 3.88 (s, 3 H); MS m/z (M+H) 291.

Example 69

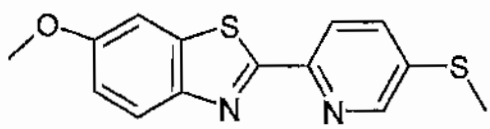
5-[1,3]Dioxolo[4,5-*f*][1,3]benzothiazol-6-yl-*N*-methylpyridin-2-amine



To [1,3]Dioxolo[4,5-*f*][1,3]benzothiazole (98 mg, 0.55 mmol) and 5-bromo-*N*-methylpyridin-2-amine (112 mg, 0.60 mmol) were subjected to the procedure used for the preparation of 2-(2-methoxypyrimidin-5-yl)-1,3-benzothiazole, with the following exceptions: 5 mol% bis(tri-t-butylphosphine) palladium (0) was used and the reaction was heated under argon at 170°C in a microwave oven for 30 min. The crude material was purified by flash chromatography (Heptane/EtOAc 1:1) to give the title compound (56 mg) as a yellow solid. ^{1}H NMR δ 8.62 (d, 1 H) 7.94 (dd, 1 H) 7.61 (s, 1 H) 7.47 (s, 1 H) 7.19 (q, 1 H) 6.57 (d, 1 H) 6.13 (s, 2 H) 2.85 (d, 3 H); MS m/z (M+H) 286.

Example 70

6-Methoxy-2-[5-(methylthio)pyridin-2-yl]-1,3-benzothiazole

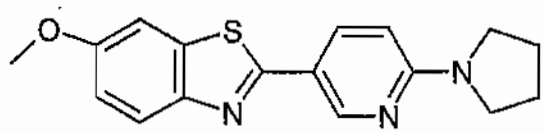


6-Methoxy-1,3-benzothiazole (35 mg, 0.21 mmol) and 2-bromo-5-(methylthio)pyridine (1.1 equiv) were reacted according to the procedure used for the preparation of 6-

methoxy-2-[5-(trifluoromethyl)pyridin-2-yl]-1,3-benzothiazole. This gave the title compound (1 mg) as a pale yellow solid. ^{1}H NMR (CHLOROFORM-*d*) δ 8.52 (d, 1 H) 8.22 (d, 1 H) 7.95 (d, 1 H) 7.67 (dd, 1 H) 7.40 (d, 1 H) 7.11 (dd, 1 H) 3.92 (s, 3 H) 2,58 (s, 3 H); MS m/z (M+H) 289.

Example 71

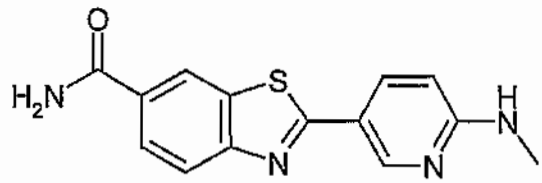
6-Methoxy-2-(6-pyrrolidin-1-ylpyridin-3-yl)-1,3-benzothiazole



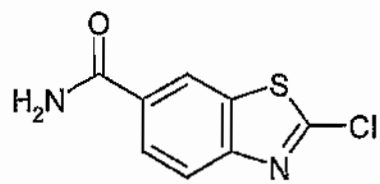
In a microwave vial were added 2-(6-fluoropyridin-3-yl)-6-methoxy-1,3-benzothiazole (75 mg, 0.29 mmol), water (2.5 mL) and pyrrolidine (0.50 mL) and the reaction was heated in a microwave oven at 100°C for 5 min. The precipitated product was filtered off, washed with water and methanol and dried in a desicator over P_2O_5 to give the title compound (76 mg) as a white solid. ^{1}H NMR (CHLOROFORM-*d*) δ 8.77 (d, 1 H) 8.13 (dd, 1 H) 7.87 (d, 1 H) 7.33 (d, 1 H) 7.05 (dd, 1 H) 6.44 (d, 1 H) 3.89 (s, 3 H) 3.63–3.46 (m, 4 H) 2.11–1.98 (m, 4 H); MS m/z (M+H) 312.

Example 72

2-(6-Methylaminopyridin-3-yl)benzothiazole-6-carboxamide



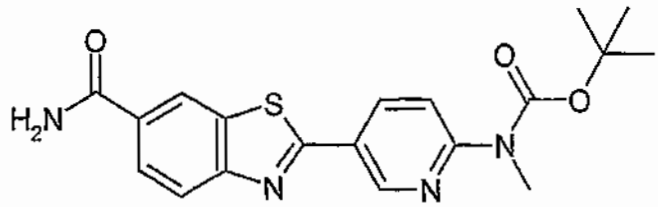
a) 2-Chloro-1,3-benzothiazole-6-carboxamide



2-Bromo-1,3-benzothiazole-6-carboxylic acid (100 mg, 0.39 mmol) and thionyl chloride (2 mL) were mixted and stirred at rt for 1 h then at 60 °C for 30 min. The mixture was

concentrated under reduced pressure and the residue was dissolved in $CHCl_3$ (3 mL). This solution was added dropwise to NH_3 (ca. 7 N in MeOH, 5 mL) at 0 °C. The mixture was stirred at rt for 1 h before it was concentrated under reduced pressure. The crude product was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc and the organic phase was dried (Na_2SO_4) and concentrated to give the the product (77 mg) as a white solid. MS m/z (M+H) 213, (M-H) 211.

