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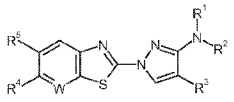
(54) Title: COMPOUNDS FOR BINDING AND IMAGING AMYLOID PLAQUES AND THEIR USE

Fig.1



Nr.	R1	R2	R3	R4	R5	W	X	Y	Z
1	H	H	H	X	H	CH	Br		
2	H	H	H	X	H	CH	F		
3	H	H	H	X	H	CH	I		
4	H	H	H	X	Z	CH	F		CN
5	H	H	H	X	Z	CH	F		CF_3
6	H	H	H	Y	Z	CH		NO_2	CN
9	H	H	H	X	Z	CH	F		C(O)H
11	H	H	H	OH	H	CH			
12	H	H	$C(O)OCH_2CH_3$	OH	H	CH			
13	H	H	H	OCH_2CH_2X	H	CH	F		
14	H	H	$C(O)OCH_2CH_3$	OCH_2CH_2X	H	CH	F		
15	H	H	H	OCH_2X	H	CH	F		
16	H	H	H	$OCH_2CH_2CH_2X$	H	CH	F		

(57) Abstract: The present invention relates to novel compounds (benzothiazolopyrazoles and thiazolopyridin-pyrazoles) useful for binding and imaging amyloid deposits and their use in detecting or treating Alzheimer's disease and amyloidosis.

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Compounds for binding and imaging amyioid plaques and their use

The present invention relates to novel compounds (benzothiazoiopyrazoles and thiazolopyridin-pyrazoles) useful for binding and imaging amyloid deposits and their use in detecting or treating Alzheimer's disease and amyloidoses.

Background of the invention

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by loss of memory, cognition, and behavioral stability. AD is defined pathologically by extracellular senile plaques comprised of fibrillar deposits of the beta-amyloid peptide (Aβ) and neurofibrillary tangles comprised of paired helical filaments of hyperphosphorylated tau. The 39 to 43 amino acids comprising Aβ peptides are derived from the larger amyloid precursor protein (APP). in the amy!oidogenic pathway, Aβ peptides are cleaved from APP by the sequential proteolysis by β- and γ-secretases. Aβ peptides are released as soluble proteins and can be detected at low levels in the cerebrospinal fluid (CSF) in normal aging brains. During the progress of AD the Aβ peptides aggregate and form amyioid deposits in the parenchyma and vasculature of the brain, which can be detected post mortem as diffuse and senile plaques and vascular amyioid during histological examination (for a recent review see: Blennow et al. Lancet. 2006 Jul 29;368(9533):387-403).

Alzheimer's disease is becoming a great health and social economical problem all over the world. There are great efforts being made to develop techniques and methods for the early detection and effective treatment of the disease. Currently, diagnosis of AD in an academic setting of memory-disorder clinics is approximately 85-90% accurate (Petreila JR et al. Radiology. 2003 226:315-36). It is based on the exclusion of a variety of diseases causing similar symptoms and the careful neurological and psychiatric examination, as well as neuropsychological testing. However, post mortem histological examination of the brain is still the only definite diagnosis of this disease. Thus the in vivo detection of one pathological feature of the disease - the deposition of amyloid aggregates in the brain -- is thought to have a big impact on the early detection of AD and differentiation from other dementias. Additionally, most disease modifying therapies that are under development are aiming at lowering the amyioid load in the brain. Thus imaging the amyioid load in the brain may provide an essential tool for patient stratification and treatment monitoring.

in addition, amyloid deposits are also known to play a role in amyloidosis, in which amyloid proteins are abnormally deposited in different organs and/or tissues, causing disease. For a recent review see Chiti et al. Annu Rev Biochem. 2006;75:333-66.

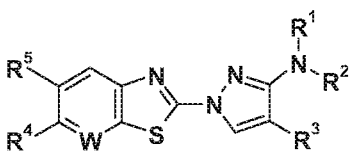
Potential iigands for visualizing amyloid aggregates in the brain must show a high binding affinity to amyloid and must cross the blood brain barrier. PET tracers that have been already investigated in humans regarding their binding patterns in brains of AD patients are [F-18]FDDNP (Shoghi-Jadid et al., Am J Geriatr Psychiatry 2002; 10:24-35), [C-1 1]PIB (Kiunk et al., Ann Neurol. 2004 55:306-319), [C-1 1]SB-13 (Verhoeff et al., Am J Geriatr Psychiatry 2004; 12:584-595, [F-18]Bay 94-9172 (Rowe et al. Lancet Neurol 2008, 7:129-135), [C-1 1]BF227 (Kudo et al., J Nucl. Med 2007; 49:554-561), and [F-18JPIB (Farrar et al. Turku PET Symposium 2007, Abstract 49). For recent reviews see Lockhardt, Drug Discov Today, 2006 11:1093-1099, Henriksen ef al., Eur J Nucl Med Mol imaging. 2008 Mar;35 Suppi 1:S75-81 , Cohen, Mol. Imaging Biol. 2007 9:204-216, Nordberg, Curr. Opin Biol. 2007, 20:398-402, Small et al., Neurology 2008 7:161-172, Nordberg, Eur. J. Nucl. Med. Mol. imaging 2008, 35, S46-S50.

Besides their specific binding to amyloid deposits in the brain, the currently most promising PET tracers show a disadvantageous non-specific accumulation, especially in white matter brain regions in AD patients as well as in HC. Generally, non-specific background binding interferes with the image quality and could e.g. impair the quantification of amyloid and the diagnosis of very early stages of the disease. The present invention provides novel tracers with high affinity for amyloid β and rapid elimination of the unspecificaliy bound tracer from the brain.

Description of the invention

The present invention is directed to compounds that bind to amyloid deposits and are able to pass through the blood-brain barrier, and are therefore useful in diagnosing Alzheimer's disease and amyloidosis in a patient, preferably at an early stage of the disease.

Accordingly, in one aspect, the invention is directed to compounds according to formula I



I

and to pharmaceutically acceptable salts and prodrugs thereof, and to all isomeric forms of said compound, including enantiomers and diasteromers as well as racemic mixtures, and any pharmaceutically acceptable salt, ester, amide, complex or prodrug thereof,

wherein

- R^1 is selected from the group consisting of H, C(0)CH_3, C(0)$(CH_2)_nCH_2X$, C(0)CF_3, C(0)$OC(CH_3)_3$, C(G)C_6H_4X, C(0)C_6H_3YZ, C(0)C_6H_3XZ, C(0)heteroraryl, substituted C(0)heteroraryl, C(0)OCH_3, C(0)OCH_2CH_3, C(0)$OCH_2C_6H_5$, C(0)$OCH_2CH{=}CH_2$, Fmoc, C(0)$OCH_2CH_2Si(CH_3)_3$, C(0)OCH_2CCl_3;

- R^2 is selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, $(CH_2)_mCH_2X$, R^1;

- R^3 is selected from the group consisting of H, C(0)OH, C(0)0$(CH_2)_nCH_3$, C(0)0$(CH_2)_mCH_2X$, C(0)NH_2, C(G)NH$(CH_2)_nCH_3$, C(0)NH$(CH_2)_mCH_2X$;

- R^4 and R^5 are independently selected from the group consisting of H, CH_3, $(CH_2)nCH_3$, $(CH_2)_nCH_2X$, OH, OCH_3, 0$(CH_2)_nCH_3$, 0$(CH_2)_nCH_2X$, O-cyclobutyl-X. O-cyclopentyl-X, G-cyclohexyl-X, 0$(CH_2CH_20)_nCH_2CH_2X$, SH, SCH_3, S$(CH_2)_nCH_3$, S$(CH_2)_nCH_2X$, NH_2, $NHCH_3$, $N(CH_3)_2$, NH$(CH_2)_nCH_3$, NH$(CH_2)_mCH_2X$, $NCH_3(CH_2)_mCH_2X$, X, Y, Z;

- W is selected from CH or N

- X is selected from the group consisting of ^{18}F, F, Cl, Br, i, ^{125}I, ^{123}i, OS0$_2CH_3$, OS0$_2CF_3$, OS0$_2C_4F_9$, OS0$_2C_6H_5$, OS0$_2C_6H_4CH_3$, OS0$_2C_6H_4N0_2$, OS0$_2C_6H_4Br$, OS0$_2C_6H_2(CH(CH_3)_2)_3$, OS0$_2C_6H_3(OCH_3)_2$;

- Y is selected from the group consisting of N0$_2$, N^+Me_3, I*aryi, S^+aryl_2;

- Z is selected from the group consisting of H, CF_3, CN, C(0)H, C(0)CH_3, C(0)0$(CH_2)_nCH_3$;
- m has the meaning of 1-4;
and n is 0-4;

including ail isomeric forms of said compound, including enantiomers and diasteromers as well as racemic mixtures,

and any pharmaceuticaiiy acceptable salt, ester, amide, complex or prodrug thereof.

In a preferred embodiment,

- R^1 is selected from the group consisting of H, C(Q)CH_3, C(Q)$(CH_2)_nCH_2X$, C(0)CF_3, C(0)OC$(CH_3)_3$, C(G)C_6H_4X, C(0)C_6H_3YZ, C(0)C_6H_3XZ, C(0)C_6H_4Y, C(0)heteroraryl, substituted C(0)heteroraryl , C(0)OCH$_2C_6H_5$, C(0)OCH$_2$CH=CH$_2$, Fmoc;

- R^2 is selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, $(CH_2)_mCH_2X$, R^1;

- R^3 is selected from the group consisting of H, C(0)OH, C(0)0$(CH_2)_nCH_3$, C(0)0$(CH_2)_mCH_2X$, C(0)NH_2, C(0)NH$(CH_2)_nCH_3$, C(0)NH$(CH_2)_mCH_2X$;

- R^4 and R^5 are independently selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, $(CH_2)_nCH_2X$, OH, OCH_3, 0$(CH_2)_nCH_3$, 0$(CH_2)_nCH_2X$, O-cycoibutyl-X. O-cyclopentyi-X, 0$(CH_2CH_2Q)_nCH_2CH_2X$, NH_2, $NHCH_3$, $N(CH_3)_2$, $NH(CH_2)_nCH_3$, $NH(CH_2)_mCH_2X$, $NCH_3(CH_2)_mCH_2X$, X, Y, Z;

- W is selected from CH or N

- X is selected from the group consisting of ^{18}F, F, Cl, Br, I, ^{125}I, ^{123}I, OS0$_2CH_3$, OS0$_2CF_3$, OS0$_2C_4F_9$, OS0$_2C_6H_5$, OS0$_2C_6H_4CH_3$, OS0$_2C_6H_4N0_2$, OS0$_2C_6H_4$Br, OS0$_2C_6H_2(CH(CH_3)_2)_3$, OS0$_2C_6H_3(OCH_3)_2$;

- Y is selected from the group consisting of N0$_2$, N^+Me_3, I^+aryl, S^+aryl$_2$;

- Z is selected from the group consisting of H, CF_3, CN, C(0)H, C(0)CH_3;
- m has the meaning of 1-3;
and n is 0-3;

Furthermore, pharmaceutically acceptable salts and prodrugs thereof, and all isomeric forms of said compound, including enantiomers and diasteromers as well as racemic mixtures, and any pharmaceutically acceptable salt, ester, amide, complex or prodrug thereof are included.

in an even more preferred embodiment,

- R^1 is selected from the group consisting of H, C(0)CH_3, C(0)$(CH_2)_nCH_2X$, C(0)CF_3, C(0)$OC(CH_3)_3$, C(0)C_6H_4X, C(0)C_6H_3YZ, C(0)C_6H_3XZ, C(0)OCH_3, C(0)OCH_2CH_3, C(0)$OCH_2C_6H_5$, FmoC;

- R^2 is selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, R^1;

- R^3 is selected from the group consisting of H, C(0)OH, C(0)$G(CH_2)_nCH_3$, C(0)$0(CH_2)_mCH_2X$;

- R^4 and R^5 are independently selected from the group consisting of H, $(CH_2)_nCH_2X$, OH, OCH_3, $0(CH_2)_nCH_2X$, O-cyclobutyl-X, $0(CH_2CH_20)_nCH_2CH_2X$, X, Y, Z;

- W is selected from CH or N

- X is selected from the group consisting of ^{18}F, F, Cl, Br, I, $OS0_2CH_3$, $OS0_2CF_3$, $OS0_2C_4F_9$, $OS0_2C_6H_5$, $OS0_2C_6H_4CH_3$, $OS0_2C_6H_4N0_2$, $OS0_2C_6H_4Br$, $OS0_2C_6H_2(CH(CH_3)_2)_3$, $OS0_2C_6H_3(OCH_3)_2$;

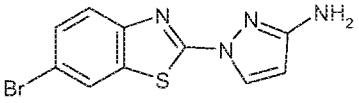
- Y is selected from the group consisting of $N0_2$, N^+Me_3, I*aryi, S^+aryl_2;

- Z is selected from the group consisting of H, CF_3, CN, C(0)H;
- m has the meaning of 1-2;
and n is 0-2;

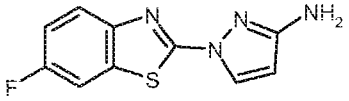
Furthermore, pharmaceuticaliy acceptable salts and prodrugs thereof, and all isomeric forms of said compound, including enantiomers and diasteromers as well as racemic mixtures, and any pharmaceutically acceptable salt, ester, amide, complex or prodrug thereof are included.

In an even more preferred embodiment, the compound is selected from the group of compounds consisting of

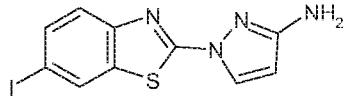
1-(6-Bromobenzothiazoi-2-yl)-1H-pyrazoi-3-ylamine 1



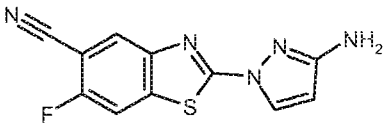
1-(6-FlLioroberszothiazol-2-yi)-1H-pyrazol-3-ylamine 2



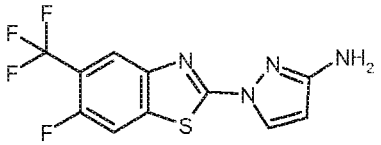
1-(6-lodobenzothiazol-2-yl)-1H-pyrazol-3-ylamine 3



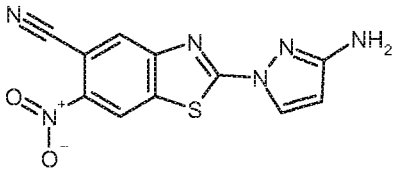
2-(3-Aminopyrazol-1-yl)-6-fluorobenzothiazoie-5-carbonitrile **4**



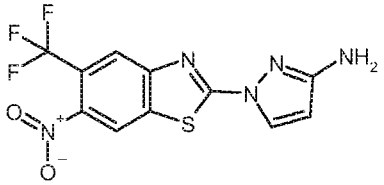
1-(6-Fluoro-5-irifiuoromethylbenzothiazol-2-yl)-1H-pyrazoi-3-ylamine 5



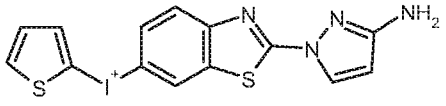
2-(3-Aminopyrazol-1-yl)-6-nitrobenzothiazoie-5-carbonitriie 6



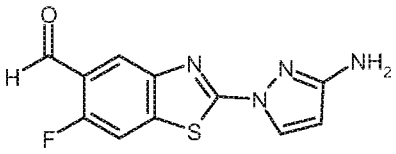
1-(6-Nitro-5-trifiuoromethylbenzothiazoi-2-yl)-1H-pyrazoi-3-yiamine *7*



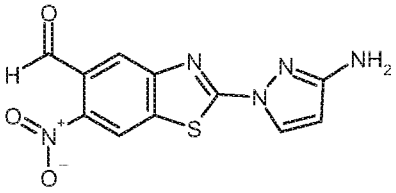
[2-(3-Arriinopyrazo!-1-yi)benzothiazoi-6-y!]ihier!-2-yi-iodoniLim 8



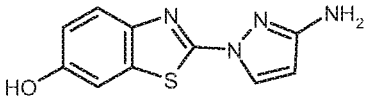
2-(3-Aminopyrazol-1-yl)-6-fluorobenzothiazole-5-carbaldehyde **9**



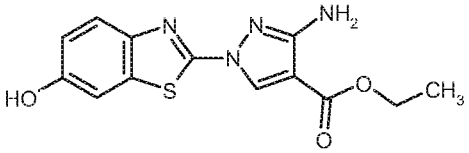
2-(3-Aminopyrazol-1-yl)-6-nitrobenzothiazole-5-carbaldehyde **10**



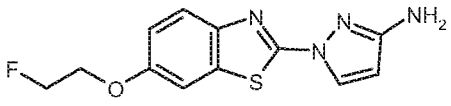
2-(3-Aminopyrazoi-1-yl)-benzothiazol-6-ol 11



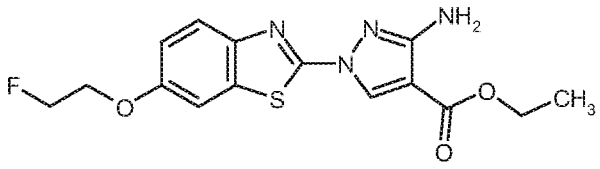
3-Amino-1-(6-hydroxy-benzothiazol-2-yl)-1H-pyrazo!e-4-carboxylic acid ethyl ester 12



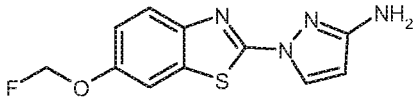
1-[6-(2-Fluoro-ethoxy)-ber5zothiazol-2-yi]-1H-pyrazol-3-y!amine 13



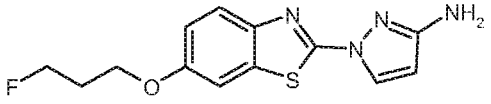
3-Arnino~1-[6-(2-fiuoro-ethoxy)-benzothiazoi-2~yl]-1 H-pyrazo!e-4-carboxy!ic acid ethyl ester 14



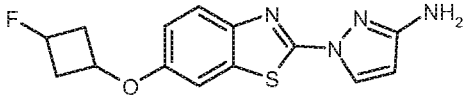
1-(6-Fluoromethoxy-berizothiazol-2-yi)-1H-pyrazol-3-ylamine 15



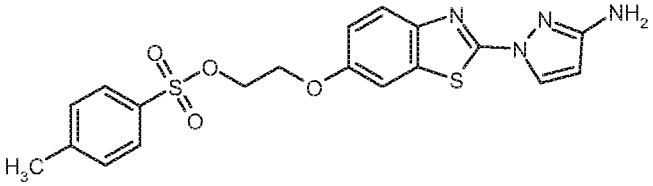
1-[6-(3-Fluoro-propoxy)~benzoihiazo!~2-ylj~1H-pyrazo!-3-ylamine 16



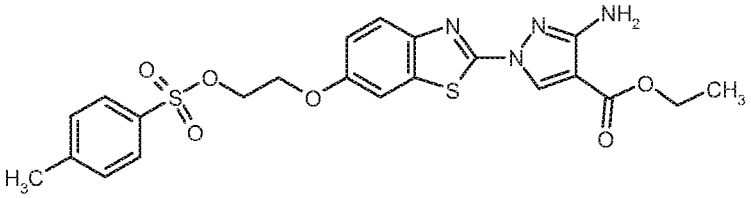
1-[6-(3-Fluoro-cyciobutoxy)-benzothiazo!-2-yl]-1H-pyrazol-3-yiamine 17



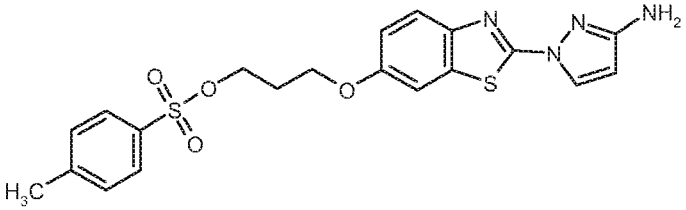
Toluene-4-sulfonic acid 2-[2-(3-aminopyrazol-1-yl)-benzotbiazol-8-yloxy]-ethyl ester 18



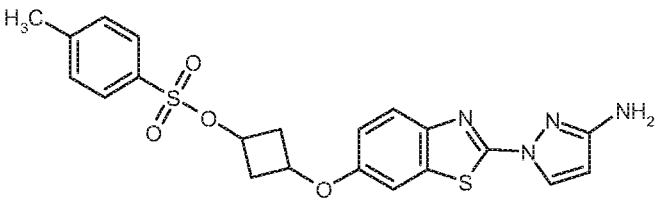
3-Arriino-1-{6-[2-(toluene-4-sLi!fony!oxy)ethoxyJ-benzothiazol-2-yi}~1H-pyrazole-4-carboxylic acid ethyl ester **19**



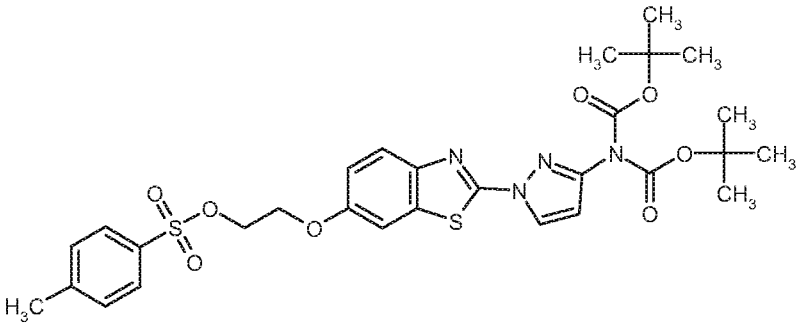
Toluene-4-sulfonic acid 3-[2-(3-amino-pyrazol-1-yl)-benzothiazol-6-yioxy]propyl ester 20



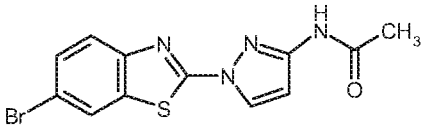
Toiuene-4-su!fonic acid 3-[2-(3-aminopyrazol-1-y!)benzoth!azo!-6-yloxy]cyc!obuty! ester 21



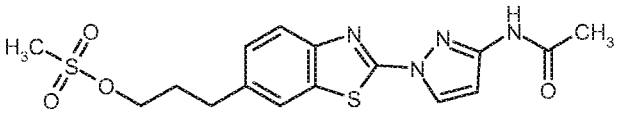
Toluene-4-sulfonic acid 2-[2-(3-di-tert-butoxycarbonylamino-pyrazol-1-yl)benzothiazol-6-yloxy]-ethyl ester **22**



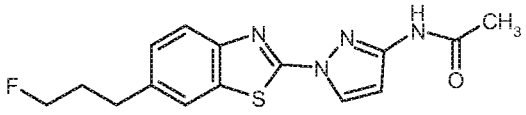
N-[1-(6-Bromobenzoihiazol-2-yl)-1H-pyrazol-3-yl3acetamide 23



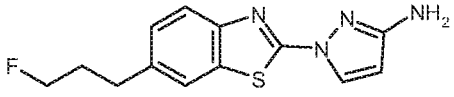
Methane-sulfonic acid 3-[2-(3-aminopyrazol-1-yl)-benzothiazoi-6-yl]propyl ester 24



N-{1-[6-(3-Fluoropropyl)benzothiazol-2-yl]-1H-pyrazol-3-yl}acetamide 25

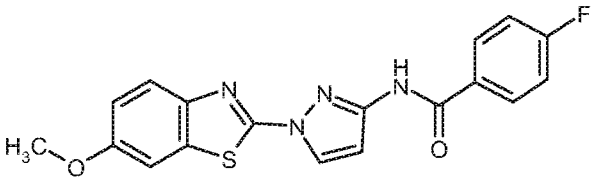


1-[6-(3-Fluoro-propy!)-benzothiazol-2-y!]-1H-pyrazol-3-yiamine 26

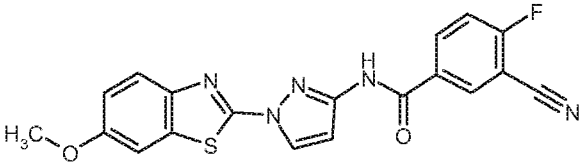


4~F!iJoro~N-[1~(6-rnethoxybenzothiazo!-2-yi)~1H-pyrazo!~3-yljbenzamide 27

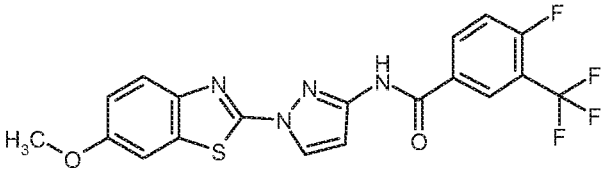
10



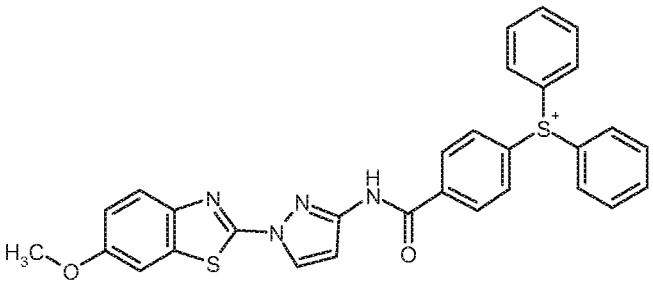
3-Cyano-4-fluoro-N-[1-(6-methoxy-benzothiazol-2-yl)-1H-pyrazol-3-yl]-benzamide 28



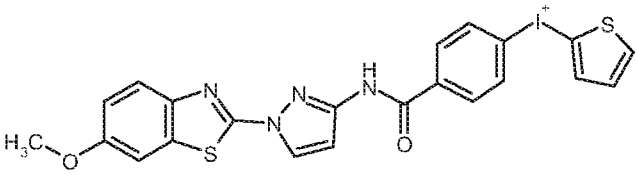
4-Fluoro-N-[1-(6-rnethoxy-benzothiazol-2-yl)-1H-pyrazoi-3-yl]-3-irif!uoromeihyl-benzamide **29**



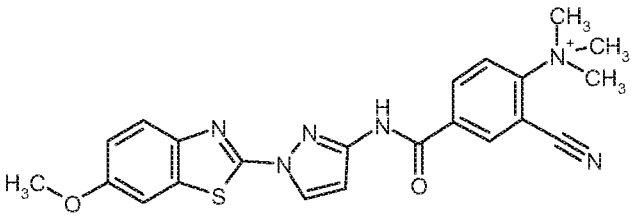
{4-[1-(6-Meihoxy-benzothiazol-2-yl)-1H-pyrazol-3-yicarbarrioyl]-phenyi}-diphenyl-sulfonium **30**



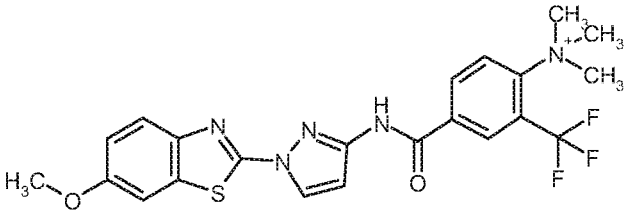
{4-[1-(6-Methoxybenzothiazol-2-yl)-1H-pyrazol-3-ylcarbamoyl]phenyl}thien-2-yl-iodonium 31



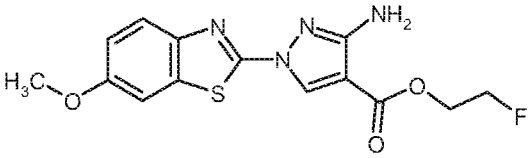
{2-Cyano-4-[1-(6-methoxybenzoth iazol-2-yl)-1H-pyrazol-3-ylcarbamoyl]phenyl}trimethyl-ammonium 32



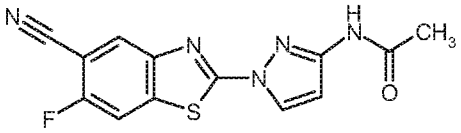
{4-[1-(6-Methoxy-benzothiazol-2-yl)-1H-pyrazol-3-yicarbamoyl3-2-triflLioromethy! -phenyl}trimethyl-ammonium **33**



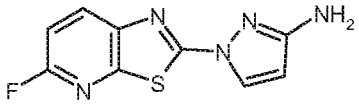
3-Arnino-1-(6-mei:hoxy-benzoihjazol-2-yl)-1 H-pyrazo!e-4-earboxylie acid 2-f!uoro-ethyl ester **34**



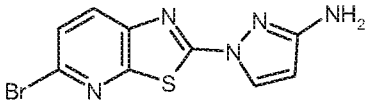
N-[1-(5-Cyano-6-fluorobenzothiazol-2-yl)-1H-pyrazoi-3-yl]-aceiamide 35



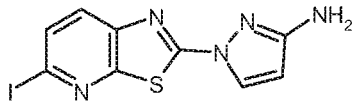
1~(6-F!uorothiazo!o[5,4~b]pyridin-2~yl)-1H-pyrazoi-3-amine 36



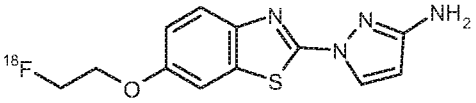
1-(6-Bromothiazolo[5,4-b]pyridin-2-yi)-1H-pyrazol-3-amine 37



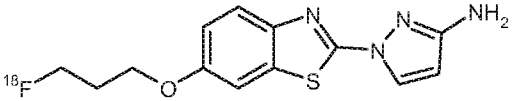
1-(6-lodothiazoio[5,4-b]pyridin-2-y!)-1 H-pyrazol-3-amine 38



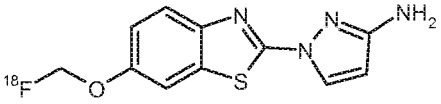
1-[6-(2-[^{18}F]Fluoroeihoxy)berizoihiazol-2-yi]-1H-pyrazol-3-y!amine [18FJ-39



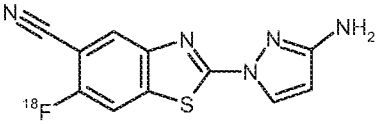
1-[6-(3-[^{18}F]F!uoropropoxy)benzothiazol-2-yij-1H-pyrazoi--3-ylamine [18F]-40



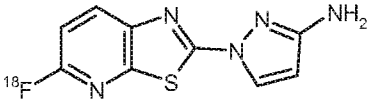
1-[6-([^{18}F]Fluoromeihoxy)benzothiazol-2-yl]-1H-pyrazo!-3-yiarnine [1SF]-41



2-(3-Aminopyrazol-1-yl)-6-[^{18}F]fluorobenzoihiazole-5-carboriiirile [18F]-42



1-(6-[^{18}F]Fluoro[1,3]thiazolo[5,4-b]pyridin-2-yi)-1H-pyrazol-3-amine [18FJ-43



If the compound is an ion, the invention also relates to the compound in combination with a suitable counterion.

For diagnostic purposes, both *in vitro* and *in vivo,* those compound of formula I are preferred that comprise or contain a detectable label, such as a radioactive nuclide. For in vitro use, histological sections such as fresh frozen samples or paraffin samples can be analyzed.

"Alkyl" refers to a straight or branched chain group consisting solely of carbon and hydrogen, containing no unsaturation and having from one to eight carbon atoms, e.g.,

methyl, ethyl, n-propyl, 1-methylethyl (iso-propyl), n-butyi, n-pentyl, 1,1-dimethyiethyi (t-butyi), n-heptyl, and the like. "Alkoxy" refers to a group of the formula -Oalkyl where alky! is as defined above.

in the context of the present invention, preferred salts are pharmaceutically acceptable salts of the compounds according to the invention. The invention also comprises saits which for their part are not suitable for pharmaceutical applications, but which can be used, for example, for isolating or purifying the compounds according to the invention.

Pharmaceutically acceptable saits of the compounds according to the invention include acid addition salts of mineral acids, carboxylic acids and sulphonic acids, for example salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesuiphonic acid, naphthalene disulphonic acid, acetic acid, trifluoroacetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maieic acid and benzoic acid.

Pharmaceutically acceptable salts of the compounds according to the invention also include salts of customary bases, such as, by way of example and by way of preference, alkali metal salts (for example sodium saits and potassium salts), alkaline earth metal salts (for example calcium saits and magnesium saits) and ammonium salts, derived from ammonia or organic amines having 1 to 18 carbon atoms, such as, by way of example and by way of preference, ethyiam ine, diethylamine, triethylamine, ethyldiisopropyiamine, rnonoethano!amine, diethanolamine, triethanolamine, dicyclo-hexyiamine, dimethyiaminoethanoi, procaine, dibenzyiamine, N-methyimorphoiine, arginine, lysine, ethylenediamine and N-methylpiperidine.

Moreover, the present invention also comprises prodrugs of the compounds according to the invention. The term "prodrugs" includes compounds which for their part may be biologically active or inactive but which, during the time they spend in the body, are converted into compounds according to the invention (for example metaboiically or hydrolyticaliy).

In particular, the present invention also comprises hydroiyzabie ester derivatives of the carboxylic acids of the formula (i). These are to be understood as being esters which can be hydrolvzed in physiological media and in particular *in vivo* by enzymaticai or chemical means to give the free carboxylic acids. Such esters are preferably straight-chain or branched (CrC_6)-alkyl esters in which the a!kyl group may be substituted by hydroxy!, (C_1-C_4)-alkoxy, amino, mono-(C_1-C_4)-alkylamino and/or di-(CrC_4)-alkylamino.

Particular preference is given to the methyl or ethyl esters of the compounds of the formula (I).

In the context of the present invention, unless specified otherwise, the substituents have the following meanings:

Aryl refers to mono-, bi- or tricyclic aromatic or heteroaromatic ring systems, optionally substituted by one or two alkyl, alkylen, alkynesubstituents and/or alkoxysubstituents.

In the context of the invention, alkyl represents a straight-chain or branched alkyl radical having the number of carbon atoms stated in each case. The following radicals may be mentioned by way of example and by way of preference: methyl, ethyl, n-propyi, isopropyi, n-butyl, isobutyl, 1-methylpropyi, tert-butyl, n-pentyl, isopentyl, 1-ethylpropyl, 1-methyibutyl, 2-methyibutyl, 3-mefhylbutyi, n-hexyl, 1-methylpentyl, 2-mefhylpentyi, 3-methylpentyl, 4-methylpentyl, 3,3-dimethylbutyi, 1-ethyibutyi, 2-ethyibutyl, 1,4-dimethyipentyl, 4,4-dimethylpentyi and 1,4,4-trirnethylpentyi.

In the context of the invention, cycloalkyl represents a monocyclic saturated alkyl radical having 3 to 7 carbon atoms. The following radicals may be mentioned by way of example and by way of preference: cyclopropyl, cyclobutyl, cyclopentyi, cyclohexyl and cycloheptyi.

In the context of the invention, alkoxy represents a straight-chain or branched alkoxy radical having 1 to 4 carbon atoms. The following radicals may be mentioned by way of example and by way of preference: methoxy, ethoxy, n-propoxy, isopropoxy, 1-methylpropoxy, n-butoxy, isobutoxy and tert-butoxy.

In the context of the invention, halogen includes fluorine, chlorine, bromine and iodine. Preference is given to fluorine.

If radicals in the compounds according to the invention are substituted, the radicals can, unless specified otherwise, be mono- or polysubstituted. in the context of the present invention, the meanings of all radicals which occur more than once are independent of one another. Substitution with one, two or three identical or different substituents is preferred. Very particular preference is given to substitution with one substifuent.

The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms in their structure. The compounds of the invention and their pharmaceutically acceptable salts may therefore exist as single enanfiomers, diastereoisomers, racemates, and mixtures of enantiomers and diastereomers. All such

single enantiomers, diastereoisomers, racemates, and mixtures thereof are within the scope of this invention.

The compounds as described above and herein are, in a preferred embodiment of the invention, bound to an Aβ peptide.

Another aspect of the invention is the use of a compound of formula I or an otherwise hereby disclosed compound as described above and herein for diagnosing and/or treating Alzheimer's disease and/or amyloidoses in a patient, in particular in a mammal, such as a human.

The treatment of a patient with Alzheimer's disease and/or amyloidoses can preferably be performed with a compound of the invention according to formula I that does not bear a radioactive label, but in which Y is e.g. hydrogen.

Preferably, the use of a compound of the invention in the diagnosis is performed using positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance (MR)-speetoscropy or tomography.

Another aspect of the invention is directed to a method of imaging amyloid deposits. Such a method comprises a) administering to a mammal a compound as described above and herein containing a detectable label, and b) detecting the signal stemming from the compound that is specifically bound to the amyloid deposits. The specific binding is a result of the high binding affinity of the compounds of the present invention to the amyloid deposits.

In a further aspect, the invention is directed to a method of diagnosing a patient with Alzheimer's disease or amyloidoses. This method comprises a) administering to a human in need of such diagnosis a compound of the invention as described above and herein with a detectable label for detecting the compound in the human as described above and herein, and b) measuring the signal from the detectable label arising from the administration of the compound to the human, preferably by using a gamma camera, by positron emission tomography (PET), or by single photon emission computed tomography (SPECT).

A further embodiment of the invention includes a diagnostic method for other neurological disorders as Alzheimer's disease comprising the exclusion of Alzheimer's

disease in a patient, that method comprising administering a compound of the invention as described above and herein to a patient and applying an imaging method of the invention.

A further aspect of the invention refers to a diagnostic composition for imaging amyloid deposits, comprising a radiolabeled compound according to formula I or a compound as described otherwise above or herein.

The diagnostic methods of the invention can also be used as post-mortem diagnostic methods using compounds as described above and herein.

Furthermore, the diagnostic methods of the invention using a compound disclosed above or herein can also be used for monitoring the therapy of Alzheimer's disease, a neurodegenerative disorder or amyloidoses.

Furthermore, the diagnostic methods of the invention using a compound described above or herein can also be used in diagnosing neurological disorders other than Alzheimer's disease by excluding Alzheimer's disease.

In a further aspect of the invention, the invention comprises a method of treating or preventing amyloidoses or Alzheimer's disease comprises administering to a human in need of such a treatment a compound of formula I or a compound otherwise described above or herein.

A further aspect of the invention refers to a pharmaceutical composition which comprises a compound of the invention as described herein, optionally together with a suitable carrier and/or additive.

Furthermore, the compounds of the invention can also be used as tools in screening, for example high throughput screening methods and in vitro assays.

Yet another aspect of the invention refers to a method of inhibiting the formation of amyloid or modulating the pathogenicity of amyloid in a mammal. This method comprises administering a suitable compound of formula I as described herein in an amount that is effective to inhibit the formation of amyloidogenic aggregates or to modulate the pathogenicity of amyloidogenic aggregates.