b) tert-Butyl [5-(6-carbamoyl-1,3-benzothiazol-2-yl)pyridin-2-yl]methylcarbamate



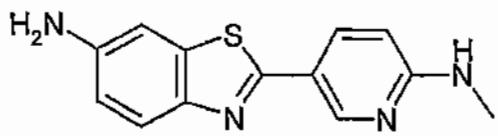
A mixture of 2-chloro-1,3-benzothiazole-6-carboxamide (77 mg, 0.36 mmol), *tert*-butyl [5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)pyridin-2-yl]methylcarbamate (0.174 g, 0.54 mmol), $Pd(dppf)Cl_2$*DCM (30 mg, 0.036 mmol) and 2 M aq. K_2CO_3 (0.8 mL) in DMF (2 mL) was stirred under argon at 80 °C for 2 h. The reaction mixture was filtered and the filtrate was partitioned between EtOAc and H_2O. The layers were separated and the aqueous phase was extraeted with EtOAc. The eombined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography (Heptane/EtOAc gradient) gave the product (66 mg) as a white solid. MS m/z (M-H) 383.

c) 2-(6-Methylaminopyridin-3-yl)benzothiazole-6-carboxamide (title compound)

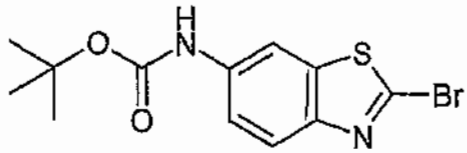
To a stirred slurry of *tert*-butyl [5-(6-carbamoyl-1,3-benzothiazol-2-yl)pyridin-2-yl]methylcarbamate (10 mg, 0.026 mmol) in DCM (1 mL) was added TFA (1 mL) dropwise at 0 °C, and the reaction mixture was stirred at rt on. The solvent was evaporated under reduced pressure. Preparative HPLC of the residue gave the title compound (6 mg) as a white solid. ^{1}H NMR δ 8.74 (d, 1H) 8.56 (s, 1H) 8.11–7.94 (m, 4H) 7.50–7.36 (m, 2H) 6.60 (d, 1H) 2.87 (d, 3H); MS m/z (M+H) 285.

Example 73

2-(6-Methylaminopyridin-3-yl)benzothiazol-6-amine

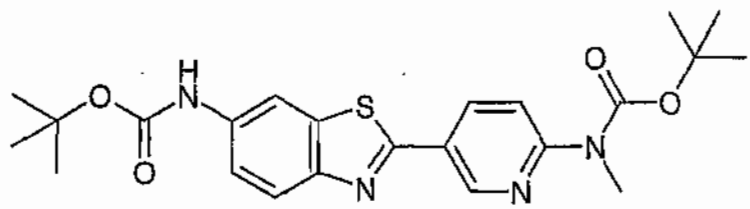


a) tert-Butyl (2-bromo-1,3-benzothiazol-6-yl)carbamate



Triethylamine (1.94 mL, 13.9 mmol) and diphenylphosphoryl azide (2.76 mL, 12.8 mmol) were added to a solution of 2-bromo-1,3-benzothiazole-6-carboxylic acid (3.0 g, 11.6 mmol) in *tert*-butanol (100 mL) and the reaction mixture was stirred at 80 °C for 4 h. The solvent was evaporated under reduced pressure and the residue was subjected to flash chromatography (Heptane/EtOAc gradient) to give *tert*-butyl (2-bromo-1,3-benzothiazol-6-yl)carbamate (1.1 g) as a white solid. MS m/z (M+H) 329, 331.

b) tert-butyl (5-{6-[(tert-butoxycarbonyl)amino]-1,3-benzothiazol-2-yl}pyridin-2-yl)methylcarbamate



tert-Butyl (2-bromo-1,3-benzothiazol-6-yl)carbamate (100 mg, 0.30 mmol) and *tert*-butyl [5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)pyridin-2-yl]methylcarbamate (0.146 g, 0.46 mmol) were subjected to the procedure used for the preparation of *tert*-butyl [5-(6-carbamoyl-1,3-benzothiazol-2-yl)pyridin-2-yl]methylcarbamate. This gave the product (110 mg) as a white solid. MS m/z (M-H) 455.

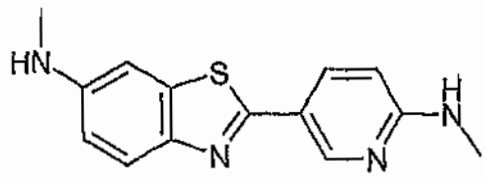
c) 2-(6-Methylaminopyridin-3-yl)benzothiazol-6-amine (title compound)

TFA (1.5 mL) was added to a solution of *tert*-butyl (5-{6-[(tert-butoxycarbonyl)amino]-1,3-benzothiazol-2-yl}pyridin-2-yl)methylcarbamate (40 mg, 0.088 mmol) in DCM (1.5 mL) at 0 °C and the reaction mixture was stirred at rt on. The solvent was evaporated under reduced pressure. Preparative HPLC of the residue gave the title compound (12 mg) as a

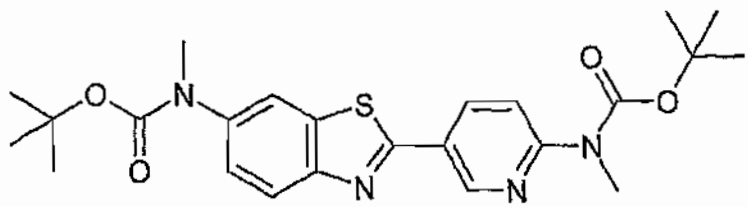
white solid. ^{1}H NMR δ 8.55 (d, 1H) 7.90 (dd, 1H) 7.59 (d, 1H) 7.12 (br q, 1H) 7.05 (s, 1H) 6.74 (dd, 1H) 6.55 (d, 1H) 5.37 (br s, 2H) 2.83 (d, 3H); MS m/z (M+H) 257, (M-H) 255.

Example 74

N-Methyl-2-(6-methylaminopyridin-3-yl)benzothiazol-6-amine



(a) tert-Butyl (5-{6-[(tert-butoxycarbonyl)(methyl)amino]-1,3-benzothiazol-2-yl}pyridin-2-yl)methylcarbamate



NaH (95%, 4.5 mg, 0.18 mmol) was added to a solution of *tert*-butyl (5-{6-[(*tert*-butoxycarbonyl)amino]-1,3-benzothiazol-2-yl}pyridin-2-yl)methylcarbamate (66 mg, 0.14 mmol) in DMF (2 mL). The mixture was cooled to 0 °C and MeI (10 µL, 0.16 mmol) was added. The reaction was stirred at rt on. Water was added and the mixture was extracted with EtOAc (3×) The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography (Heptane/EtOAc gradient) gave the product (60 mg) as a white solid. MS m/z (M+H) 471.

(b) N-Methyl-2-(6-methylaminopyridin-3-yl)benzothiazol-6-amine (title compound)

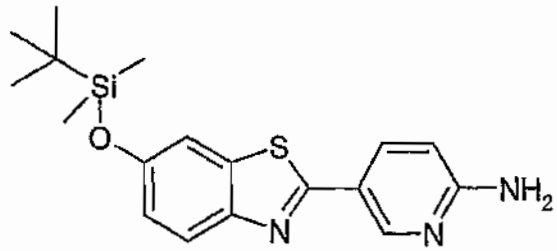
tert-Butyl (5-{6-[(tert-butoxycarbonyl)(methyl)amino]-1,3-benzothiazol-2-yl}pyridin-2-yl)methylcarbamate (53 mg, 0.11 mmol) was reacted according to the procedure used for the preparation of 2-(6-methylaminopyridin-3-yl)benzothiazol-6-amine. This gave the title compound (20 mg) as a yellow solid. ^{1}H NMR δ 8.56 (d, 1H) 7.91 (dd, 1H) 7.63 (d, 1H) 7.12 (br q, 1H) 7.00 (d, 1H) 6.75 (dd, 1H) 6.55 (d, 1H) 5.99 (br q, 1H) 2.84 (d, 3H) 2.73 (d, 3H); MS m/z (M+H) 271.

Preeursor examples

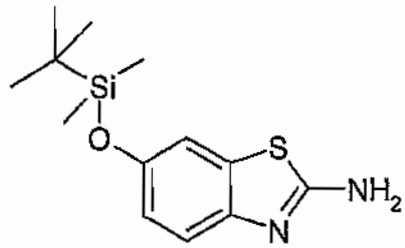
Below follows a number of non-limiting examples of compounds of the invention. The below examplified compounds are useful as precursors for the preparation of [^{11}C]methyl labeled compounds of the invention. The general methods used for the preparation of these precursors were the same as those used for the preparation of the compound examples herein.

Precursor Example 1

5-(6-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,3-benzothiazol-2-yl)pyridin-2-amine

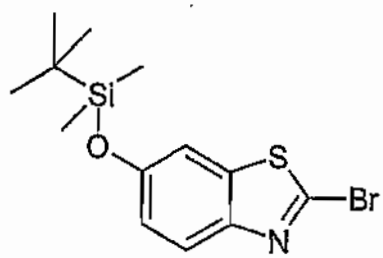


a) 6-{[tert-Butyl(dimethyl)silyl]oxy}-1,3-benzothiazol-2-amine



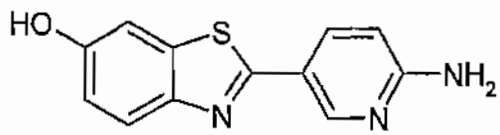
A solution of 2-amino-6-hydroxybenzothiazole (5.00 g, 30.1 mmol), TBDMSCl (5.40 g, 1.2 equiv) and imidazole (2.46 g, 1.2 equiv) in DMF (160 ml) was stirred at ambient temperature for 16 h. The reaction mixture was then partitioned between water and ethyl acetate. The aquous phase was extracted twice with ethyl acetate and the combined organics dried ($MgSO_4$) and concentrated *in vacuo*. The crude product thus obtained was purified by silica gel chromatography by gradient elution (*n*-heptane:ethyl acetate) to yield 3.0 g of the title compound as a yellowish solid. ^{1}H NMR δ 7.23 (br s, 2H) 7.18 (d, 1H) 7.16 (d, 1H) 6.70 (dd, 1H) 0.95 (s, 9H) 0.16 (s, 6H); MS m/z (M+H) 281.

(b) 2-Bromo-6-{[tert-butyl(dimethyl)silyl]oxy}-1,3-benzothiazole



To a eool (0 °C) suspension of 6-{[*tert*-butyl(dimethyl)silyl]oxy}-1,3-benzothiazol-2-amine (2.00 g, 7.13 mmol) and copper(II)bromide (2.40 g, 1.5 equiv) in acetonitrile (70 ml), was added *tert*-butyl nitrite (1.27 ml, 1.5 equiv) in one portion. The reaction mixture was then allowed to come to ambient temperature and stirred for another 5 h before partitioning between water and ethyl acetate. The aqueous phase was extracted twice with ethyl acetate and the combined organics were washed successively with water and brine before drying ($MgSO_4$) and concentration *in vacuo*. The obtained crude product thus obtained was purified by silica gel chromatography by gradient elution (*n*-heptane:ethyl acetate) to yield 1.95 g of the title compound as a red oil. ^{1}H NMR δ 7.85 (d, 1H) 7.62 (d, 1H) 7.03 (dd, 1H) 0.96 (s, 9H) 0.22 (s, 6H); MS m/z (M+H) 344, 346.

(c) 2-(6-Aminopyridin-3-yl)-1,3-benzothiazol-6-ol



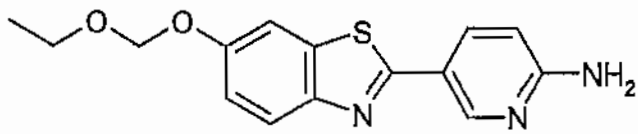
A mixture of 2-bromo-6-{[*tert*-butyl(dimethyl)silyl]oxy}-1,3-benzothiazole (500 mg, 1.45 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (383 mg, 1.2 equiv), aqueous potassium carbonate (2.0 M, 2.9 ml, 4.0 equiv) and $Pd(dppf)Cl_2$ (119 mg, 0.10 equiv) in DMF (6.0 ml) was stirred at 80 °C under argon for 2 h. The mixture was then added to DCM (100 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The crude thus obtained was purified by silica gel chromatography by gradient elution (*n*-heptane:ethyl acetate) to yield 237 mg of the title compound. ^{1}H NMR δ 9.74 (s, 1H) 8.53 (d, 1H) 7.94 (dd, 1H) 7.73 (d, 1H) 7.35 (d, 1H) 6.93 (dd, 1H) 6.61 (s, 2H) 6.55 (d, 1H); MS m/z (M+H) 244.