The invention also refers to a method for synthesizing a compound of the invention according to formula I as described herein. The general synthetic methods of the compounds of the invention are as follows.

F-18 radiolabeling

A further aspect of the invention refers to a method of radiofluorination of a compound of formula I for the manufacture of radiolabeled compound of formula I comprising the step of reacting a compound of formula I with a fiuorination agent. Useful Radiofluorination methods are well known to the person skilled in the art.

In a preferred embodiment, the fiuorination agent is 4,7, 13, 16,21 ,24-Hexaoxa-1 ,10 diazabicyclo[8.8.8]-hexacosane $K^{18}F$ (crownether salt Kryptofix $K^{18}F$), $K^{18}F$, $H^{18}F$, $KH^{18}F_2$ or tetraalkylammonium salt of ^{18}F. More preferably, fiuorination agent is $K^{18}F$, $H^{18}F$, or $KH^{18}F_2$.

The solvents used can be Dimethylformamide, DMF, Dimethylsuifoxyde, DMSO, Acetonitrile, MeCN, Dimethyiacetamide, DMA, DMAA etc., preferably DMSO, MeCN or DMF. The solvents can also be a mixture of solvents as indicated above.

[F-18] radiolabeling procedures are well known to the person skilled in the art. For example, radiolabeling can be performed as described in the following.

[F-18]F!uoride can be produced by proton bombardment in a cyclotron using a silver target (1 mL) filled with [0-18] water for the $^{18}0$ (p,n)^{18}F reaction. The aqueous [F-18]fluoride can be passed through a cartridge (e.g. QMA-resin cartridge Waters, Sep Pak Light QMA Part.No.: WAT023525). The trapped [F-18]fluoride can then be eluted from the cartridge by adding e.g. a Kryptofix K2.2.2/ K_2C0_3 solution (Kryptofix is 4,7,13,16,21,24-Hexaoxa-1 ,10-diazabicyclo[8.8.8]hexacosane). The nucleophilic substitution of the precursor works preferably in the presence of a base such as NBu_4OH, $(NBu_4)_2C0_3$, NBu_4HC0_3, K_2C0_3, Cs_2C0_3 etc. and at elevated temperatures. The addition of crown ethers such as Kryptofix (K2.2.2) can influence the reaction positively, especially in the presence of K_2C0_3 as the base.

The potassium fluoride Kryptofix complex is preferably dried by repeated azeotropic distillation with sequential addition of acetonitrile. Solvents such as acetonitrile, DMF, DMSO etc. can be used as a reaction solvent. The labeling product can be purified by solid phase extraction using cartridges. Preferred cartridges are Sep-Pak Plus C18

cartridge (Waters, WAT02051 5). The cartridge can be rinsed with water and the compound can be e!uted with acetonitri!e. The eluted compound can be diluted with water and can then be subjected to preparative HPLC purification. Preferred HPLC columns are reversed phase columns such as Gemini 5 µ C 18 110 A, 250 * 10 mm (Phenomenex, 00G-4435-NQ). Mixtures of buffer solution, acids, water etc. with organic solvents such as acetonitrile, methanol, ethanol etc. can be used as mobile.

The solution can then be diluted with e.g. water to be passed through a cartridge for concentration and solvent change.

General synthesis of F-18 compounds: alkyl-F and (hetero)aryl-F

Precursors for alkyl-F-18 compounds of general formula I (formula I with Y = ^{18}F) are e.g. tosylates, brosylates, nosylates, mesylates, triflates, nonafiates etc. (formula I with Y = leaving group) which can be synthesized from the respective hydroxy compounds according to methods known in the art (J. March, Advanced Organic Chemistry, 4th ed. 1992, John Wiley & Sons, pp 352ff). An additional method is described in Examples 3f, 4e and 5a and comprises the synthesis by suitable bis(tosylates) and the like, e.g. TsO-$(CH_2)_n$-OTs.

Other precursors for alkyl-F-18 compounds of general formula I (formula I with Y = ^{18}F) are e.g. iodides and bromides and the like whose conversion to the respective fluorides is also known in the art (J. March, see above).

Precursors for aryl-F-18 compounds of general formula I are e.g. aryl or heteroaryi bromides, nitro compounds, trialkyl ammonium , aryliodonium which can be converted to the respective F-18 compounds of this invention by methods known in the art (L. Cai, S. Lu, V. Pike, Eur. J. Org. Chem 2008, 2853-2873). Starting materials for these precursors are commercially available or can be synthesized by methods known in the art (R.C. Larock, Comprehensive Organic Transformations, VCH Publishers 1989).

A further aspect of the invention refers to a kit comprising a non-radiolabeled compound of the invention, the compound optionally being in a dry condition or having an inert, pharmaceutically acceptable carrier and/or solvent and/or auxiliary substances added.

The compounds according to the invention can act systemicaily and/or locally. For this purpose, they can be administered in a suitable manner, such as, for example, orally,

parenteraliy, pulmonally, nasaliy, sublingually, lingualiy, buccally, rectaliy, dermaliy, transdermal, conjunetivaliy, otically or as an implant or stent.

For these administration routes, the compounds according to the invention can be administered in suitable administration forms.

Suitable for oral administration are administration forms which work in accordance with the prior art and release the compounds according to the invention rapidly and/or in modified form and which comprise the compounds according to the invention in crystalline and/or amorphicized and/or dissolved form, such as, for example, tablets (uncoated or coated tablets, for example with enteric coats or coats which dissolve in a delayed manner or are insoluble and which control the release of the compounds according to the invention), films/wafers or tablets which dissolve rapidly in the oral cavity, films/lyophilizates, capsules (for example hard or soft gelatin capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions.

Parenteral administration may take place by circumventing a bioabsorption step (for example intravenously, infraarterially, intracardially, intraspinaiiy or intraiumbarly), or with bioabsorption (for example intramuscularly, subcutaneous!y, intracutaneously, percutaneously or intraperitoneaily). Administration forms suitable for parenteral administration are inter alia preparations for injection or infusion in the form of solutions, suspensions, emulsions, lyophilizates or sterile powders.

Suitable for other administration routes are, for example, medicaments suitable for inhalation (inter alia powder inhalers, nebulizers), nose drops, solutions or sprays, tablets to be administered lingualiy, sublinguaiiy or buccaliy, films/wafers or capsules, suppositories, preparations to be administered to ears or eyes, vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, transdermal therapeutic systems (for example plasters), milk, pastes, foams, powders for pouring, implants or stents.

Preference is given to oral or parenteral administration, in particular to oral and intravenous administration.

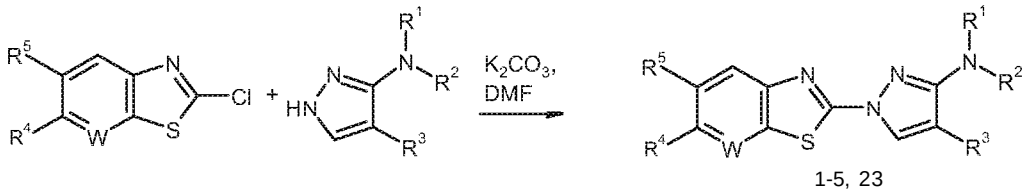
The compounds according to the invention can be converted into the administration forms mentioned. This can be carried out in a manner known per se by mixing with inert non-toxic pharmaceutically suitable auxiliaries. These auxiliaries include inter alia carriers (for example microcrysfailine cellulose, lactose, mannitoi), solvents (for example liquid polyethylene glycols), emulsifiers and dispersants or wetting agents (for

example sodium dodecyi sulphate, polyoxysorbitan oieate), binders (for example polyvinylpyrrolidone), synthetic and natural polymers (for example albumin), stabilizers (for example antioxidants, such as, for example, ascorbic acid), colorants (for example inorganic pigments, such as, for example, iron oxides), and flavour and/or odor corrigents.

**Another aspect of this invention is related to methods of preparing compounds of the general formula **

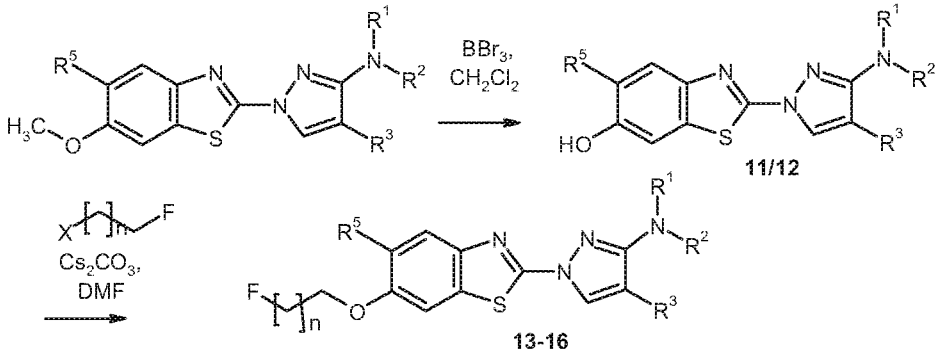
The condensation of 2-chiorobenzothiazoies and 3-aminopyrazoles in the presence of potassium carbonate in DMF is shown in **scheme 1.** Compounds 1-5, 23 and intermediates were synthesized accordingly with the respective benzothiazole and pyrazole building blocks.

Scheme 1



The synthesis of the fluoroalkoxy substituted benzothiazol-pyrazole derivatives 13-16 is shown in **scheme** 2. Demethylation of 6-methoxybenzothiazol-pyrazole derivatives with BBr_3 in dichioromethane gave the intermediate 11/12 in 99% yield. Direct alkylation of compound 11/12 with 1-ha!ofluoroalkanes in the presence of caesium carbonate in DMF gave the fluoroalkoxylated compounds, which can be used as the cold reference for radio labeling and affinity studies.

Scheme 2

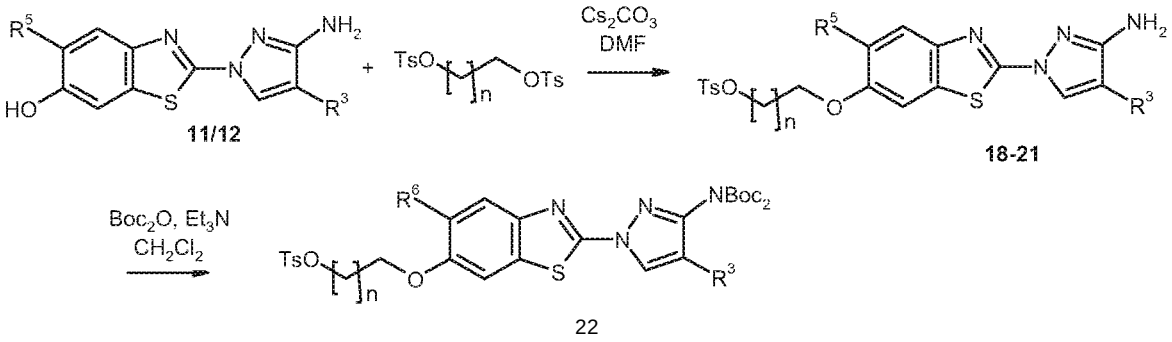


The synthesis of the corresponding benzothiazol-pyrazole labeling precursors 18-22 is shown in scheme 3. Reaction of intermediate 11 with bis-p-to!uenesu!fonates led to compound 18.

Compounds 19 and 21 were synthesized accordingly. Compound 20 could be synthesized accordingly from intermediate 12.

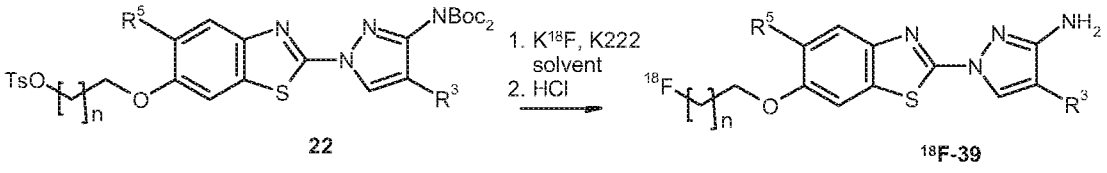
To increase the yield in the subsequent radiolabeling step the free amine (if $R^1$and R^2 = H) was protected with two Boc groups in compound 22. The labeling proceeds also without further protection.

Scheme 3



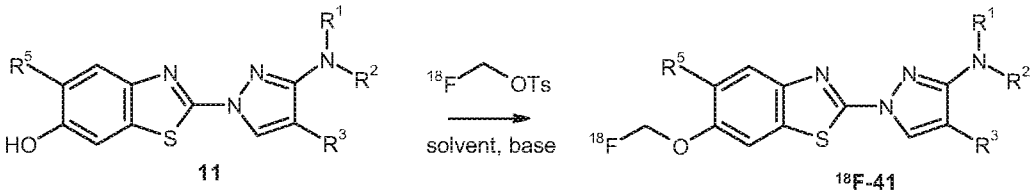
The radio-labeling of the benzothiazol-pyrazole labeling precursor 22 is shown in scheme 4. Treatment of 22 with F-18 potassium fluoride and Kryptofix 222 in DMSO/MeCN gave the F-18 fluoroalkylated compound ^{18}F-39.

Scheme 4



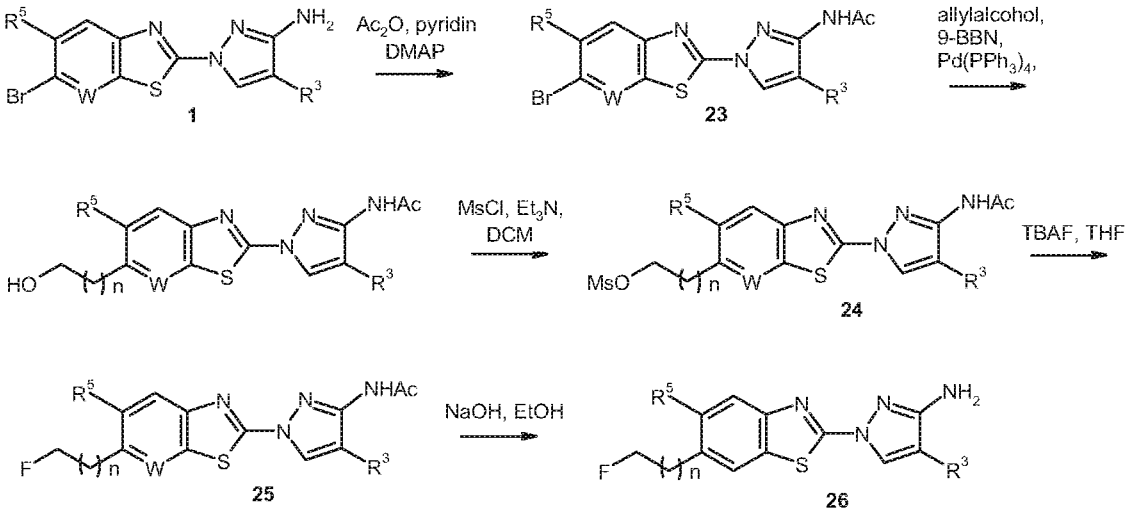
Fluoroalkylated compounds can also be synthesized by indirect labeling as exemplified in scheme 5. Compound ^{18}F-41 was synthesized by conversion of compound 11 with F-18 fluoromethyl tosylate Compounds ^{18}F-39 and ^{18}F-40 could be synthesized accordingly via the corresponding F-18 fiuoroaikyi tosyiates.

Scheme 5



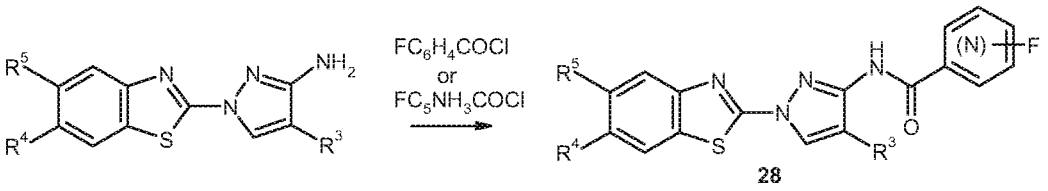
The exemplary synthesis of fluoroalkylated benzothiazol-pyrazole derivatives 26 is shown in scheme 6. Acylation of compound 1 (if R^1 and R^2 = H) gave the protected derivative 23, which was followed by a palladium catalysed alkylation towards the 6-(hydroxypropyl)benzothiazol. The alcohol was then e.g. mesyiated yielding the intermediate and labeling precursor 24. Cold fluorination with TBAF gave compound 25 which was deprotected to yield the product 2β. 2β can be used as the cold reference for radio labeling and affinity studies.

Scheme 6



The exemplary synthesis of fluorobenzoyi acyiated benzothiazol-pyrazole derivatives and their precursors 28-33 is shown in scheme 7. Acylation of benzothiazol-pyrazoleamine gave the fluorobenzoyied derivative 28, which can be used as cold reference for radio labeling and affinity studies. Compounds 29-33, cold references and corresponding precursors, could be synthesized accordingly with the respective benzothiazole and acyl building blocks.

Scheme 7



The exemplary synthesis of 6-halogenated 1-(thiazo!o[5,4-b]pyridin-2-yl)-1H-pyrazoles is shown in scheme 8. Starting from a 2,6-halogenated 3-aminopyridine the 2-aminothiazolo[5,4-b]pyridine was synthesized by thiourea formation followed by a copper-(I) mediated thiazoi cyciizafion. The condensation of 2-chlorothiazolo[5,4-bjpyridine, derived from the amine via Sandmeyer reaction, and 3-aminopyrazoles in the presence of caesium carbonate in DMF lead to compound 36-38. 36 (Ha! = F) can be used as the cold reference for radio labeling and affinity studies and 37 and 38 (Hal = Br / I) can be used as the precursor for radio labeling.

Scheme 8

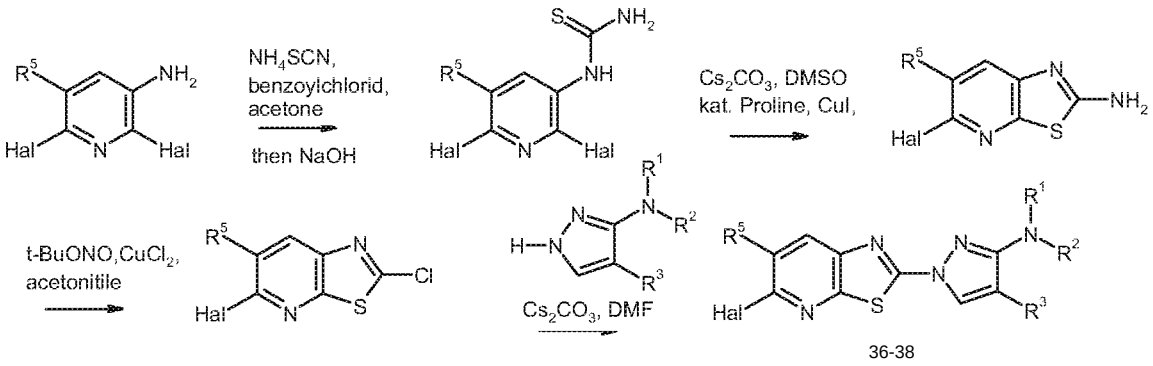
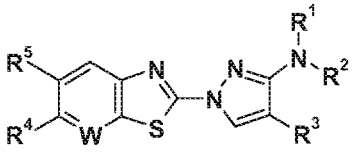


Fig. 1 summarizes exemplified compounds.