(d) 5-(6-{[tert-Butyl(dimethyl)silyl]oxy}-1,3-benzothiazol-2-yl)pyridin-2-amin (title compound)

A solution of 2-(6-aminopyridin-3-yl)-1,3-benzothiazol-6-ol (177 mg, 0.73 mmol), TBDMSCl (121 mg, 1.1 equiv) and imidazole (124 mg, 2.5 equiv) in DMF (2.0 ml) was stirred at ambient temperature for 2 h. The reaction mixture was then partitioned between water and ethyl acetate. The aqueous phase was extracted twice with ethyl acetate and the combined organics dried ($MgSO_4$) and concentrated *in vacuo*. The crude product thus obtained was purified by silica gel chromatography, using a mixture of DCM and methanol (95:5) as eluent, to yield 200 mg of the title compound as a white solid. ^{1}H NMR δ 8.56 (d, 1H) 7.96 (dd, 1H) 7.80 (d, 1H) 7.54 (d, 1H) 6.98 (dd, 1H) 6.67 (s, 2H) 6.56 (d, 1H) 0.97 (s, 9H) 0.22 (s, 6H); MS m/z (M+H) 358.

Precursor Example 2

5-[6-(Ethoxymethoxy)-1,3-benzothiazol-2-yl]pyridin-2-amine



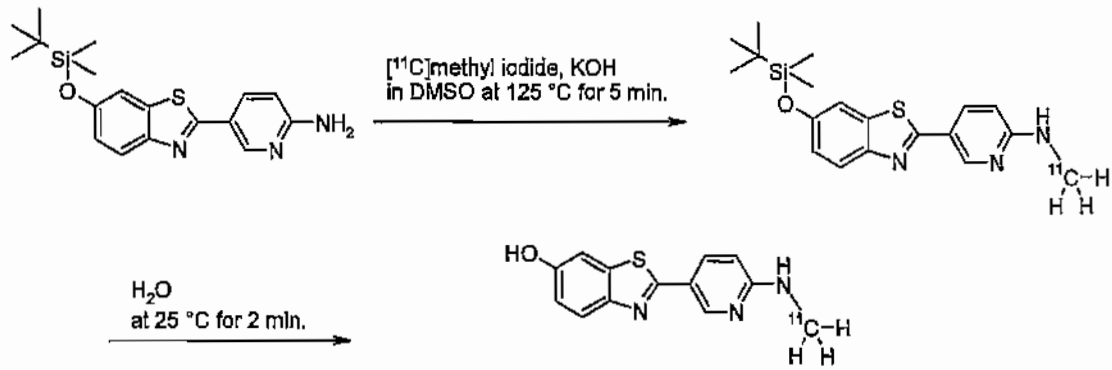
Chloromethyl ethyl ether (0.24 mL) was added in one portion to a rapidly stirred solution of 2-(6-aminopyridin-3-yl)-1,3-benzothiazol-6-ol (0.319 g, 1.31 mmol) and K_2CO_3 (0.543 g) in DMF (10 mL) at 0 °C. The reaction was stirred at rt on. The mixture was concentrated under reduced pressure and the residue was subjected to flash chromatography (DCM/MeOH 99:1 → 95:5) to yield the title compound (31 mg). ^{1}H NMR δ 8.57 (d, 1H) 7.97 (dd, 1H) 7.84 (d, 1H) 7.71 (d, 1H) 7.16 (dd, 1H) 6.66 (br s, 2H) 6.56 (d, 1H) 5.30 (s, 2H) 3.69 (q, 2H) 1.15 (t, 3H); MS m/z (M+H) 302, (M-H) 300.

^{11}C-labeled compound examples

Below follows non-limiting example(s) of compounds of the invention. The corresponding non-labeled analogs display an IC_{50} of less than 20μM in the competition binding assay described herein.

^{11}C-Example 1

[*N-Methyl*-^{11}C]-2-(6-Methylamino-pyridin-3-yl)-benzothiazol-6-ol



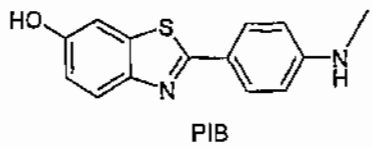
[*N*-Methyl-^{11}C]-2-(6-Methylamino-pyridin-3-yl)-benzothiazol-6-ol

Unlabeled 2-[6-(methylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol, prepared as described herein, was used as analytical reference and standard. Other chemicals and reagents used were obtained from commereial sources and were of analytical grade. [^{11}C]methane was obtained via the $^{14}N(p,\alpha)^{11}C$ reaction on nitrogen with 10% hydrogen, with 18 MeV protons using a GEMS PET trace cyclotron. The [^{11}C]methane was passed through a heated column containing I_2 to produce [^{11}C]methyl iodide (Larsen *et al.* Appl. Radiat. Isot. 1997, 48, 153 and Sandell *et al* J. Labelled Compd Radiopharm. 2000, 43, 331). The generated [^{11}C]MeI was trapped at rt in a vessel containing 5-(6-{[*tert*-butyl(dimethyl)silyl]oxy}-1,3-benzothiazol-2-yl)pyridin-2-amine (2.5mg), DMSO (300μl) and KOH (10mg). The reaction mixture was then heated at 125°C for 5min., followed by removal of the TBDMS-group by treatment with water (200μl) at rt for 2 min. The crude material thus obtained was purified by reversed phase HPLC, using a Waters μ-Bondapak C-18 column (300 x 7.8 mm, 10 mm) equipped with a UV-detector (λ=254nm) and GM tube for radiation detection, employing CH_3CN - aq. HCO_2NH_4 (0.1M) 30:70 v/v as the mobile phase at a flowrate of 6 ml/min. Analysis of the obtained title compound revealed