In particular the invention relates to

1. A compound of formula I



I

wherein

- R^1 is selected from the group consisting of H, C(0)CH $_3$, C(0)(CH $_2$)$_n$CH$_2$X, C(0)CF $_3$, C(0)OC(CH $_3$)$_3$, C(0)C $_6$H4X, C(0)C $_6$H3XZ, C(0)heteroraryl, substituted C(0)heteroraryl ;

- R^2 is selected from the group consisting of H, CH_3, $(CH_2)nCH_3$, $(CH_2)_mCH_2X$, R^1;

- R^3 is selected from the group consisting of H, C(0)OH, $C(0)0(CH_2)_nCH_3$, $C(0)0(CH_2)_mCH_2X$, $C(0)NH_2$, $C(0)NH(CH_2)_nCH_3$, $C(0)NH(CH_2)_mCH_2X$;

- R^4 and R^5 are independently selected from the group consisting of H, CH_3, $(CH_2)nCH_3$, $(CH_2)nCH_2X$, OH, OCH_3, $0(CH_2)_nCH_3$, $0(CH_2)_nCH_2X$, O-cyciobufyl-X, O-cyclopentyi-X, O-cyclohexyl-X, $0(CH_2CH_20)_nCH_2CH_2X$, SH, SCH_3, $S(CH_2)_nCH_3$, $S(CH_2)_nCH_2X$, NH_2, $NHCH_3$, $N(CH_3)_2$, $NH(CH_2)_nCH_3$, $NH(CH_2)_mCH_2X$, $NCH_3(CH_2)_mCH_2X$, X, Z;

- W is selected from CH or N

- X is selected from the group consisting of F, ^{18}F, I, ^{125}I, ^{123}I;

- Z is selected from the group consisting of H, CF_3, CN, C(0)H, $C(0)CH_3$, $C(0)0(CH_2)_nCH_3$;
- m has the meaning of 1-4;
and n has the meaning of 0-4;

including ail isomeric forms of said compound, including enantiomers and diasteromers as well as racemic mixtures,

and any pharmaceutically acceptable salt, ester, amide, complex or prodrug thereof, wherein the formula comprises only one X.

2. A compound according to count 1, wherein

- R^1 is selected from the group consisting of H, $C(0)CH_3$, $C(0)(CH_2)_nCH_2X$, $C(0)CF_3$, $C(0)OC(CH_3)_3$, $C(0)C_6H_4X$, $C(0)C_6H_3XZ$, C(0)heteroraryl, substituted C(0)heteroraryl;

- R^2 is selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, $(CH_2)_mCH_2X$, R^1;

- R^3 is selected from the group consisting of H, C(0)OH, $C(0)0(CH_2)_nCH_3$, $C(0)0(CH_2)_mCH_2X$, $C(0)NH_2$, $C(0)NH(CH_2)_nCH_3$, $C(0)NH(CH_2)_mCH_2X$;

- R^4 and R^5 are independently selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, $(CH_2)_nCH_2X$, OH, OCH_3, $0(CH_2)_nCH_3$, $0(CH_2)_nCH_2X$, O-cyciobutyl-X, O-cyclopentyi-X, $0(CH_2CH_20)_nCH_2CH_2X$, NH_2, $NHCH_3$, $N(CH_3)_2$, $NH(CH_2)_nCH_3$, $NH(CH_2)_mCH_2X$, $NCH_3(CH_2)_mCH_2X$, X, Z;

- W is selected from CH or N

- X is selected from the group consisting of F, ^{18}F, I, ^{125}I, ^{123}I;

- Z is selected from the group consisting of H, CF_3, CN, C(0)H, $C(0)CH_3$;
- m has the meaning of 1-3;
and n has the meaning of 0-3;

including ail isomeric forms of said compound, including enantiomers and diasteromers as well as racemic mixtures,

and any pharmaceutically acceptable salt, ester, amide, complex or prodrug thereof,

wherein the formula comprises only one X.

3. A compound according to count 1 or 2, wherein

- R^1 is selected from the group consisting of H, $C(0)CH_3$, $C(0)(CH_2)_nCH_2X$, $C(0)CF_3$, $C(0)OC(CH_3)_3$, $C(0)C_6H_4X$, $C(0)C_6H_3XZ$;

- R^2 is selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, R^1;

- R^3 is selected from the group consisting of H, C(0)OH, $C(0)0(CH_2)nCH_3$, $C(0)0(CH_2)_mCH_2X$;

- R^4 and R^5 are independently selected from the group consisting of H, $(CH_2)_nCH_2X$, OH, OCH_3, $0(CH_2)_nCH_2X$, O-cyclobutyl-X, $0(CH_2CH_20)_nCH_2CH_2X$, X, Z;

- W is selected from CH or N

- X is selected from the group consisting of F, ^{18}F;

- Z is selected from the group consisting of H, CF_3, CN, C(0)H;
- m has the meaning of 1-2;
and n has the meaning of 0-2,

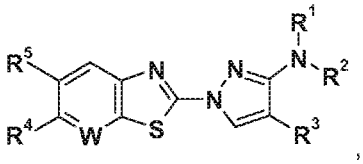
including ail isomeric forms of said compound, including enantiomers and diasteromers as well as racemic mixtures,

and any pharmaceutically acceptable salt, ester, amide, complex or prodrug thereof,

wherein the formula comprises only one X.

4. A compound according to counts 1, 2 or 3, wherein X is ^{18}F.

5. A compound of formula I



I

wherein

- R^1 is selected from the group consisting of H, C(0)CH_3, C(0)$(CH_2)nCH_2X$, C(0)CF_3, C(0)$OC(CH_3)_3$, C(0)C_6H_4X, C(0)C_6H_3YZ, C(0)C_6H_3XZ, C(0)heteroraryl, substituted C(0)heteroraryl, C(0)OCH_3, C(0)OCH_2CH_3, C(0)$OCH_2C_6H_5$, C(0)$OCH_2CH{=}CH_2$, Fmoc, C(0)$OCH_2CH_2Si(CH_3)_3$, C(0)OCH_2CCi_3;

- R^2 is selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, $(CH_2)_mCH_2X$, R^1;

- R^3 is selected from the group consisting of H, C(0)OH, C(0)0$(CH_2)_nCH_3$, C(0)0$(CH_2)mCH_2X$, C(0)NH_2, C(0)NH$(CH_2)_nCH_3$, C(0)NH$(CH_2)_mCH_2X$;

- R^4 and R^5 are independently selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, $(CH_2)_nCH_2X$, OH, OCH_3, 0$(CH_2)_nCH_3$, 0$(CH_2)_nCH_2X$, O-cyciobutyl-X, O-cyclopentyl-X, O-cyclohexyl-X, 0$(CH_2CH_20)_nCH_2CH_2X$, SH, SCH_3, $S(CH_2)_nCH_3$, $S(CH_2)_nCH_2X$, NH_2, $NHCH_3$, $N(CH_3)_2$, NH$(CH_2)_nCH_3$, NH$(CH_2)_mCH_2X$, $NCH_3(CH_2)_mCH_2X$, X, Y, Z;

- W is selected from CH or N

- X is selected from the group consisting of F, Cl, Br, I, OSO_2CH_3, OSO_2CF_3, $OSO_2C_4F_9$, $OSO_2C_6H_5$, $OSO_2C_6H_4CH_3$, $OSO_2C_6H_4NO_2$, $OSO_2C_6H_4Br$, $OSO_2C_6H_2(CH(CH_3)_2)_3$, $OSO_2C_6H_3(GCH_3)_2$;

- Y is selected from the group consisting of NO_2, N^+Me_3, I*aryi, S^+aryl_2;

- Z is selected from the group consisting of H, CF_3, CN, C(0)H, $C(0)CH_3$, $C(0)O(CH_2)_nCH_3$;
- m has the meaning of 1-4;
and n has the meaning of 0-4;

including ail isomeric forms of said compound, including enantiomers and diasteromers as well as racemic mixtures,

and any pharmaceutically acceptable salt, ester, amide, complex or prodrug thereof,

wherein the formula comprises only one X,
and wherein the formula comprises only one Y.

8. A compound according to count 5, wherein

- R^1 is selected from the group consisting of H, $C(0)CH_3$, $C(0)(CH_2)_nCH_2X$, $C(0)CF_3$, $C(0)OC(CH_3)_3$, $C(0)C_6H_4X$, $C(0)C_6H_3YZ$, $C(0)C_6H_3XZ$, $C(0)C_6H_4Y$, C(0)heteroraryl, substituted C(0)heteroraryl , $C(0)OCH_2C_6H_5$, $C(0)OCH_2CH=CH_2$, Fmoc;

- R^2 is selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, $(CH_2)_mCH_2X$, R^1;

- R^3 is selected from the group consisting of H, C(0)OH, $C(0)O(CH_2)nCH_3$, $C(0)O(CH_2)_mCH_2X$, $C(0)NH_2$, $C(0)NH(CH_2)_nCH_3$, $C(0)NH(CH_2)_mCH_2X$;

- R^4 and R^5 are independently selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, $(CH_2)_nCH_2X$, OH, OCH_3, $O(CH_2)_nCH_3$, $O(CH_2)_nCH_2X$, O-cyciobutyl-X, O-cyclopentyl-X, $O(CH_2CH_2O)_nCH_2CH_2X$, NH_2, $NHCH_3$, $N(CH_3)_2$, $NH(CH_2)_nCH_3$, $NH(CH_2)_mCH_2X$, $NCH_3(CH_2)_mCH_2X$, X, Y, Z;

- W is selected from CH or N

- X is selected from the group consisting of F, Cl, Br, I, OSO_2CH_3, OSO_2CF_3, OSO2C4F9, $OSO_2C_6H_5$, $OSO_2C_6H_4CH3$, $OSG_2C_6H_4NO_2$, $OSO_2C_6H_4Br$, $OSO_2C_6H_3(OCH_3)_2$;

- Y is selected from the group consisting of NO_2, N^+Me_3, I^+aryl, S^+aryl_2;

- Z is selected from the group consisting of H, CF_3, CN, C(0)H, $C(0)CH_3$;

- m has the meaning of 1-3;
and n has the meaning of 0-3;

including ail isomeric forms of said compound, including enantiomers and diasteromers as well as racemic mixtures,

and any pharmaceutically acceptable salt, ester, amide, complex or prodrug thereof

wherein the formula comprises only one X,
and wherein the formula comprises only one Y.

7. A compound according to count 5 or 8, wherein

- R^1 is selected from the group consisting of H, $C(0)CH_3$, $C(0)(CH_2)_nCH_2X$, $C(0)CF_3$, $C(0)OC(CH_3)_3$, $C(0)C_6H_4X$, $C(0)C_6H_3YZ$, $C(0)C_6H_3XZ$, $C(0)OCH_3$, $C(0)OCH_2CH_3$, $C(0\}OCH_2C_6H_5$, Fmoc;

- R^2 is selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, R^1;

- R^3 is selected from the group consisting of H, C(0)OH, $C(0)0(CH_2)nCH_3$, $C(0)0(CH_2)_mCH_2X$;

- R^4 and R^5 are independently selected from the group consisting of H, $(CH_2)_nCH_2X$, OH, OCH_3, $0(CH_2)_nCH_2X$, O-cyclobutyi-X, $0(CH_2CH_20)_nCH_2CH_2X$, X, Y, Z;

- W is selected from CH or N

- X is selected from the group consisting of F, Cl, Br, I, OSO_2CH_3, OSO_2CF_3, $OSO_2C_4F_g$, $OSO_2C_6H_5$, $OSO_2C_6H_4CH_3$;

- Y is selected from the group consisting of NO_2, N^+Me_3, I^+aryl, S^+aryi_2;

- Z is selected from the group consisting of H, CF_3, CN, C(0)H;
- m has the meaning of 1-2;
and n has the meaning of 0-2,

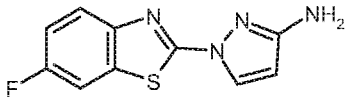
including ail isomeric forms of said compound, including enantiomers and diasteromers as well as raeemic mixtures,

and any pharmaceutically acceptable salt, ester, amide, complex or prodrug thereof,

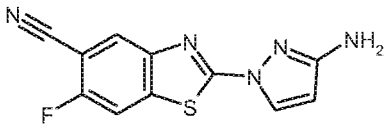
wherein the formula comprises only one X,
and wherein the formula comprises only one Y.

8. A compound selected from the group consisting of

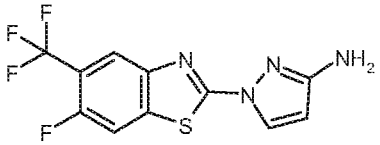
1-(6-Fiuorobenzothiazol-2-yl)-1H-pyrazoi-3-ylamine 2



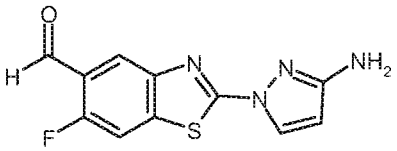
2-(3-Aminopyrazol-1-yl)-6-fluoro-benzothiazole-5-carbonitrile **4**



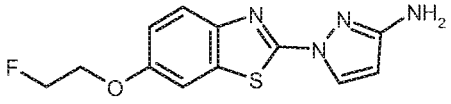
1-(6-Fiuoro-5-trifiuoromethyibenzothiazol-2-yl)-1H-pyrazol-3-ylamine 5



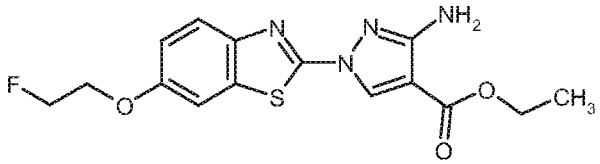
2-(3-Aminopyrazoi-1-yl)-8-fiuorobenzothiazole-5-carbaldehyde 9



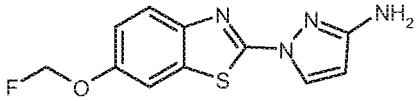
1-[6-(2-Fluoroeihoxy)benzothiazol-2-yl]-1H-pyrazol-3-y!amine 13



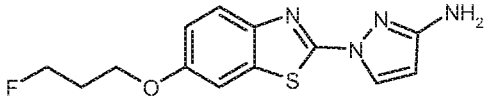
3-Amino-1-[6-(2-fluoroeihoxy)benzoihiazol-2-yl]-1H-pyrazole-4-carboxylic acid ethyl ester 14



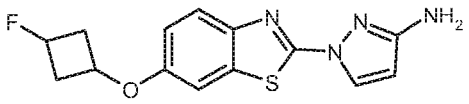
1-[6-(Fiuoromethoxy)benzothiazoi-2-yl]-1H-pyrazoi-3-ylamine 15



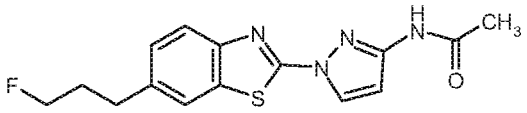
1-[6-(3-Fluoropropoxy)berizothiazol-2-yl]-1H-pyrazol-3-yiamine 16



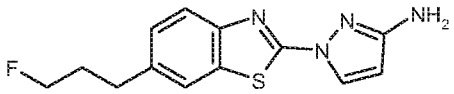
1-[6-(3-Fluorocyc!obutoxy)benzothiazo!-2-yi]-1H-pyrazol-3-yiamine 17



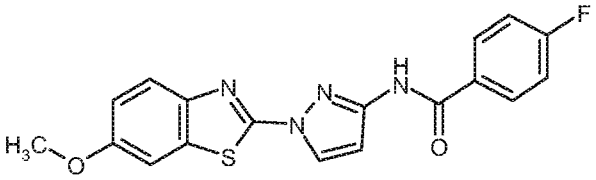
N-{1-[6-(3-Fluoropropyl)benzothiazol-2-yl]-1H-pyrazol-3-yl}acetamide 25



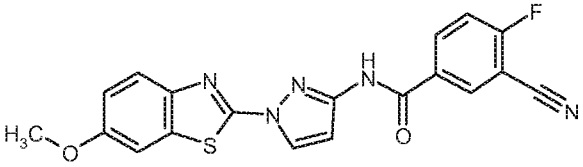
1-[6-(3-Fluoropropyl)benzothiazo!-2-yl]-1H-pyrazol-3-yiarnir!e 26



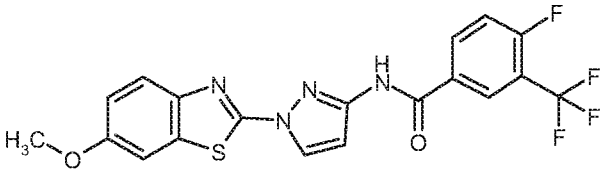
4-F!uoro-N-[1-(6-methoxybenzoihiazol-2-yi)-1H-pyrazo!-3-yl]benzamide 27



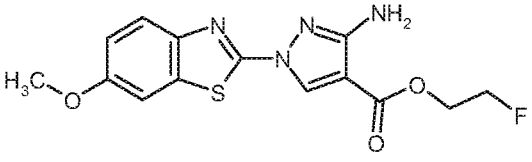
3-Cyano-4-fluoro-N-[1-(6-methoxybenzothiazol-2-y!)-1H-pyrazol-3-yl]benzamide 28



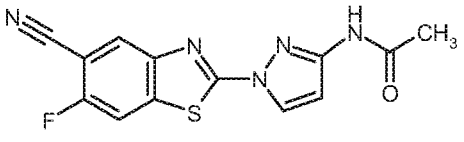
4-FlLioro-N-[1-(6-rneihoxybenzothiazol-2-yl)-1H-pyrazol-3-y!]-3-(trifluoromethyl)benzamide **29**



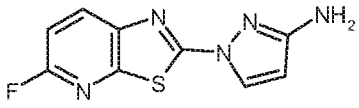
3-Amino-1-(8-methoxybenzothiazol-2-yl)-1H-pyrazole-4-carboxylic acid 2-fiLioroethyl ester **34**



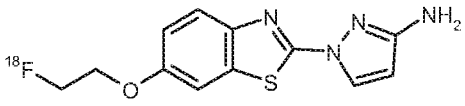
N-[1-(5-Cyano-6-fluorobenzothiazol-2-yl)-1H-pyrazol-3-yl]acetamide 35



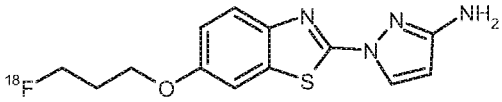
^(S-Fluorothiazolo^^-bjpyridin^-yl^lH-pyrazoi-S-amirie 36



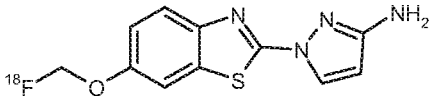
1-[6-(2-[18F]Fluoroethoxy)benzothiazol-2-yl]-1H-pyrazol-3-ylamine [18FJ-38]



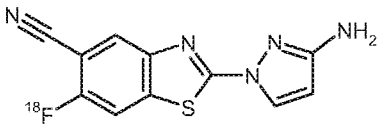
1-[6-(3-[18F]Fluoropropoxy)benzothiazol-2-yl]-1H-pyrazol-3-ylamine [18F]-40



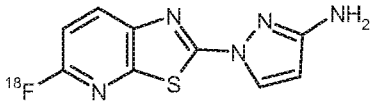
1-[6-([18F]Fluoromethoxy)benzothiazol-2-yl]-1H-pyrazol-3-ylamine [18F]-41



2-(3-Aminopyrazol-1-yl)-8-[18F]fluoro-benzothiazole-5-carbonitrile [18F]-42

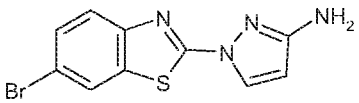


1-(6-[18F]Fluorothiazolo[5,4-b]pyridin-2-yl)-1H-pyrazol-3-amine [18FJ-43

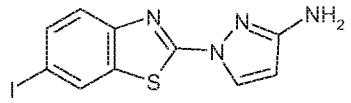


9. A compound selected from the group consisting of

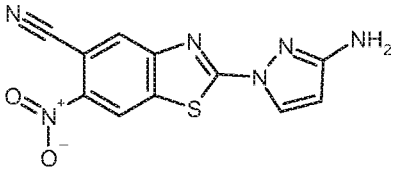
1-(6-Bromobenzothiazol-2-yl)-1H-pyrazol-3-ylamine 1



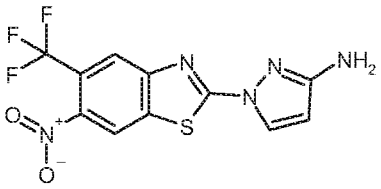
1-(6-Iodobenzothiazol-2-yl)-1H-pyrazol-3-ylamine 3



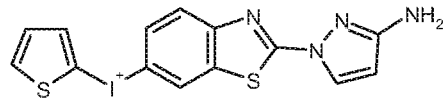
2-(3-Aminopyrazol-1-yl)-6-nitrobenzothiazole-5-carbonitrile β



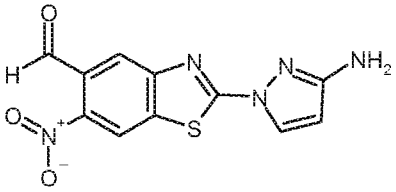
1-(6-N!tro-5-trifluoromeihylbenzoih!azo!-2-yi)-1H-pyrazol-3-ylamjr!e 7



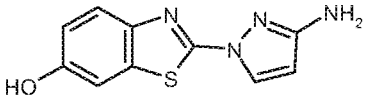
[2-(3-Aminopyrazol-1-yl)-benzothiazol-6-yl]thien-2-yi-iodoniLirri 8



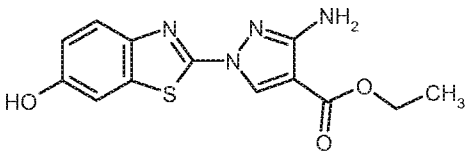
2-(3-Amirsopyrazol-1-yl)-8-nitrobenzothiazole-5-carbaldehyde 10



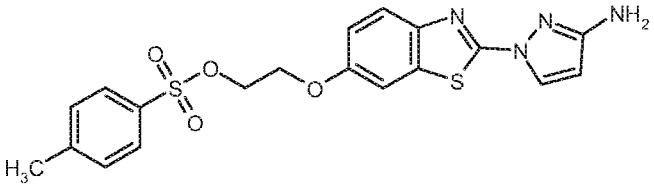
2~(3-Aminopyrazo!-1-yi)~benzothiazo!~8-o! 11



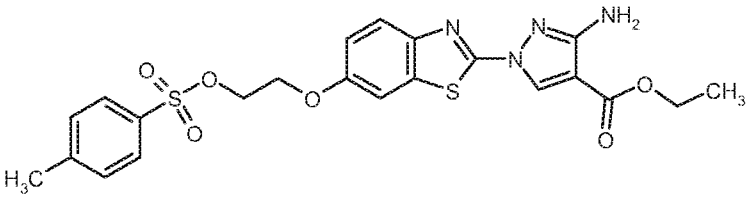
3-Amino-1-(8-hydroxybenzothiazol-2-yl)-1H-pyrazoie-4-carboxylic acid ethyl ester 12



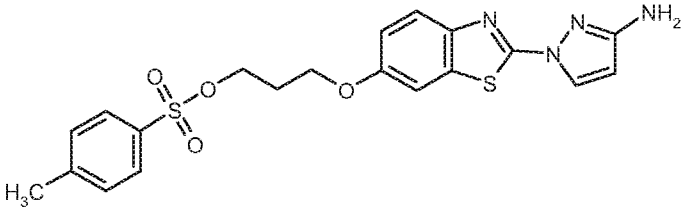
Toluene-4-sulfonic acid 2-[2-(3-amino-pyrazol-1-yl)benzothiazo!-6-yloxy] ethyi ester 18



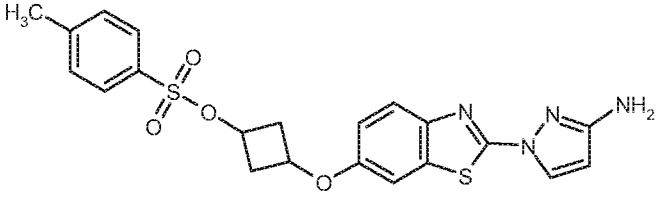
3-Amino-1-{6-[2-(toiuene-4-sulfonyioxy)ethoxy]benzothiazo!-2-yl}-1H-pyrazo!e-4-carboxylic acid ethyl ester **19**



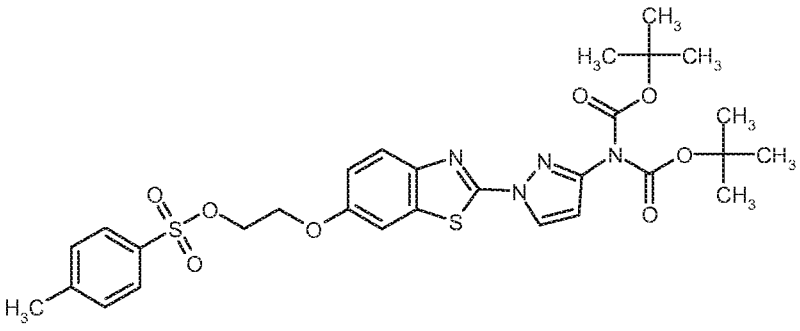
Toluene-4-sulfonic acid 3-[2-(3-amino-pyrazol-1-yl)benzothiazol-6-yloxy] propyl ester 20



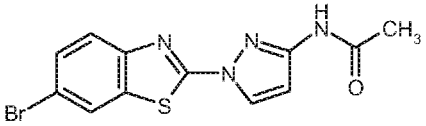
Toiuene-4-su!fonic acid 3-[2-(3-amino-pyrazo!-1-yl)benzotbiazal-6-y!oxy] cyclobutyl ester **21**



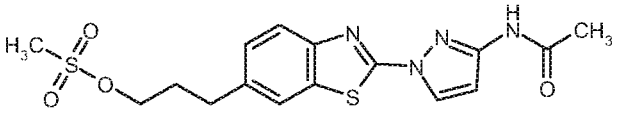
Toiuene-4-sulfonic acid 2~[2-(3-di-tert-bijtoxycarbonylaminopyrazol-1-y!)benzothiazo!-6-yioxy] ethyl ester 22



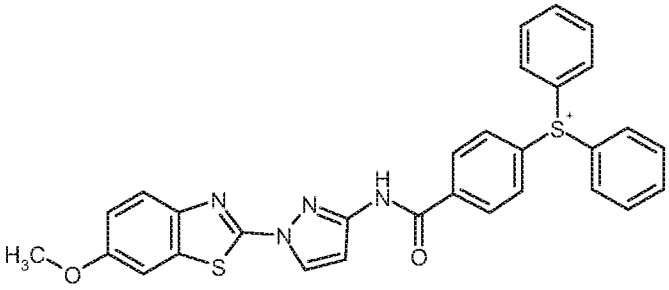
N-[1-(6-Bromobenzothiazol-2-yl)-1H-pyrazol-3-yl]acetamide **23**



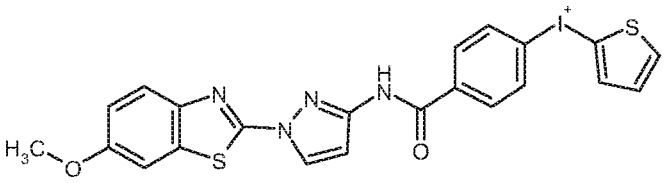
Methane sulfonic acid 3-[2-(3-aminopyrazol-1-yl)benzothiazol-6-yl]propyl ester **24**



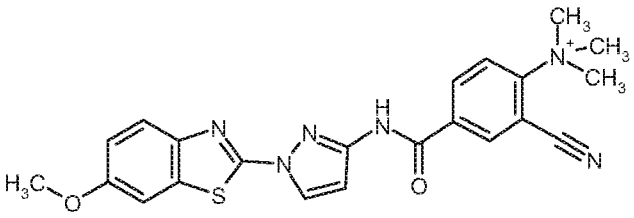
{4-[1~(6-Methoxybenzoihiazo!~2-yl)-1H~pyrazo!~3-ylcarbamoyi]-phenyl}diphenyi-sulfonium **30**



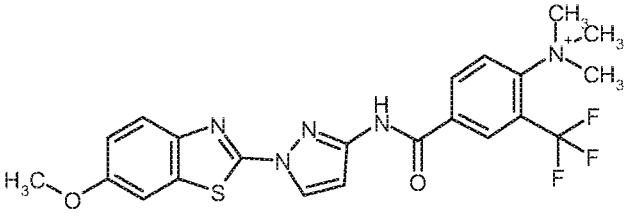
{4-[1-(6-Methoxybenzothiazol-2-yl)-1H-pyrazol-3-ylcarbamoyl]phenyl}thien-2-yl-iodorsium 31



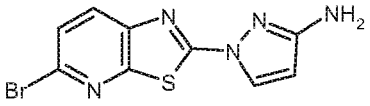
{2-Cyano-4-[1-(6-iTseihoxybenzothiazol-2-yr)-1H-pyrazoi-3-ylcarbamoy[|-pheny!}trimethyl-ammoniurri 32



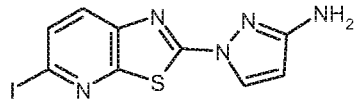
{4-[1-(6-Methoxybenzothiazol-2-yl)-1H-pyrazol-3-ylcarbamoyl]-2-trifluoromethyl-phenyl}trimethyl-ammonium **33**



1-(6-Bromothiazolo[5,4-bjpyridin-2-yl)-1H-pyrazol-3-amirie 37

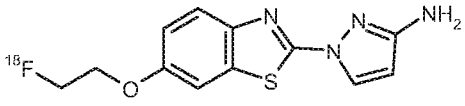


1-(6-!odothiazolo[5,4-b]pyridin~2-yl)-1H-pyrazo!~3-amine 38

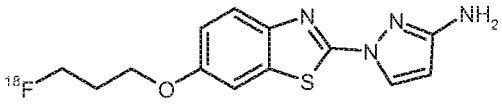


10. A compound selected from the group consisting of

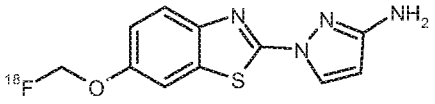
1-[6-(2-[^{18}F]Fluoroethoxy)benzothiazoi-2-y!]-1H-pyrazo!-3-yiamine **[18F]-39**



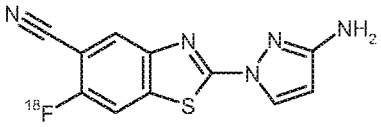
1-[6-(3-[^{18}F]Fluoropropoxy)benzothiazol-2-y!]-1H-pyrazol-3-yiamine [18F]-40



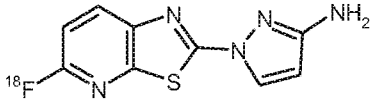
1-[6-([^{18}F]Fluoromethoxy)benzoth!azol-2-yi]-1H-pyrazo!-3-yiarnine [18F]-41



2-(3-Aminopyrazol-1-yl)-6-[^{18}F]fluoro-benzothiazole-5-carbonitrile **[18F]-42**



1-(6-[^{18}F]Fiuoroihiazolo[5,4-b]pyridin-2-yi)-1H-pyrazol-3-amine [18FJ-43



11. A compound according to count 8, wherein F has the meaning of ^{18}F when F is not part of a -CF_3-group.

12. An ^{18}F-radioaei:ively labelled compound according to counts 1 - 4, 10 or 11 as a compound for diagnostic imaging.

13. A compound according to count 12 as a compound for diagnostic imaging of a disease selected from the group of diseases comprising Alzheimer's disease, a neurodegenerative disorder, or an amyloidosis.

14. Use of a ^{18}F radioactively labelled compound according to counts 1 - 4, 10 or 11 in a method for the preparation of a pharmaceutical composition or a diagnostic composition suitable for use in diagnostic imaging of a disease selected from the group of diseases comprising Alzheimer's disease, a neurodegenerative disorder, or an amyloidosis.

15. A pharmaceutical or diagnostic composition comprising a ^{18}F radioactively labelled compound according to counts 1 - 4, 10 or 11 and a pharmaceutically acceptable carrier.

16. A pharmaceutical or diagnostic composition according to count 15 for diagnostic imaging of a disease selected from the group of diseases comprising Alzheimer's disease, a neurodegenerative disorder, or an amyloidosis.

17. A method for the preparation of a ^{18}F radiofiuorinafed compound according to counts 1 - 4, 10 or 11, the method comprising reacting a suitable precursor molecule of counts 5 - 7, or 9 with a radiofluorinating agent.

18. A method according to count 16 for the preparation of a compound according to count 10, the method comprising reacting a suitable precursor molecule of count 9 with a radiofluorinating agent.

19. A method for diagnosing a disease in a mammal selected from the group consisting of Alzheimer's disease, a neurodegenerative disorder, or an amyloidosis, the method comprising administering a radioactively labelled compound of counts 1 - 4, 10, **11,** 12, or 13 or a composition according to count 15 or 16 to said mammal, imaging said mammal and detecting the signal.

20. The method according to count 19, wherein a compound of count 10 is used.

21. A method according to counts 19 or 20, wherein the effect of a therapy is monitored.

22. A method of imaging amyloid plaques in a mammal, said method comprising administering a compound according to counts **1 - 4, 10, 11, 12 or 13, a** composition according to counts 15 or 16 to said mammal, imaging said mammal and detecting the signal.

23. A method according to count 22, wherein a compound according to count 10 is used.

Brief description of the figures:

Fig. 1: list of compounds prepared.

Fig. 2: HPLC **chromatogram** of compound **[18FJ-39.**

Fig. 3: HPLC chromatograms of compound **[18FJ-40** in comparison **with** compound **16.**

Fig. 4: HPLC chromatograms of [18F]MeBr and compound **[18F]-41** in comparison with compound **15.**

Fig. 5: HPLC chromatograms compound **[18FJ-42** in comparison **with** compound **4.**

Fig. 6: HPLC chromatograms of compound **[18F]-43** in comparison **with** compound **36.**

Fig. 7: Autoradiographical analysis of binding of compound **^{18}F-39** to brain sections from cortex of Alzheimer's disease patients (AD) and controls without Aβ plaques (HC)

(healthy control). Blocking of specific signals was performed with an excess of cold compound. Arrows point to plaque-specific signals.

Fig. 8: Autoradiographical analysis of binding of compound ^{18}F-40 to brain sections from cortex of Alzheimer's disease patients (AD) and controls without Aβ plaques (HC) (healthy control). Blocking of specific signals was performed with an excess of cold compound. Arrows point to plaque-specific signals.

Fig. 9: Autoradiographical analysis of binding of compound ^{18}F-41 to brain sections from cortex of Alzheimer's disease patients (AD) and controls without Aβ plaques (HC) (healthy control). Blocking of specific signals was performed with an excess of cold compound. Arrows point to plaque-specific signals.

Fig. 10: Autoradiographical analysis of binding of compound ^{18}F-43 to brain sections from cortex of Alzheimer's disease patients (AD) and controls without Aβ plaques (HC) (healthy control). Blocking of specific signals was performed with an excess of cold compound. Arrows point to plaque-specific signals.

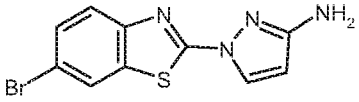
Abbreviations

Boc	ierf-Butoxycarbonyl
br	Broad signal (in NMR data)
CI	Chemical ionisation
d	Doublet
DAD	Diode array detector
dd	Doublet of doublet
ddd	Doublet of doublet of doublet
dt	Doublet of triplet
DMF	*N*,/V-Dirnethylformamide
DMSO	Dimethy!sulfoxide
EI	Electron ionisation
ELSD	Evaporative light scattering detector
ESI	Electrospray ionisation
EtOAc	Ethyl acetate
Fmoc	Fiuorenyimethyloxycarbonyi
Hal	Haiogenide
HPLC	High pressure liquid chromatography

GBq	Giga Bequere!
K2.2.2	4, 7, 13, 16, 21, 24-hexaoxa-1 ,10-diazabicyclo[8.8.8]hexacosane
K_2CO_3	Potassium carbonate
MBq	Mega Bequerel
MeCN	Acetonitrile
MS	Mass spectrometry
MTB	Methyl *tert*-butyl ether
m	Multiple!
mc	Centred multipiet
NH_4Cl	Ammonium chloride
NMR	Nuclear magnetic resonance spectroscopy : chemical shifts (δ) are given in ppm.
q	Quadrupled (quartet)
PMB	para-Methoxybenzyl
RT	Room temperature
s	Singlet
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethyl silyl
THF	Tetrahydrofuran
THP	Tetrahydropyran
UPLC	Ultra performance liquid chromatography

Experimental Part

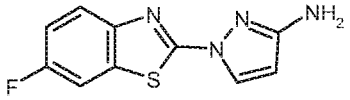
1-(8-Bromo-benzothiazoi-2-yi)-1 H-pyrazo!-3-ylamine 1



A mixture of 2-Ch!oro~6-bromo benzothiazoie (1.0 g, 4.02 mmo!), 3-Amino pyrazole (670 mg, 8.05 mmol) and K_2C0_3 (1.38 g, 10 mmol) in DMF (16 **mL)** was stirred at 120℃ for 3 h under microwave heating. The reaction mixture was poured into water, the precipitate was filtered off, washed with water and purified by chromatography on silica gel to give 470 mg (40%) of compound **1.**

^{1}H-NMR (400 MHz, $CDCi_3$): δ = 8.19 (d, 1H), 7.92 (d, 1H), 7.65 (d, 1H), 7.52 (dd, 1H), 5.97 (d, 1H), 4.04 (br s, 2H) ppm. **LC/MS ES÷ m/z 295.27 (M+1).**

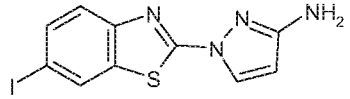
1-(8-Fluoro-benzothiazol-2-yl}-1H-pyrazoS-3-ySamine *2*



A mixture of **2-Chloro-6-fluoro** benzothiazoie (200 mg, 1.07 mmol), 3-Amino pyrazole (178 mg, 2.14 mmol) and K_2C0_3 (885 mg, 6.40 mmol) in DMF (5 mL) was stirred at 100℃ for 24 h. The reaction mixture was poured into water and extracted with ether. The combined organic phases were washed with brine, dried over sodium sulphate, filtrated and concentrated. The residue was purified by chromatography on silica gel to give 130 mg (52%) of compound **2**.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.26 (d, 1H), 7.92 (dd, 1H), 7.77 (dd, 1H), 7.32 (ddd, 1H), 5.97 (d, 1H), 5.73 (br s, **2H)** ppm. **ESI-MS** m/z 235 (M+1).