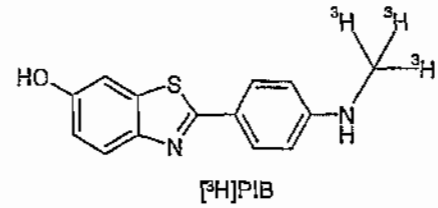
an incorporation yield of [^{11}C]MeI of about 50%, a radiochemical purity of >99%, and a specific radioactivity of 3861 Ci/mmol.

Biological examples

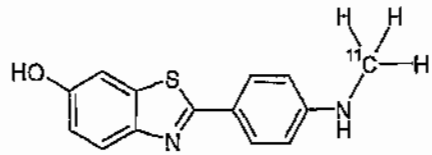
[*N-Methyl*-$^{3}H_3$]-2-(6-Methylamino-pyridin-3-yl)-benzothiazol-6-ol (Example 32) and [*N-methyl*-^{11}C]-2-(6-methylamino-pyridin-3-yl)-benzothiazol-6-ol (^{11}C-Example 1), both compounds of the present invention, are referred to below either by these names or by "[^{3}H]AZAD" and "[^{11}C]AZAD", respectively. The following compounds were used as comparative compounds and are referred to in the text below by their indicated corresponding names.



PIB



[^{3}H]PIB



[^{11}C]PIB

Compounds of the present invention were tested in one or several of the following assays/experiments/studies:

Competition binding assay

Competition binding was performed in 384-well FB filter plates using synthetic Aβ 1-40 in 2.7 nM of [^{3}H]PIB (or another ^{3}H-labeled radioligand when so mentioned) in phosphate buffer at pH 7.5, by adding various concentrations of non-radioactive compounds originally dissolved in DMSO. The binding mixture was incubated for 30 min at room temperature, followed by vacuum filtration, and subsequentially by washing twice with 1 % Triton-X100. Scintillation fluid was thereafter added to the collected Aβ 1-40 on the

filter plate, and the activity of the bound remaining radioligand ([^{3}H]PIB or another ^{3}H-labeled radioligand) was measured using 1450 Microbeta from PerkinElmer.

Dissociation experiments

Dissociation experiments were performed in 96-well polypropylene deep well plates. 2 μM human synthetic Aβ 1-40 fibrils in phosphate buffer pH 7.5, or buffer alone as control, was incubated with 9 nM of a ^{3}H-labeled radioligand of the present invention for 4 h at room temperature. Dissociation was started at different time points, by the addition of an equal volume of a non-labeled compound of the present invention, or a reference compound (10 μM), in 4 % DMSO in phosphate buffer at pH 7.5. The radioactivity still bound to the Aβ 1-40 fibrils at the end of the incubation was detected on FB filters after filtration in a Brandel apparatus using a wash buffer containing 0.1 % Triton-X100.

In vivo rat brain entry studies

Brain exposure after i.v administration was determined in rat brains using cassette dosing. Four different compounds were dosed followed by plasma and brain sampling at 2 and 30 minutes after the dosing. 2 to 30 min brain concentration ratios, and percentage of total of injected dose after 2 mins found in brain, were calculated. The compound concentrations were determined by analysis of protein precipitated plasma samples by reversed-phase liquid chromatography coupled to a electrospray tandem mass spectrometer.

Binding to amyloid plaques in post-mortem human AD brains and trangenic mice brains

Slide-mounted brain sections (10 μm) from APP/PS1 transgenic mice were collected at the level of the lateral septum (bregma + 0.98 mm; see Paxinos and Franklin, 2001). Human cortical sections (7 μm) from two AD patients and 1 control subject were obtained from a Dutch tissue bank.

Sections were preincubated for 30 minutes at room temperature in 50 mM Tris HCl (pH 7.4) in the presence or absence of 1 μM PIB. Sections were transferred to buffer containing tritium-labeled compound (1 nM) with or without PIB (1 μM) and incubated for

30 minutes at room temperature. Incubation was terminated by 3 consecutive 10 minute rinses in buffer (1°C) followed by a rapid rinse in distilled water (1°C). Sections were air dried in front of a fan. Dried sections and plastic tritium standards (Amersham microscales-^{3}H) were apposed to phosphoimage plates (Fuji) in a cassette and exposed overnight. The following morning, the image plates were proeessed with a Fuji phospoimager (BAS 2500) using BAS Reader software. The resulting image was converted to TIF format using Aida software, optimized with Adobe Photoshop (v 8.0) and quantified using Image-J (NIH). Data were statistically analyzed using Excel.

Binding in APP/PS1 mouse brain after compound administration in-vivo

Naïve, awake mice were restrained and intravenously infused via the tail vein with either a tritium labeled compound of the present invention, or a tritium labeled reference compound via the tail vein. In one type of experiment, the animals were rapidly anesthetized with isofluorane and decapitated tweuty minutes after compound administration (1 mCi). In another type of experiment, mice were given 1 mCi of a compound and were anesthetized and decapitated at a timepoint of 20, 40 or 80 minutes after administration. Brains were removed and frozen with powdered dry iee. Brains were sectioned (10 μm) in the coronal plane at the level of the striatum with a cryostat, thaw-mounted onto superfrost microscope slides and air-dried.