1-(6-Iodobenzothiazol-2-y!)-1 H-pyrazol-3-ylamine 3

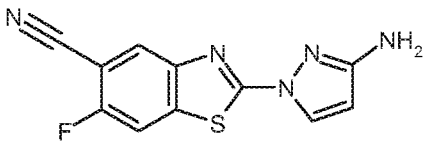


A mixture of 2-chioro-6-iodobenzothiazole (190 mg, 0.64 mmol), 3-amino pyrazole (53 mg, 1.0 mmol) and K_2C0_3 (178 mg, 1.0 mmol) in DMF (0.86 mL) was stirred at 120℃

for 20 minutes under microwave heating. Then additional 3-amino pyrazole (53 mg, 1.0 mmoi) and K_2C0_3 (356 mg, 2.0 mmol) were added and sirring under microwave conditions was continued for one hour. The reaction mixture was poured into water, the precipitate was filtered off, washed with water and purified by chromatography on silica gel to give 8.6 mg (4%) of compound 3.

^{1}H NMR (300 MHz, DMSO-cfe) δ = 5.76 (s, 2 H), 5.97 (d, 1H), 7.55 (d, 1H), 7.73 (d, 1H), 8.26 (d, 1H), 8.39 (s, 1H) ppm. LC/MS ES+ m/z 343.08 (M+1).

2-(3-Amino-1 H-pyrazoi-1 -yi)-8-fiiioro-1 ,3-benzothiazoie-5-carbonitriie 4



Benzoyl chloride (18.5 g, 132 mmol) was added to a solution of ammonium thiocyanate (12 g, 158 mmol) in acetone (350 mL) over 5 minutes and the mixture was refluxed for 15 minutes. 3-Bromo-4-fluoroaniline (25 g, 132 mmol) was added to the mixture at 40℃ and refluxing was continued for 30 minutes. The hot solution was poured over ice (400 mL) and the mixture was stirred for 5 minutes until a precipitate formed, which was collected by filtration and washed with 50% methanol in water (50 mL). To the precipitate was added a 5% sodium hydroxide solution (1000 mL) and the suspension was stirred for 2 hours at 60℃. The mixture was allowed to cool down to room temperature and stored at room temperature for 3 days while a precipitate formed, which was collected by filtration, washed with water and dried under reduced pressure to yield 22.2 g (67%) *1-(3-bromo-4-fluorophenyl)thiourea:*

^{1}H-NMR (300 MHz, DMSO-cfe) δ = 7.34 (dd, 1H), 7.35 (ddd, 1H), 7.59 (br, 2H), 7.85 (dd, 1H) 9.75 (br, 1H) ppm.

1-(3-Bromo-4-fluorophenyi)thiourea (3.77g, 15.1 mmol) was solved in acetic acid (156 mL) and cooled to 10℃. Bromine (3.63 g, 22.7 mmol) in acetic acid (69 mL) was added and after 15 minutes the mixture was heated to 100°C for 2 hours. A solution of sodium bisulphite was added and the mixture was heated shortly to 100℃ under vigorous stirring while the mixture lost its bromine colour. The mixture was concentrated under reduced pressure, the residue suspended in aqueous ammonia and the alkaline mixture was extracted multiple times with dichioromethane. The organic extracts were concentrated and solved in methanol (40 mL). Water (60 mL) was added and the forming precipitate collected by filtration. The precipitate was purified by chromatography on silica gel (ethyl acetate in hexane 12 to 50%) to give 0.90 g (23%)

of *5-bromo-6-fluoro-1,3-benzothiazol-2-amine:* ^{1}H NMR (300 MHz, DMSO-d_6) δ = 7.57 (d, 1H), 7.67 (s, 2H), 7.78 (d, 1H) ppm.

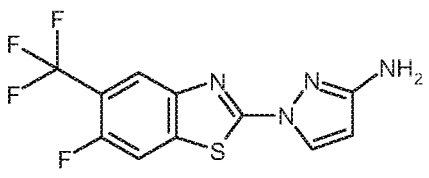
To 5-bromo-6-fluoro-1,3-benzothiazol-2-amine (590 mg, 2.39 mmol) in 1-methylpyrrolidin (3 mL) was added copper(I)cyanide and the mixture was heated to 200 °C for 3 hours. After cooling to room temperature a sodium bicarbonate solution was added and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with saturated NH_4Cl-solution and brine, dried over sodium sulphate and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate in dichloromethane 2 to 40%) and finally triturated with dichloromethane to yield 127 mg (25%) *2-amino-6-fluoro-1,3-benzothiazole-5-carbonitrile as a white solid:* ^{1}H NMR (300 MHz, DMSO-d_6) δ = 7.76 (d, 1H), 7.84 (s, 2H), 7.93 (d, 2H) ppm.

To 2-amino-6-fluoro-1,3-benzothiazole-5-carbonitrile (2 g, 10.3 mmol) in acetonitrile (120 mL) was added copper(II)chloride and the mixture was cooled to 0°C. *Ted.*-butyl nitrite (1.6 g, 15.5 mmol) in acetonitrile (100 mL) was added slowly and the mixture was stirred for 3.5 hours. Ethyl acetate was added and the mixture was washed with saturated NH4Cl-solution, saturated sodium bicarbonate solution, brine and water. After evaporation of the solvent the residue was purified by chromatography on silica gel (dichloromethane in hexane 10 to 50%) to give 250 mg (11%) *2-chloro-6-fluoro-1,3-benzothiazole-5-carbonitrile* as a solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ = 8.35 (d, 2H), 8.67 (d, 1H) ppm.

2-Chloro-6-fluoro-1,3-benzothiazole-5-carbonitrile (75 mg, 0.35 mmol) in DMF was added to a stirred suspension of potassium carbonate (97.5 mg, 0.70 mmol) and 1H-pyrazol-3-amine (29.3 mg, 0.35 mmol) in DMF (0.47 mL) and heated to *80°C* for 6.5 hours. The mixture was poured into ice water and stirred for 10 minutes. The forming precipitate was collected by filtration and washed thoroughly with water. The precipitate was triturated under ultrasonic radiation in a mixture of methanol, ethyl acetate and dichloromethane (1:1:1, 10 mL) to yield 19 mg (19%) of the title compound 4 after filtration.

^{1}H NMR (400 MHz, DMSO-d6) δ = 5.85 (s, 2 H), 6.01 (d, 1 H), 8.23 - 8.28 (m, 2 H), 8.32 (d, 1H) ppm. ESI-MS m/z 260 (M+1).

1-[6-Fluoro-5-(trifluoromethyl)-1,3-benzothiazol-2-yl]-1H-pyrazol-3-amine 5



Benzoyl chloride (1.53 g, 10.8 mmol) was added to a solution of ammonium thiocyanate (0.94 g, 12.4 mmol) in acetone (17 mL) over 5 minutes and the mixture was refluxed for 15 minutes. 2-Bromo-4-fluoro-5-(trifiuoromethyl)aniline (2.0 g, 7.7 mmol) in acetone (14 mL) was added to the mixture at 40℃ and refluxing was continued for 90 minutes. The hot solution was poured over ice (100 mL) and the mixture was stirred for 5 minutes until a precipitate formed, which was collected by filtration and washed with 50% methanol in water (30 mL). To the precipitate was added a 5% sodium hydroxide solution (100 mL) and the suspension was stirred for 2 hours at 80℃. The mixture was allowed to cool down to room temperature and extracted with diethyl ether and ethylacetate. The combined organic extracts were washed with brine and concentrated under reduced pressure to yield 2.37 g (96%) *1-[2-bromo-4-fluoro-5-(trifluoromethyl)phenyi]thiourea:*

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.45 (br., 2H), 7.96 (d, 1H), 8.01 (d, 1H), 9.42 (s, 1H) ppm.

To 1-[2-Bromo-4-fluoro-5-(frifiuoromethyi)phenyl]thioure (1.0g, 3.15 mmol) which was dried under high vacuum and flushed with argon, were added caesium carbonate (2.0 g, 6.3 mmol), copper(l)iodide (30 mg, 0.16 mmol), DL-proline (36 mg, 0.32 mmol) and DMSO (11 mL). The mixture was stirred at room temperature while the addition of copper(i)iodide (30 mg, 0.16 mmol), DL-proiine (36 mg, 0.32 mmol) and DMSO (5 mL) was repeated after 30, 60, 120 and 150 minutes. After 3 hours the mixture was quenched with a saturated NH_4Cl-solution ice water mixture and stirred for 5 minutes and then basified with aqueous ammonia. The aqueous phase was multiple times extracted with dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulphate and evaporated under reduced pressure to yield after trituration with 10% dichloromethane in hexane 580 g (74%) of *6-fluoro-5-(trifluoromethyl)-1,3-benzothiazol-2-amine:*

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.53 (d, 1H), 7.76 (s, 2H), 7.88 (d, 1H) ppm.

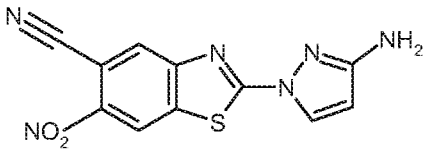
To 6-fluoro-5-(trifluoromethyl)-1 ,3-benzothiazol-2-amine (220 g, 0.93 mmol) in acetonitrile (18 mL) was added copper(li)chioride (188 mg, 1.4 mmol) and the mixture was cooled to 0℃. Tert.-butyl nitrite (144 mg, 1.4 mmol) in acetonitrile (9 mL) was added slowly and the mixture was stirred for 30 minutes at 0℃ and additional 3.5 hours at room temperature. The mixture was diluted with ethyl acetate, washed with saturated NH_4Cl-solution, with saturated sodium bicarbonate solution, brine and water. Evaporation yields 100 mg (35%) of *2-chloro-6-fluoro-5-(trifluoromethyl)-1,3-benzothiazole:*

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.37(d, 1H), 8.43 (d, 1H) ppm.

2-Chloro-6-fluoro-5-(trifluoromethyl)-1 ,3-benzofhiazole (100 mg, 0.39 mmol) in DMF (3.2 mL) and aeetonitrile (3.2 mL) was added to a stirred suspension of caesium carbonate (81 mg, 0.59 mmol) and I H-pyrazol-3-amine (39 mg, 0.47 mmol) in DMF (2.1 mL) and acetonitrile (2.1 mL) and heated to 70°C for 90 minutes. Additional caesium carbonate (81 mg, 0.59 mmol) was added after 15, 30, 45, 60, and 75 minutes. The mixture was poured into ice water and stirred for 10 minutes. The forming precipitate was collected by filtration and washed with water to yield 55 mg (44%) of the title compound **5.**

^{1}H NMR (400 MHz, **DMSO-cfe)** δ = 5.84 (s, 2H), 6.01 (d, 1H), 8.09 (d, 1H), 8.24 (d, **1H)** 8.25 (d, 1H) ppm. **ESSMS** m/z 303 **(M+1).**

2-(3-Amino-1 H-pyrazoi-1 -yi)-8-nitro-1 ,3-benzothiazoie-5-carborsitriie 6



Benzoyl chloride (6.4 mL, 54.9 mmol) was added to a solution of ammonium thiocyanate (5.0 g, 65.5 mmol) in acetone (174 mL) and the mixture was refluxed for 15 minutes. **1,5-Dibromo-4-nitroaniline** (11.6 g, 39.2 mmol, C. Wang *et ai. Synthesis* **2003,** *13,* 2089-2095) was added to the mixture at **40°C** and refluxing was continued for 14 hours. The hot solution was poured over ice (2000 mL) and the mixture was stirred for 5 minutes until a precipitate formed, which was collected by filtration and washed **with** 50% methanol in water (100 mL). To the precipitate was added a 5% sodium hydroxide solution (400 mL) and the suspension was stirred for 4 hours at 60°C. The mixture was allowed to cool down to room temperature and filtered. The filtrate was washed with diethyl ether then thoroughly extracted with a ethyl acetate in diethyl mixture (50%). The combined extracts were dried over sodium sulphate and evaporated under reduced pressure to yield 8.92 g (61 %) *1-(2,5-Dibromo-4-nitrophenyl)thiourea:* **^{1}H** NMR (300 MHz, **DMSO-cfe)** δ = 7.82 **(br.** s., 1 H) 8.40 (br. s., 1 **H)** 8.41 (s, 1 H) 8.45 (s, 1 H) 9.57 (br, 1H) ppm.

To 1-(2,5-dibromo-4-nitrophenyl)thiourea (2.9 g, 8.17 mmol), which was dried under high vacuum and flushed with argon, **were** added caesium carbonate (5.32 g, 16.3 mmol), copper(l)iodide (77.8 mg, 0.41 mmol), DL-proline (94 mg, 0.82 mmol) and DMSO **(30m L).** The mixture was stirred at room temperature while the addition of copper(l)iodide (77.8 mg, 0.41 mmol), DL-proiine (94 mg, 0.82 mmol) and DMSO (1QmL) was repeated after 30, 60 and 90 minutes. After 2 hours the mixture was

quenched with a saturated NH_4Cl-solution ice water mixture and stirred for 5 minutes and then basified with aqueous ammonia. The aqueous phase was multiple times extracted with a dichloromethane - methanol mixture (10:1). The combined organic extracts were washed with brine, dried over sodium sulphate and evaporated under reduced pressure to yield 2.84 g (98%) of *5-bromo-6-nitro-1,3-benzothiazol-2-amine:* ^1H NMR (400 MHz, DMSO-d_6) δ = 7.65 (s, 1H) 8.29 (s, 2H) 8.51 (s, 1H) ppm.

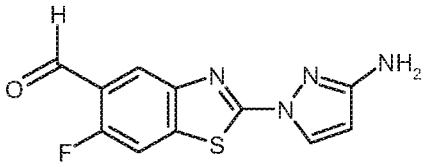
To 5-bromo-6-nitro-1 ,3-benzothiazo!-2-amin (2.14g, 8.35 mmol) in acetonitrile (180 mL) was added copper(i i)chloride (1.24 g, 9.2 mmol) and the mixture was cooled to O'C. Tert.-butyl nitrite (1.29 g, 12.5 mmol) in acetonitrile (52 mL) was added slowly and the mixture was stirred for 30 minutes at 0℃ and addit ional 2 hours at room temperature. The mixture was diluted with ethyl acetate, washed with saturated NH_4Cl-soiution, with saturated sodium bicarbonate solution, brine and water. After evaporation of the solvent the residue was purified by chromatography on silica gel (dichloromethane in hexane 70%) to give 1.28 g (52%) *5-bromo-2-chloro-6-nitro-1,3-benzothiazole:* ^1H NMR (400 MHz, DMSO-cfe) δ = 8.56 (s, 1H), 8.92 (s, 1H) ppm.

5-Bromo-2-chloro-6-nitro-1 ,3-benzothiazole (500 mg, 1.7 mmol) in DMF (14 mL) and acetonitrile (14 mL) was added to a stirred suspension of caesium carbonate (353 mg, 2.56 mmol) and 1H-pyrazol-3-amine (170 mg, 2.04 mmol) in DMF (9 mL) and acetonitrile (9 mL) and heated to 50℃ for 30 minut es. Additional caesium carbonate (176 mg, 1.27 mmol) was added and stirring was continued for 60 minutes at 50℃ and 90 minutes at 70℃. The mixture was poured into ice water and stirred for 10 minutes. The forming precipitate was coliected by extractions with ethyl acetate, the organic phase was washed with brine, concentrated under reduced pressure and purified by chromatography on silica gel (ethyl acetate in dichloromethane 0 to 20% + 0.2% triethylam ine) to yield 300 mg (49%) *1-(5-bromo-6-nitro-1,3-benzothiazol-2-yl)-1H-pyrazol-3-amine:* ^1H NMR (300 MHz, DMSO-d_6) δ = 5.98 (s, 2H), 6.05 (d, 1H), 8.18 (s, 1H), 8.28 (d, 1H), 8.84 (s, 1 H) ppm.

To 1-(5-bromo-6-nitro-1 ,3-benzothiazol-2-yl)-1 H-pyrazol-3-amine (200 mg, 0.59 mmol) in 10 ml 1,2-dimethylimidazoie was added copper(l)cyanide (68 mg, 0.76 mmol). The microwave vessel was closed and radiated in a microwave reactor (CEM discover) at 100℃ for 10 minutes and additional 3 hours at 120° C. The reaction mixture was treated with saturated sodium bicarbonate solution and extracted with an ethyl acetate diethyl ether mixture (1:1). The extract was washed with brine concentrated under reduced pressure and taken up in hexane (300 mL) and dichloromethane (50 mL) and stirred. The forming precipitate was collected by filtration and purified by chromatography on silica gel (ethyl acetate in dichloromethane 0 to 20% + 0.2% triethylamine) to yield 26 mg (13%) of the title compound 6.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.01 (br, 2 H) 6.09 (d, 1H) 8.33 (d, 1 H) 8.45 (s, 1 H) 9.23 (s, 1 H) ppm. ESI-MS m/z 287 (M+1).

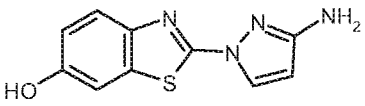
2-{3-Amino-1H-pyrazol-1-yl)-6-fiuoro-1,3-benzothiazoie-5-carbaidehyde **10**



A 1M solution of diisobutyl aluminium hydride in toluene (0.93 mL, 0.93 mmol) was added to a solution of 2-(3-amino-1H-pyrazol-1-yl)-6-fluoro-1 ,3-benzothiazole-5-carbonitrile (40 mg, 0.154) in THF (mL) at -30℃ and stirred for 3 hours. Acetone (1ml_) was added and the mixture was quenched with saturated sodium tartrate solution. After multiple extractions with ethyl acetate the organic phase was concentrated under reduced pressure and purified by chromatography on silica gel (ethyl acetate in dichloromethane 0 to 33%) to yield 4.5 mg (12%) of the title compound 10.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 4.08 (br., 2H), 6.00 (d, 1H), 7.61 (d, 1H), 8.21 (d, 1H), 8.25 (d, 1H), 10.41 (s, 1H) ppm. **LC/MS** ES÷ m/z 262.9 (M+1).

2-(3-Amino-pyrazoS-1-yi)-benzothiazof-6-ol 11



A mixture of 2-Chloro-6-methoxy benzothiazoie (500 mg, 2.5 mmol), 3-Amino pyrazole (416 mg, 5.0 mmol) and K_2C0_3 (1.38 g, 10 mmol) in DMF (10 mL) was stirred at 100℃ for 24 h. The reaction mixture was poured into water and extracted with dichloromethane. The combined organic phases were washed with brine, dried over sodium sulphate, filtrated and concentrated. The residue was purified by chromatography on silica gel to give 270 mg (44%) of *1-(6-methoxy-benzothiazoi-2-yl)-1H-pyrazol-3-ylamine.*

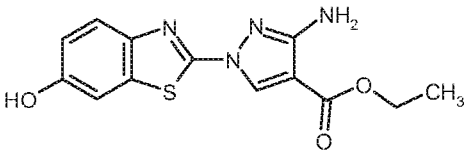
^{1}H-NMR (300 MHz, d6-DMSG): δ = 8.18 (d, 1H), 7.62 (d, 1H), 7.55 (d, 1H), 7.00 (dd, 1H), 5.88 (d, 1H), 5.60 (br s, 2H), 3.77 (s, 3H) ppm. **ESI-MS** m/z 247 (M+1).

1-(6-Methoxy-benzothiazol-2-yl)-1H-pyrazol-3-ylamine (179 mg, 0.73 mmol) was suspended in dichloromethane (11 mL) and BBr_3 (1M in CH_2Cl_2, 11 mL, 11 mmol) was added slowly at OX. After 4h methanol was slowly added and the mixture was stirred

for another 10 min and then concentrated. The residue was taken up in methanol again and the precipitate was filtered off and purified by chromatography on silica gel to give 167 mg (99%) of compound **11.**

^{1}H-NMR (300 MHz, d6-DMSO): δ = 9.60 (s, 1H), 8.15 (d, 1H), 7.52 (d, 1H), 7.26 (d, 1H), 6.84 (dd, 1H), 5.86 (d, 1H), 5.57 (br s, 2H) ppm. ESI-MS m/z 233 (M+1).

3-Amino-1 -{6-hydroxy-benzothiazol-2-yl}-1 H-pyrazole-4-carboxylic acid ethyl ester 12



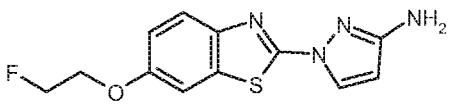
A mixture of 3-amino-1 H-pyrazole-4-carboxylic acid ethyl ester (730 mg, 4.71 mmol), potassium carbonate (1.3g, 9.42 mmol) and 2-Chloro-6-methoxy benzothiazole (940 mg, 4.71 mmol) in DMF (20 mL) was stirred for 30 h at 80°C poured into water and extracted with dichloromethane. The combined organic phases were washed with brine, dried over sodium sulphate, filtrated and concentrated. The residue was purified by chromatography on silica gel to give 738 mg (49%) of *3-amino-1-(6-methoxy-benzothiazol-2-yl)-1H-pyrazole-4-carboxylic acid ethyl ester.*

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.69 (s, 1H), 7.78 (d, 1H), 7.33 (d, 1H), 7.10 (dd, 1H), 5.1 (br s, 2H), 4.37 (q, 2H), 3.92 (s, 3H), 1.41 (t, 3H) ppm. **ESI-MS** m/z 319 (M+1).

3-Amino-1 -(6-methoxy-benzothiazol-2-yl)-1 H-pyrazole-4-carboxylic acid ethyl ester (50 mg, 0.16 mmol) was suspended in dichloromethane (1.5 mL) at 0°C and treated with tribromo-borane (1M in dichloromethane, 1.57 mL, 1.57 mmol). After dissolving and complete conversion, methanol was added and the reaction mixture was stirred 10 min at RT followed by evaporation of the solvent in vacuum. The residue was taken up in methanol and concentrated again twice. The final residue was purified by chromatography on silica gel to give 16.5 mg (34%) of compound 2a.

^{1}H-NMR (300 MHz, MeOD): δ = 8.60 (s, 1H), 7.62 (d, 1H), 7.23 (d, 1H), 6.94 (dd, 1H), 4.30 (q, 2H), 1.35 (t, 3H) ppm. ESI-MS m/z 305 (M+1), 303 (M-1).

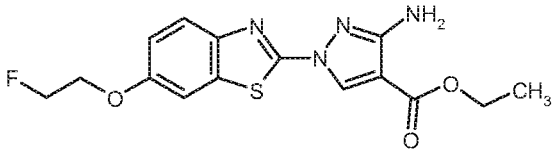
1-[6-(2-Fluoro-ethoxy)-benzothiazol-2-yl]-1 H-pyrazol-3-ylamine 13



2-(3-Amino-pyrazol-1 -y!)-benzothiazo!-6-o! 2 (50 mg, 0.22 mmo!) was solved in DMF (1 m!_) and treated with Fluoro-2-iodethane (45 mg, 0.26 mmo!) and Cs_2C0_3 (168 mg, 0.52 mmol). After 24 h at RT, the reaction mixture was poured into water and the precipitate was filtered off, washed with water and dried to yield 38 mg (63%) of compound 13.

^{1}H-NMR (300 MHz, **(J6-DMSO):** δ = 8.18 (d, 1H), 7.63 (d, 1H), 7.60 (d, 1H), 7.04 (dd, 1H), 5.89 (d, 1H), 5.61 (br s, 2H), 4.80 (dd, 1H), 4.65 (dd, 1H), 4.30 (dd, 1H), 4.20 (dd, **1H)** ppm. **ESI-Mss m/z 279 (M+1).**

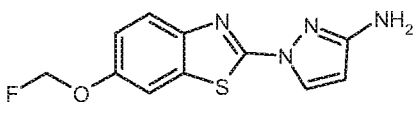
3-**Amino-1** -[**6**-{**2-fSuoro-ethoxy)-benzothiazoi -2-yi]-1 H-pyrazole-4-carboxyiic acid ethyl ester 14**



A mixture of 3-amino~1 -(6-hydroxybenzothiazol-2~yl)-1 H-pyrazoie-4-carboxyiic acid ethyl ester **12** (100 mg, 0.33 mmol), **Cs_2C0_3** (257 mg, 0.79 mmol) and **fluoro-2-**iodethane (69 mg, 0.39 mmol) in DMF (2 mL) was stirred at RT for 1 h. The reaction mixture was taken up in ethyl acetate and water followed by phase separation. The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed with brine, dried over sodium sulphate, filtrated and concentrated. The residue was purified by chromatography on silica gel to yield 76 mg (66%) of compound **14.**

^{1}H-NMR (300 MHz, **d6-DMSO):** δ = 8.61 (s, 1H), 7.73 (d, 1H), 7.66 (d, 1H), 7.11 (dd, **1H),** 6.03 (br s, 2H), 4.81 (dd, **1H),** 4.65 (dd, 1H), 4.32 (dd, 1H), 4.22 (m, 4H), 1.27 (t, 3H) ppm. **ESI-MS** m/z 351 .27 **(M+1).**

1-(8 -Fluorometh0xy-benz0thiazoi-2-yS)-1 H-pyrazol-3-ylamine 15

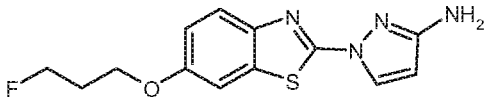


2-(3-Aminopyrazoi-1 -yl)-benzothiazol-6-ol 11 (50 mg, 0.22 mmol) was solved in DMF (1 mL) at **10**℃ and treated with NaH (10 mg, 0.46 mmol, 60%) for **1h.** Bromo

fluoromethane (111 mg, 0.99 mmol) was solved separately in DMF (1 mL) and added slowly. The reaction mixture was stirred at RT for 20 min and poured into water. The precipitate was filtered off, washed with water and purified by thin layer chromatography on silica gel to yield 18.6 mg (33%) of compound **15**.

^{1}**H-NMR** (400 MHz, $CDCl_3$): δ = 8.19 **(d,** 1H), 7.74 (d, **1H),** 7.52 (d, 1H), 7.19 **(dd, 1H),** 5.95 (d, 1H), 4.04 (br s, 2H), 5.75 (d, 2H) ppm. **LC/MS ES+ m/z 265.11 (M+1).**

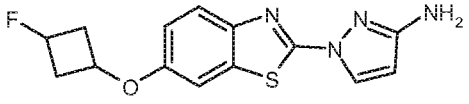
1-[6-{3-FlL!oro-propoxy)-benEothiazo!-2-y[]-1 H-pyrazoi-3-yiamine 16



2-(3-Amino-pyrazol-1-yl)-benzothiazol-6-ol 11 (50 mg, 0.22 mmol) was solved in DMF (1 mL) and treated with Cs_2C0_3 (168 mg, 0.52 mmol) and **1-bromo-3-fluoropropane** (36,4 mg, 0.26 mmol). The reaction mixture was stirred RT for 3h min and poured into water. The precipitate was filtered off, washed with water and purified by thin layer chromatography on silica gel to yield 18.6 mg (33%) of compound **16.**

^{1}**H-NMR** (400 MHz, d6-DMSO): δ = 8.18 (d, 1H), 7.62 (d, 1H), 7.58 (d, 1H), 7.01 (dd, 1H), 5.88 (d, 1H), 5.61 (br s, 2H), 4.59 (ddd, 2H), 4.09 (t, **2H),** 2.09 (dddd, 2H) ppm. **LC/MS ES+** m/z 293.08 **(M+1).**

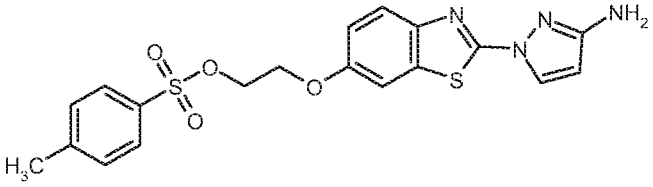
1-[6-{3-FlL!oro-cyc!obutoxy)-benzothiazoi-2-yi]-1 H-pyrazol-3-ylamine 17



Toiuene-4-suifonic acid **3-[2-(3-amino-pyrazol-1**-yi)-benzothiazol-6-yloxy]~cyclobutyi ester **4d** (35 mg, 0.077) was solved in THF (1mL). TBAF (36 mg, 0.11 mmol) was added and the reaction mixture was stirred at 75^ for 5h. The mixture was concentrated and the residue was purified by chromatography on silica gel to give 10 mg (43%) of **17.**

^{1}**H-NMR** (300 MHz, $CDCl_3$): δ = 8.18 (d, 1H), 7.70 (d, 1H), 7.16 (d, 1H), 6.96 (dd, 1H), 5.94 (d, 1H), 4.86 (dddd, 1H), 4.28 **(m,** 1H), 4.00 (br s, 2H), 3.06 (m, 2H), 2.50 (m, 2H) ppm. **LC/MS ES+** m/z 305.16 (M+1).

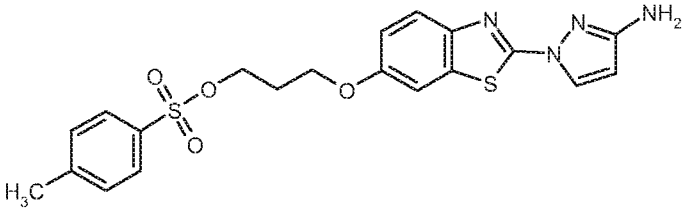
Toluene-4-sulfonic acid 2-[2-{3-arnino-pyrazoi-1-yi)-benzothiazoi-6-yioxy]-athy[ester 18



2-(3-Amirso-pyrazol-1-yl)-benzoihiazol-8-oi 2 (50 mg, 0.22 mmol) was solved in DMF (1 m!_) and treated with Cs_2C0_3 (105 mg, 0.32 mmol) and Ethylenglyeoi-di-(p-toluenesLiifonate) (399 mg, 1.08 mmol). The reaction mixture was stirred at 50° for 2h and poured into saturated NH_4Cl solution. The precipitate was filtered off, washed with water and purified by chromatography on silica gel to yield 27 mg (29%) of compound 18.

^{1}H-NMR (400 MHz, d6-DMSO): δ = 8.18 (d, 1H), 7.75 (d, 2H), 7.59 (d, 1H), 7.46 (d, 1H), 7.42 (d, 2H), 6.89 (dd, 1H), 5.89 (d, 1H), 5.62 (br s, 2H), 4.32 (m, 2H), 4.17 (m, 2H), 2.36 (s, 3H) ppm. LC/MS ES÷ rn/z 431 .35 (M+1).

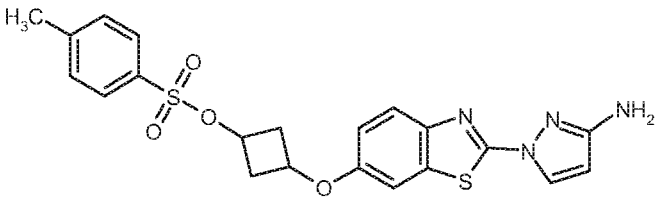
Toluene-4-sulfonic acid 3-[2-(3-amino-pyra.*ol-1 -yl)-benzothiazoi-6-yioxy]-propyl ester 20



2-(3-Amino-pyrazol-1-yl)-benzothiazoi-6-ol 11 (50 mg, 0.22 mmol) was solved in DMF (1 mL) and treated with Cs_2C0_3 (105 mg, 0.32 mmol) and 1,3-propanediol-di-(p-toluenesuifonate) (413 mg, 1.08 mmol). The reaction mixture was stirred at 50° for 2h and poured into saturated NH_4Cl solution. The precipitate was filtered off, washed with water and purified by chromatography on silica gel to yield 37 mg (38%) of compound 20.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.18 (d, 1H), 7.75 (d, 2H), 7.67 (d, 1H), 7.22 (d, 2H), 7.12 (d, 1H), 6.88 (dd, 1H), 5.94 (d, 1H), 4.27 (t, 2H), 4.00 (br s, 2H), 3.99 (t, 2H), 2.33 (s, 3H), 2.14 (p, 2H) ppm. LC/MS ES+ m/z 445.20 (M+1).

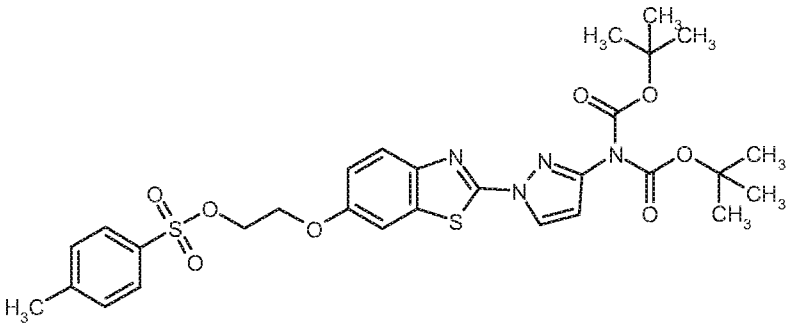
Toluene-4-stsifonic acid 3-[2-{3-amino-pyrazoS-1 -yi)-benzothiazoi-6-yioxy]-cyclobutyl ester 21



2-(3-Aminopyrazol-1 -yl)-benzothiazol-6-ol 11 (120 mg, 0.52 mmol) was solved in DMF (3 mL) and treated with Cs_2CO_3 (252.5, 0.77 mmol) and 1,3-cyclobutanediol bis(4-methylbenzenesulfonate) (205 mg, 0.52 mmol). The reaction mixture was stirred at 40° for 11h and poured into saturated NH_4Cl solution. The precipitate was filtered off, washed with water and purified by chromatography on silica gel to yield 75 mg (32%) of compound **21.**

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, 1H), 7.80 (d, 2H), 7.67 (d, 1H), 7.36 (d, 2H), 7.05 (d, 1H), 6.88 (dd, 1H), 5.93 (d, 1H), 5.08 (m, 1H), 4.85 (m, 1H), 4.00 (br s, 2H), 2.67 (m, 2H), 2.56 (m, 2H), 2.46 (s, 3H) ppm. LC/MS ES+ m/z 457.17 (M+1).

Toiuene-4-suifonic acid 2-[2-{3-ds-tert-butoxycarbonyiamino-pyrazo!-1 -yi)-**benzothiazol-6-yloxy]-ethyl ester 22**

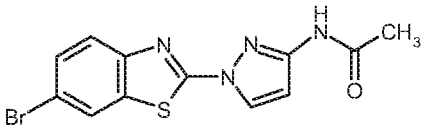


Toluene-4-sulfonic acid 2-[2-(3-aminopyrazol-1 -yl)benzothiazol-6-yloxy]ethyl ester 18 (100 mg, 0.23 mmol) was solved in dichloromethane (3 mL). Boc_20 (200 mg, 0.93 mmol), triethyiamine (94 mg, 0.93 mmol) and DMAP (6 mg, 0.05 mmol) were added.

The reaction mixture was stirred at SO℃ for 4h and concentrated. The residue was purified by chromatography on siiica gel to yieid 88 mg (60%) of 22.

^{1}H-NMR (400 MHz, $CDCi_3$): δ = 8.37 (d, 1H), 7.82 (d, 2H), 7.74 (d, 1H), 7.34 (d, 2H), 7.17 (d, 1H), 6.95 (dd, 1H), 6.43 (d, 1H), 4.41 (t, 2H), 4.22 (t, 2H), 2.44 (s, 3H), 1.48 (s, 18H) ppm. **LC/MS** ES÷ m/z 631.38 (M+1).

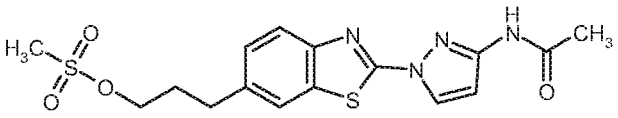
N-[1-(6-Brorno-benzothsazoS-2-yS)-1 H-pyrazoi-3-yi]-aeetamide **23**



1-(6-Bromobenzothiazol-2-yl)-1 H-pyrazol-3-ylam ine 1 (50 mg, 0.17mmol) was soived in pyridine (1 mL). Acetic acid anhydride (0.048 mL, 0.51 mmoi) and DMAP (6 mg, 0.05 mmol) were added. The reaction mixture was stirred at RT for 20h and poured into saturated NH_4CI solution. The precipitate was filtered off, washed with water and purified by chromatography on silica gel to yield 38 mg (67%) of compound 23.

^{1}H-NMR (300 MHz, d6-DMSO): δ = 10.98 (s, 1H), 8.51 (d, 1H), 8.32 (d, 1H), 7.77 (d, 1H), 7.62 (dd, 1H), 6.94 (d, 1H), 2.03 (s, 3H) ppm. LC/MS ES+ m/z 237.23 (M).

Methanesuifonic acid 3-[2-{3-amino-pyrazoS-1 -yi)-benzothiazoi-6-yi]-propyi ester 24



Aiiyi alcohol (62.52 µL, 0.92 mmoi) was soived in THF (3mL) at 0℃. 9-BBN (5.52 mL, 2.76 mmoi, 0.5M in THF) was slowly added. The reaction mixture was stirred at RT for 17h.

N-[1-(6-Bromo-benzofhiazol-2-yl)-1 H-pyrazol-3-yi]-acetamide 23 (155 mg, 0.46 mmol) was suspended in DMF (2mL). $Pd(Ph_3)_4$ (106 mg, 0.092 mmoi) and potassium carbonate (0.8 mL, 2.4 mmol, 3M in water) were added.

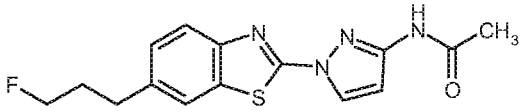
Both reaction mixtures were brought together and stirred at 65℃ for 4h. The solution was concentrated and the residue was solved in ethylacetate, washed with brine, dried over sodium sulphate and concentrated again. The residue was purified by chromatography on silica gel to give 86 mg (59%) of *N-{1-[6-(3-Hydroxypropyl)-henzothiazol-2-yl]-1H-pyrazol-3-yl}-acetamide.*

^{1}H-NMR (400 MHz, d6-DMSO): δ = 10.96 (s, 1H), 8.50 (d, 1H), 7.84 (d, 1H), 7.74 (d, 1H), 7.31 (d, 1H), 6.91 (d, 1H), 4.47 (t, 1H), 3.39 (m, 2H), 2.70 (t, 2H), 2.03 (s, 3H), 1.73 (m, 2H) ppm. LC/MS ES÷ m/z 217.16 (M+1).