Methods designed to optimize the imaging of bound ligand after *in vivo* administration were thereafter employed. To selectivcly reduce unbound radioactivity levels, one-half of the sections were rinsed (3 X 10 minutes) in cold (1°C) Tris buffer (50 mM, pH7.4) followed by a rapid rinse in cold (1°C) deionized watcr. Sections were then air dried in front of a fan. Rinsed as well as unrinsed sections and tritium standards were exposed to phosphoimage plates (Fuji). Phosphoimage plates were processed with a Fujifilm BAS-2500 phosphoimager using BAS Reader software.

PET studies in non-human primates

The monkey PET study aimed to assess and compare a [^{11}C]-labelled compound of this invention to [^{11}C]PIB regarding measures of brain availability, non-specific binding in the

brain, whole body biodistribution, elimination and exploration of regional differenees in uptake. Five brain PET measurements were performed in three monkeys under anesthesia. In eaeh PET-measurement a sterile physiological phosphate buffer (pH = 7.4) solution containing 52-55 MBq of either a [^{11}C]-labelled compound of this invention, or [^{11}C]PIB, was injeeted as a bolus into a sural vein over a period of 5 seeonds with simultaneous start of PET-data acquisition. Radioaetivity in brain was measured continuously for 93 minutes. Only [^{11}C]PIB measurement was performed in the first monkey. In the other two monkeys a [^{11}C]-labelled compound of the present invention was measured first and [^{11}C]PIB was administered in a subsequent measurement. The time between radioligand injections was approx. 2 h. PET measurements were evaluated with respect to the time-activity curve for the whole brain expressed as percent injected radioactivity dose.

Whole body PET-measurement was performed in one monkey. A sterile physiological phosphate buffer (pH = 7.4) solution containing 51 MBq of [^{11}C]PIB in the first measurement, and 57 MBq of a [^{11}C]-labelled compound of the present invention in the second measurement, was injected as a bolus into a sural vein over a period of 5 seeonds with simultaneous start of PET-data acquisition that lasted for 87 min. The time between radioligand injections was 2 h. PET measurements were assessed visually by creating planar maximum intensity projeetion images of deeay uncorrected data and also converting decay corrected images to ones eontaining parts-per-million (ppm) values of the total injected radioactivity.

Biological Example 1

Charaeterization of specific binding of novel heteroaryl substituted benzothiazole derivatives to Aβ amyloid fibrils *in vitro*

Speeific bindning was determined according to the competition binding assay described herein. The determined IC_{50}'s in the competion binding assays (using [^{3}H]PIB as radioligand) of 5 compounds of the present invention are shown in Table 1. Results (activity of remaining [^{3}H]PIB versus increasing concentration of non-labeled compounds) from typical competion assay experiments are exemplified in Figure 1. In a similar way, competition studies with ^{3}H-labeled heteroaryl substituted benzthiazole derivates of the present invention were also conducted. Such results, from a typical competition study, are

examplified in Figure 2. PIB and 2-[6-(methylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol (a novel compound of the present invention) both displaced [*N-methyl*-$^3H_3$]-2-(6-methylamino-pyridin-3-yl)-benzothiazol-6-ol (a ^3H-labeled compound of the present invention). The binding of [*N-methyl*-$^3H_3$]-2-(6-methylamino-pyridin-3-yl)-benzothiazol-6-ol (example 32) to Aβ1-40 fibrils, was reversible as evident from the dissoeiation experiment exemplified in Figure 3.

Table 1. IC_{50}'s obtained of 5 exemplified eompounds of the present invention when run in the competion binding assay.

NAME	EXAMPLE	IC50 (nM)
5-(6-Methoxy-1,3-benzothiazol-2-yl)-N-methylpyridin-2-amine	25	58
2-[6-(Methylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol	27	58
2-(6-Methoxypyridin-3-yl)-1,3-benzothiazole-6-carboxamide	9	170
2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazol-6-ol Acetate	6	176
N-{2-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]-1,3-benzothiazol-6-yl}acetamide	15	186

Biological Example 2

***In vivo* rat brain entry study**

With referenee to figure 4, it can be seen that 2-[6-(methylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol (example 27), a compound of the present invention, enters the rat brain

quickly with an uptake value of 1 % of the injected dose at the 2 min time point, and clears rapidly from rat brain tissue with a 2 minute to 30 minute brain concentration ratio of >15. The results from the correponding experiment, run under the same settings but with PIB instead of 2-[6-(methylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol, is included for comparison (Figure 4).

Biological Example 3

Binding to amyloid plaques in post-mortem human AD brains and trangenic mice

Postmorten brain tissue sections from AD brain and aged APP/PS1transgcnic mice were stained with [*N-methyl*-$^3H_3$]-2-(6-methylamino-pyridin-3-yl)-benzothiazol-6-ol (example 32). The APP/PS1 mouse is a double transgenic model combining two human gene mutations known to cause AD. In APP/PS1 mouse brain sections and in human cortical sections, [*N-methyl*-$^3H_3$]-2-(6-methylamino-pyridin-3-yl)-benzothiazol-6-ol and [^{3}H]PIB labeled dense corc plaques. In both tissues, binding was attenuated by 1 μM PIB. In superficial gray matter regions of human cortieal sections, dense core plaque labeling in gray matter was visible against a background of diffuse labeling. The diffuse labcling was confined to gray matter regions whereas densc core plaque labeling could be seen outside of the superficial gray regions.

[*N-Methyl*-$^3H_3$]-2-(6-mcthylamino-pyridin-3-yl)-benzothiazol-6-ol and [^{3}H]PIB labeling were quantified in gray and white matter regions of human cortical sections. Specific binding was determined by subtracting binding in tissues co-cxposed to 1 μM PIB. Analysis of these data showed that spccific [*N-methyl*-$^3H_3$]-2-(6-methylamino-pyridin-3-yl)-benzothiazol-6-ol binding levels in superficial gray layers of human eortex was approximately 40% greater than binding observed with [^{3}H]PIB ($p = 0.0033$, $t = 4.13$; Student's t-tcst). This difference was attributed to the substantially reduced levels of nonspecific binding obscrved in [*N-methyl*-$^3H_3$]-2-(6-methylamino-pyridin-3-yl)-benzothiazol-6-ol labelcd tissues compared to those exposed to [^{3}H]PIB. Further analysis of labeling in superficial cortical laycrs of tissue treatcd with or without PIB revcaled large differenccs between [*N-methyl*-$^3H_3$]-2-(6-methylamino-pyridin-3-yl)-benzothiazol-6-ol and

[^{3}H]PIB in the ratio of total binding compared to nonspecific binding ([*N-methyl*-$^3H_3$]-2-(6-methylamino-pyridin-3-yl)-benzothiazol-6-ol; 10.78:1 vs PIB; 2.48:1). A represenative example of [*N-methyl*-$^3H_3$]-2-(6-methylamino-pyridin-3-yl)-benzothiazol-6-ol (right hand pictures) and [^{3}H]PIB (left hand pictures) binding of amyloid plaques in human AD brain (upper pictures), and of APP/PS1 transgenic mice brain (lower pictures), is shown in Figure 5.

Biological Example 4

Binding of [^{3}H]AZAD in APP/PS1 Mouse Brain after Compound Administration *In Vivo*

The *in vivo* binding properties of [^{3}H]AZAD, a compound of the present invention (example 32), was explored in this example with special relevance to PET imaging methods in a transgenie mouse model (APP/PS1) engineered to overproduce human amyloid-β.

In one experiment the *in vivo* properties of [^{3}H]AZAD were directly compared with those of [^{3}H]PIB: After administration, followed by decapitation 20 minutes thereafter, both [^{3}H]AZAD and [^{3}H]PIB labeled cortical structures (Figure 6), which based on their size and distribution resemble the appearance of amyloid plaques labeled immunohistochemically with amyloid-β antibodies (Klunk *et al.* J. Neurosci. 2005, 25, 10598). Background binding levels (quantified in Figure 7), especially in white matter tracts such as the corpus callosum and anterior commissure, but also in regions composed primarily of gray matter such as the striatum were more heavily labeled with [^{3}H]PIB than with [^{3}H]AZAD in rinsed as well as in unrinsed tissue. In brain areas rich in gray matter such as the striatum, nonspecific binding was generally lower than in white matter regions for both compounds, and in unrinsed tissue, did not differ significantly between the compounds. However, while nonspecific binding was not significantly reduced in rinsed tissues from mice given [^{3}H]PIB in brain areas rich in gray matter (striatum), the *in vitro* rinse procedure did reduce nonspecific [^{3}H]AZAD binding by 78.5% (Ligand x Rinse interaction: $p<0.0001$; df=1,6; F=72.72). In white matter regions, exemplified by the corpus callosum, nonspecific [^{3}H]PIB binding was higher than that of [^{3}H]AZAD

regardless of rinse condition. Furthermore, while the *in vitro* rinse was only marginally effective in corpus callosum from mice given [^{3}H]PIB, it dramatically reduced [^{3}H]AZAD levels in corpus callosum (ligand x rinse interaction: $p<0.0001$; df=1,6; F=107.8). The ratio of the cortical plaque labeling divided by the area of cortex measured for both [^{3}H]PIB and [^{3}H]AZAD on rinsed brain sections are shown in Figure 8.

A second experiment focused on the timecourse of the uptake and clearance of [^{3}H]AZAD at timepoints relevant to [^{11}C]-PET imaging. Autoradiograms illustrating [^{3}H]AZAD binding in APP/PS1 transgenic mouse brain sections 20, 40 and 80 minutes after administration are shown in figure 9. One-way ANOVA of cortical plaque labeling in rinsed tissue at different exposure intervals (figure 10) showed that [^{3}H]AZAD binding was highest at 20 minutes and declined such that levels were barely detectable after 80 minutes ($p=0.0424$; df=2,5; F=10.84). In addition to [^{3}H]AZAD cortical plaque labeling, total radioactivity levels in plaque free regions were compared to provide a measure of nonspecific labeling (figure 11). Two-way ANOVA of total radioactivity levels at different exposure intervals showed that levels decreased significantly as the duration of exposure increased (main effect of exposure duration, $p=0.0063$; df=2,6; F=13.26)

Biological Example 5

PET studies in monkey

The time course of total brain radioactivity reflects the availability of the ligand in the target organ. For reference radioligands, e.g. [^{11}C]raclopride, the fraction of the total injected radioactivity present in the brain during the first 5-10 min is usually above 1-2%. [^{11}C]AZAD rapidly entered brain and the exposure was about 1-3% of total injected radioactivity (Figure 12). Brain uptake of [^{11}C]AZAD peaked in the first minute after injection surpassing that of [^{11}C]PIB at this early time point. Brain concentration of [^{11}C]AZAD thereafter declined rapidly with lower concentrations as compared to [^{11}C]PIB at all time points. Because of lack of specific binding sites, i.e. amyloid plaques, in the studied monkeys in this example, no comparison could be made between [^{11}C]AZAD and [^{11}C]PIB with regard to their *in vivo* binding characteristics to such plaques. The brain uptake in this experiment is, however, illustrative of and reflects unspecific binding (Figure

13). Taken together, these findings support that [^{11}C]AZAD enters brain tissue in primates and has significantly lower unspeeific binding as compared to [^{11}C]PIB at time points of relevance for PET-detection of amyloid plaques. Whole body PET measurements were performed to investigate and compare the peripheral distribution and elimination routes of [^{11}C]AZAD and [^{11}C]PIB. As can be seen in Figure 14 and 15, the two ligands have similar elimination routes consisting of urinary excretion and hepatobiliary secretion. 1 hour post administration, most of the radioactivity was localized in the bladder and gastroenteral tract. Accumulation in other organs, e.g. lungs or bone marrow, was very low. [^{11}C]AZAD had faster elimination and lower non-eliminatory (e.g. lung) disposition as compared to [^{11}C]PIB. These results indicate a favourable radiation safety of [^{11}C]AZAD.

Brief description of the figures

Figure 1. Activity ("% Activity") of remaining [^{3}H]PIB versus increasing concentration of non-labeled compounds ("log compound") of the present invention (square: 2-[6-(methylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol [ex. 27]; triangle: 5-(6-methoxy-1,3-benzothiazol-2-yl)-N-methylpyridin-2-amine [example 25]) in the competition binding assay.

Figure 2. Activity ("% Aetivity") of remaining [*N-methyl*-$^{3}H_3$]-2-(6-methylamino-pyridin-3-yl)-benzothiazol-6-ol (example 32) versus increasing concentration ("log compound") of a non-labeled compound of the present invention (triangle: 2-[6-(methylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol [example 27]), and PIB (squares) in the competition binding assay.

Figure 3. Example of a dissociation experiment: Dissociation of [*N-methyl*-$^{3}H_3$]-2-(6-methylamino-pyridin-3-yl)-benzothiazol-6-ol (example 32) from Aβ1-40 fibrils over time.

Figure 4. Brain and plasma concentration at 2 and 30 minutes after i.v. administration in rat of PIB (upper graph "A"), and 2-[6-(methylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol (lower graph "B"), a compound of the present intervention (example 27).

Figure 5. Example of amyloid binding post mortem in human brain tissue section (upper) and APP/PS1 mice brain slice (lower), using [^{3}H]PIB (left) and [*N-methyl*-$^3H_3$]-2-(6-methylamino-pyridin-3-yl)-benzothiazol-6-ol (right), a novel compound of the present intervention, for staining. The inserted panels shows the binding in the presence of 1 μM PIB.

Figure 6. Autoradiograms illustrating labeling after *in vivo* administration of [^{3}H]PIB (left pictures) and [^{3}H]AZAD (right pictures) in brain sections from APP/PS1 mice. The brain sections were either unrinced (upper pictures) or rinced (lower pictures).

Figure 7. Quantitative comparison of nonspecific binding between [^{3}H]PIB and [^{3}H]AZAD, A; white matter regions (Corpus Callosum), and B; in gray matter regions (Striatum).

Figure 8. Cortical plaque-load analysis. Data are expressed as a ratio of the cortical [^{3}H]AZAD plaque labeling divided by the area of cortex measured.

Figure 9. Autoradiograms illustrating binding in rinsed and unrinsed sections at different exposure intervals after [^{3}H]AZAD administration *in vivo*.

Figure 10. Quantitative comparison of cortical plaque labeling with [^{3}H]AZAD after different exposure intervals in sections rinsed *in vitro*.

Figure 11. Analysis of total radioactivity levels in rinsed and unrinsed sections collected from animals exposed *in vivo* to [^{3}H]AZAD for 20, 40 or 80 minutes.

Figure 12. Time course of brain uptake in monkey brain after administration of [^{11}C]AZAD and [^{11}C]PIB (MX means monkeyX, where X is an integer each individual monkey has been assigned).

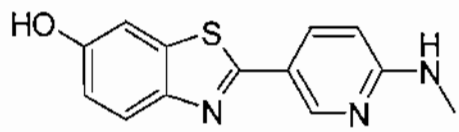
Figure 13. Colour-coded PET images (summation images, 9-93 minutes) showing distribution of radioactivity in monkey brain after administration of [^{11}C]AZAD and [^{11}C]PIB.

Figure 14. Colour coded PET images showing radioactivity exposure in monkey whole body (coronal maximum intensity projections, decay uncorrected data) after injection of a: [^{11}C]PIB, b: [^{11}C]AZAD.

Figure 15. Biodistribution of [^{11}C]PIB and [^{11}C]AZAD in monkey whole body (three-dimensional, left-oblique anterior view of parts-per-million injected dose images, decay corrected data). "ppm ID/voxel" denotes parts per million of injected (radioactivity) dose per voxel (decay corrected data).

Claims

1. A compound 2-[6-(Methylamino)pyridin-3-yl]-1,3-benzothiazol-6-ol



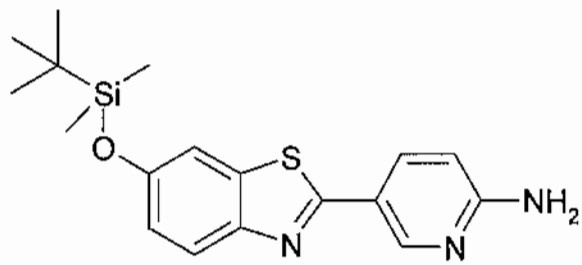
wherein one or more of the atoms is optionally a detectable isotope;
as a free base or a pharmaceutically aeeeptable salt, solvate or solvate of a salt thereof.

2. A compound according to claim 1, wherein one to three of the atoms represent a detectable isotope selected from ^{3}H, ^{19}F and ^{13}C, or wherein one of the atoms is a detectable isotope selected from ^{18}F, ^{11}C and ^{14}C.

3. A compound according to claim 1, wherein one or more of the atoms is a radiolabeled atom selected from ^{3}H, ^{18}F, ^{19}F, ^{11}C, ^{13}C, ^{14}C, ^{75}Br, ^{76}Br, ^{120}I, ^{123}I, ^{125}I and ^{131}I.

4. A compound according to claim 3, wherein said radiolabeled atom is selected from ^{18}F and ^{11}C.

5. A compound 5-(6-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,3-benzothiazol-2-yl)pyridin-2-amine



6. Use of the compound according to claim 5 as synthetic precursor in a process of preparation of a labeled eompound according to any one of claims 1 to 4, wherein one of the atoms is a detectable isotope selected from ^{11}C.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4, together with a pharmaceutically acceptable carrier.

8. A pharmaceutical composition for *in vivo* imaging of amyloid deposits, comprising a radio-labeled compound according to any one of claims 1 to 4, together with a pharmaceutically acceptable carrier.

9. A compound as defined in any one of claims 1 to 4 for use in therapy.