N-{1-[6-(3-Hydroxy-propyl)-benzothiazol-2-yl]-1H-pyrazol-3-yl}-acetamide (120 mg, 0.38 mmol) was solved in dichloromethane (5 ml_) at 0°C. Methanesulfonyl chloride (0.059 mL, 0.76 rrirno!) and triethyiamine (0.21 rnL, 1.52 mmol) were added. The reaction mixture was stirred for 2 h at RT, diluted with diehiormethane, washed with saturated NH_4CI-soiution and brine, dried over sodium sulphate and concentrated. The residue was purified by chromatography on silica gel to give 85 mg (57%) of 24.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, 1H), 7.89 (s, 1H), 7.79 (d, 1H), 7.64 (s, 1H), 7.31 (d, 1H), 7.07 (d, 1H), 4.26 (t, 1H), 3.01 (s, 2H), 2.88 (t, 2H), 2.21 (s, 3H), 2.14 (m, 2H) ppm. **LC/MS** ES÷ m/z 395.18 (M+1).

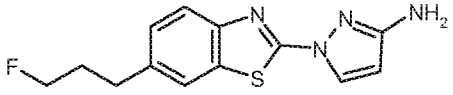
N-{1-[6-(3-Fluoropropyl)-benzothiazol-2-yl]-1H-pyraz©!-3-yl}aeetamide 25



Methanesuifonic acid 3-[2-(3-amino-pyrazol-1-yl)-benzothiazoi-6-ylj-propyl ester 24 (80 mg, 0.2 mmol) was solved in THF (3 mL). TBAF (96 mg, 0.3 mmol) was added and the reaction mixture was stirred at 75°C for 5h and con centrated. The residue was purified by chromatography on silica gel to give 30 mg (47%) of 25.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, 1H), 7.89 (s, 1H), 7.79 (d, 1H), 7.64 (s, 1H), 7.31 (d, 1H), 7.07 (d, 1H), 4.48 (dt, 2H), 2.88 (t, 2H), 2.21 (s, 3H), 2.08 (m, 2H) ppm. LC/MS ES÷ m/z 319.24 (M+1).

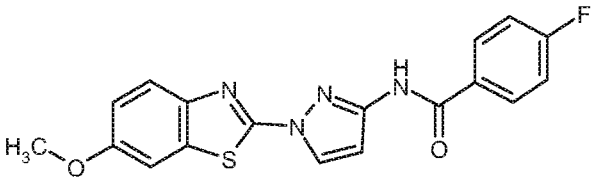
1-[6-{3-FStsoro-propyi)-benzothiazoi-2-yi]-1 H-pyrazoi-3-ylamine 26



N-{1-[6-(3-Fluoropropyl)-benzothiazol-2-yl]-1H-pyrazol-3-yl}acetamide 25 (30 mg, 0.09 mmol) was stirred for 48 hours in 0.5 M solution of sodium hydroxide in ethanol (0.5 ml, 0.25 mmol) and then heated to 40°C for 8 hours. (3 mL). The reaction mixture was neutralized with 1 M hydrochloric acid and concentrated. The residue was purified by chromatography on silica gel to give 3.7 mg (14 %) of compound 26.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.99 - 2.16 (m, 2 H), 2.82 - 2.92 (m, 2 H), 4.03 (br. s., 2 H), 4.43 (t, 1 H), 4.55 (t, 1 H), 5.96 (d, 1 H), 7.29 (d, 5 H), 7.63 (d, 1 H), 7.74 (d, 1 H), 8.22 (d, 1 H) ppm. LC/MS ES÷ m/z 277.19 (M+1).

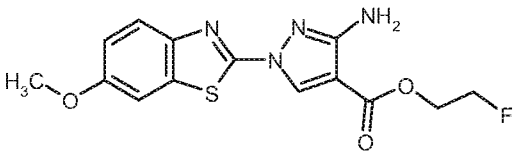
4-Fluoro-N-[1-(6-methoxy-benzothiazol-2-yl)-1H-pyrazoS-3-yl]-benzamida 27



1-(6-Methoxy-benzothiazol-2-yl)-1 H-pyrazol-3-ylamine (145 mg, 0.59 mmol) was solved in pyridine (4 m!_). 4-Fluorobenzoylchloride (0.097 mL, 0.82 mmol) was added. The reaction mixture was stirred at RT for 45 min followed by the addition of heptane (30 mL). After 10 min the precipitate was filtered off, washed with heptane and purified by chromatography on silica gel to give 88 mg (41 %) of compound **27.**

^{1}H-NMR (400 MHz, d6-DMSO): δ = 11.41 (s, 1H), 8.56 (d, 1H), 8.10 (dd, 2H), 7.75 (d, 1H), 7.65 (d, 1H), 7.33 (dd, 2H), 7.08 (m, 2H), 3.80 (s, 3H) ppm. ESI-MS m/z 369.19 (M+1).

3-Amino-1 -(6-methoxy-benzothiazoi-2-yi)-1 H-pyrazole-4-carboxyiic acid 2-fluoro-ethyi ester 34



3-Amino-1 -(6-methoxy-benzothiazol-2-yl)-1 H-pyrazole-4-carboxylic acid ethyl ester (150 mg, 0.47 mmol) was solved in ethanol (6 mL) and treated with sodium hydroxide (760 mg, 18.84 mmol). After stirring the suspension for 48 h, 2N HCl was added until pH3, the precipitate was filtrated, washed with water and 6 mL cold dichloromefhane/efhanoi 1/1 and dried in vacuum to yield 88 mg (65%) of *3-Amino-1-(6-methoxy-benzoihiazoi-2-yl)-1H-pyrazole-4-carhoxylic acid.*

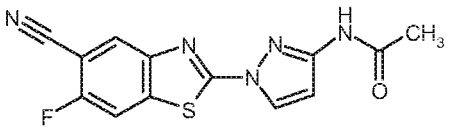
^{1}H-NMR (300 MHz, d6-DMSO): δ = 8.55 (s, 1H), 7.72 (d, 1H), 7.62 (d, 1H), 7.06 (dd, 1H), 5.99 (br s, 2H), 3.79 (s, 3H) ppm. ESI-SVSS m/z 291.21 (M+1).

To a mixture of 3-amino-1 -(6-methoxy-benzothiazoi-2-yi)-1 H-pyrazole-4-carboxylic acid **13** (84 mg, 0.29 mmol), 2-fiuorethanol (20 mg, 0.32 mmol) and BOP (141 mg, 0.32

mmol) in DMF (5 mL) was slowly added N-Ethyl-N,N-diisopropylamine. After stirring for 30 h at 50℃, the mixture was concentrated and the residue was purified by chromatography on silica gel to give 4 mg (4%) of compound **12.**

^{1}**H-NMR** (300 MHz, d6-DMSO): δ = 8.71 (s, 1H), 7.78 (d, **1H),** 7.69 (d, **1H),** 7.12 (dd, **1H), 6.10** (br s, **2H),** 4.83 (dd, 1H), 4.67 (dd, 1H), 4.53 (dd, 1H), 4.45 (dd, 1H), 3.84 (s, 3H) ppm. ESI-MS **m/z** 337.4 **(M+1).**

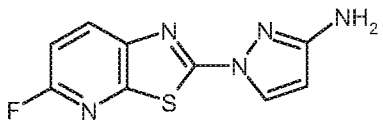
N-[1-(5-Cyano-6-fiuorobenzothiazoi-2-yi)-1 H-pyrazo!-3-yl]-acetamide 35



2-Chloro-6-fluoro-1,3-benzothiazole-5-carbonitrile (50 mg, 0.24 mmol) in DMF (0.15 ML) was added to a stirred suspension of potassium carbonate (65 mg, 0.47 mmol) and **3-**acetyiam inopyrazoi (29.4 mg, 0.24 mmol) in DMF (0.32 mL) and stirred for 1 hour at room temperature. The mixture was poured into ice water and stirred for 10 minutes. The forming precipitate was collected by filtration and washed thoroughly with water. The residue was purified by chromatography on silica gel (ethyl acetate in dichioromethane 5 to 95%) to yield 41 mg (19%) of the title compound.

^{1}H-NMR (400 MHz, **DMSO-cfe)** δ = 2.07 (s, 3 H), 7.00 **(d,** 1 H), 8.31 (d, 1 H), 8.48 **(d,** 1 H), 8.56 (d, 1 H), 11.05 (s, 1 H) ppm. ES!-iV!S m/z 300 **(M-1).**

1-(6-FSuoroihiazoSo[5,4-b]pyridin-2-y[)-1 H-pyraz;oi-3-arnina 36



Benzoyl chloride (5.8 mL, 50 mmol) was added to a solution of ammonium thiocyanate (4.35 g, 57 mmol) in acetone (79 mL) and the mixture was refluxed for 15 minutes. 6-**Fluoropyridin-3-amine** (4.0 g, 35.7 mmol) in acetone (52 mL) was added to the mixture at **40**℃ and refluxing was continued for 1.5 hours. The hot solution was poured over ice water (400 mL) and the mixture was stirred for 5 minutes until a precipitate formed, which was collected by filtration and washed with 50% methanol in water (50 mL). To the precipitate was added a 5% sodium hydroxide solution (200 mL) and the suspension was stirred for 2.5 hours at 60℃. The **m**ixture was allowed to cool down to room temperature and then thoroughly extracted with ethyl acetate. The combined

extracts were washed with brine, dried over sodium sulphate and evaporated under reduced pressure to yield 5.9 g (91 %) *1-(6-fluoropyridin-3-yi)thiourea:*

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 7.15 (dd, 1H), 7.40 -7.90 (br, 2H), 8.05 (ddd, 1H), 8.17 (dd, 1H), 9.82 (br. s., 1H) ppm.

1-(6-f!uoropyridin-3-y!)thiourea: (1.0 g, 5.8 mmol) was solved in acetic acid (56 ml_) and bromine (1.21 g, 7.6 mmol) in acetic acid (57 mL) was added over 30 minutes. The mixture was heated to Ioo℃ for 2 hours and solid s odium bisulphite was added. The mixture was poured into ice water and stirred vigorously for 5 minutes. Aqueous ammonia was added and the alkaline mixture was extracted multiple times with diethylether and ethyl acetate. The combined organic extracts were washed with consecutively with aqueous ammonium chloride solution and brine, dried over sodium sulphate, evaporated under reduced pressure and purified by chromatography on silica gel (ethyl acetate in dichloromethane 0 to 100%, followed by methanol in ethyl acetate 0 to 20% + 1% triethylamine) to give 73 mg (7%) of *6-fiuorothiazo!o[5,4-b]pyridin-2-amine:*

^{1}H NMR (300 MHz, DMSO-d_6) δ = 7.00 (dd, 1 H), 7.77 (br. 2H), 7.78 (dd, 1H) ppm.

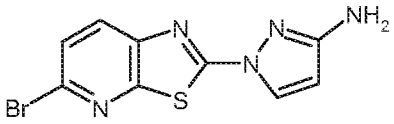
To 6-fiuorothiazolo[5,4-b]pyridin-2-amine (55 mg, 0.33 mmol) in acetonitriie (6 mL) was added copper(l l)chloride (66 mg, 0.49 mmol and the mixture was cooled to O'C. *Tert.*-butyl nitrite (58 µL, 0.49 mmol) in acetonitriie (3 mL) was added slowly and the mixture was stirred for 3.5 hours. Ethyl acetate was added and the mixture was washed with saturated NH_4Cl-solution, saturated sodium bicarbonate solution and brine. Evaporation of the solvent yielded 74 mg (96%) *2-chioro-6-fiuorothiazolo[5,4-b]pyridine:*

^{1}H NMR (400 MHz, DMSO -d_6) δ = 7.46 (dd, 1H), 8.60 (dd, 1H) ppm.

2~Chloro-6-fiuorothiazolo[5,4-b]pyridine (70 mg, 0.30 mmol) in DMF (2.5 mL) and acetonitriie (2.5 mL) was added to a stirred suspension of caesium carbonate (62 mg, 0.45 mmol) and 1H-pyrazol-3-amine (29.6 mg, 0.36 mmol) in DMF (1.5 mL) and acetonitriie (1.5 mL). After heating to 70℃ for 2.5 hours, while additional portions of caesium carbonate (60 mg, 0.44 mmol) were added after 15, 30, 45, 60 and 75 minutes, the mixture was poured water (20 mL) and stirred for 10 minutes. The aqueous phase was extracted with ethyl acetate, the combined organic layers were washed with brine and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate in dichloromethane 0 to 20% + 1% triethylam ine) to yield 29 mg (39%) of the title compound:

^{1}H-NMR (400 MHz, DMSO -d_6) δ = 5.84 (s, 2 H), 6.00 (d, 1 H), 7.29 (dd, 1 H), 8.27 (d, 1H), 8.30 (dd, 1H) ppm. **LC/SVSS ES÷ m/z 235.9 (M+1).**

1-(8-Bromoth!azoio[5,4-b]pyrsdin-2-y!)-1 H-pyrazol-3-am!ne 37



Benzoyl chloride (1.9 mL, 16.7 mmol) was added to a solution of ammonium thiocyanate (1.45 g, 19.1 mmol) in acetone (21 mL) and the mixture was refiuxed for 15 minutes. 3-Amino~2,6-dibromopyridine (3.0 g, 11.9 mmol, Parlow, J.J.; South, M. S. *Tetrahedron* 2003, *59,* 7695 - 7702) in acetone (26 mL) was added to the mixture at 40℃ and refiuxing was continued for 1.5 hours. The hot solution was poured over ice (100 mL) and the mixture was stirred for 5 minutes until a precipitate formed, which was collected by filtration and washed with 50% methanol in water (30 mL). To the precipitate was added a 5% sodium hydroxide solution (100 mL) and the suspension was stirred for 2 hours at 60℃. The mixture was allowed to cool down to room temperature over 17 hours while stirring and filtered. The filtrate was washed with diethyl ether then thoroughly extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulphate and evaporated under reduced pressure to yield 3.22 g (83%) *1-(2, 6-dibromopyridin-3-yl)thiourea:*

^{1}H NMR (300 MHz, DMSO-d_6) δ = 7.69 (d, 1H), 8.01 (d, 1H), 9.40 (s, 1H) ppm.

To 1-(2,6-dibromopyridin~3-yl)thiourea (4.1 g, 13.2 mmol), which was dried under high vacuum and flushed with argon, were added caesium carbonate (8.59 g, 26.4 mmol), copper(i)iodide (126 mg, 0.66 mmol), DL-proiine (152 mg, 1.3 mmol) and DMSO (94 mL). The mixture was stirred at room temperature while the addition of copper(l)iodide (42 mg, 0.22 mmol), DL-proline (51 mg, 0.44 mmol) and DMSO (5 mL) was repeated after 30, 60 and 90 minutes. After 2 hours the mixture was quenched with a saturated NH_4CI-solution ice water mixture and stirred for 5 minutes and then basified with aqueous ammonia to pH 8. The aqueous phase was multiple times extracted with a dichioromethane - methanol mixture (10:1). The combined organic extracts were washed with brine, dried over sodium sulphate and evaporated under reduced pressure. The solid raw product was triturated with a hexane-dichloromethane mixture (10:1) to yield 1.6 g (51 %) of *6-bromothiazolo[5,4-b]pyridin-2-amine:*

^{1}H NMR (400 MHz, DMSO-cfe) δ = 7.42 (d, 1H), 7.56 (d, 1H), 8.00 (s, 2H) ppm.

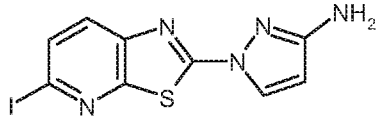
To 6-bromothiazoio[5,4-b]pyridin-2-amine (1.1g, 4.8 mmol) in acetonitriie (92 mL) was added copper(l l)chloride (964 mg, 7.2 mmol) and the mixture was cooled to OX. Tert.-butyl nitrite (739 mg, 7.2 mmol) in acetonitriie (46 mL) was added slowly and the mixture was stirred for 30 minutes at 0℃ and addit ional 4 hours at room temperature. The mixture was diluted with ethyl acetate, washed with saturated NH_4CI-solution, with saturated sodium bicarbonate solution, brine and water. Evaporation yielded 580 mg (47 %) *6-bromo-2-chlorothiazolo[5, 4-b]pyridine*\

^{1}H NMR (300 MHz, DMSO-cfe) δ = 7.87 (d, 1 H), 8.36 (d, 1 H) ppm.

6-Bromo-2-chlorothiazolo[5,4-b]pyridine (580 mg, 2.3 mmol) in DMF (14 **ml_)** and acetoniirile (14 **mL)** was added to a stirred suspension of caesium carbonate (482 mg, 3.5 mmol) and 1H-pyrazoi-3-amine (212 mg, 2.6 mmol) in DMF (9 mL) and acetonitrile (9 mL) and heated to *7Q°C for* 4 hours, while additional portions of caesium carbonate (241 mg, **1.7** mmol) were added after 15, 30, 45, 60, 75, 150, 165 and 180 minutes. The mixture was poured into ice water and stirred for 10 minutes. The forming precipitate was collected by filtration and washed with water. The vacuum dried precipitate was multiple times treated with dichloromethane and filtered. The combined dichioromethane filtrates yielded 380 mg of the title compound after evaporation of the solvent.

^{1}H-NMR (300 MHz, **DMSO-cfe)** δ = 5.90 (s, 2H), 6.03 (d, 1H), 7.69 (d, 1H), 8.05 (d, 1H), 8.28 (d, 1H) ppm. **ESS-MS** m/z 266/268 **(M+1).**

1-(6-Iodothiazolo[5,4-b]pyridin-2-yl)-1H-pyrazol-3-amine **38**



Benzoyl chloride (284 mg, 2.0 mmol) was added to a solution of ammonium thiocyanate (176 mg, 2.3 mmol) in acetone (3 mL) and the mixture was refluxed for 15 minutes. 3-Amino-2,6-diiodopyridine (0.5 g, 1.45 mmol,) in acetone (2.7 mL) was added to the mixture at room temperature and stirring was continued for 3 hours. The solution was poured into ice water and the mixture was stirred for 5 minutes until a precipitate formed, which was collected by filtration and washed with 50% methanol in water. To the precipitate was added a 5% sodium hydroxide solution (50 mL) and the suspension was stirred for 20 hours at room temperature and filtered. The filtrate was washed with diethyl ether then thoroughly extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulphate and evaporated under reduced pressure. The combined residues were purified by chromatography on silica gel (ethyl acetate in dichioromethane 0 to 100% + 1% triethylamine) to yield 40 mg (5.3 %) of *6-iodothiazolo[5,4-b]pyridin-2-amine:*

^{1}H NMR (300 MHz, **DMSO-cfe)** δ = 7.36 (d, 1H), 7.60 (d, 1H), 7.94 (s, 2H) ppm.

To 6-iodothiazolo[5,4-b]pyridin-2-amine (60 mg, 0.22 mmol) in acetonitriie (4 mL) was added copper(II)chloride (45 mg, 0.33 mmol) and the mixture was cooled to 0°C. **Tert.-**butyl nitrite (33 mg, 0.33 mmol) in acetonitriie (2 mL) was added and the mixture was stirred for 90 minutes at 0°C and additional 20 hours at room temperature. The mixture was diluted with ethyl acetate, washed with saturated NH_4Cl-solution, with saturated

sodium bicarbonate solution and brine. Evaporation yielded 55 mg (85 %) *2-chloro-6-iodoihiazoio[5,4-b]pyridine:*

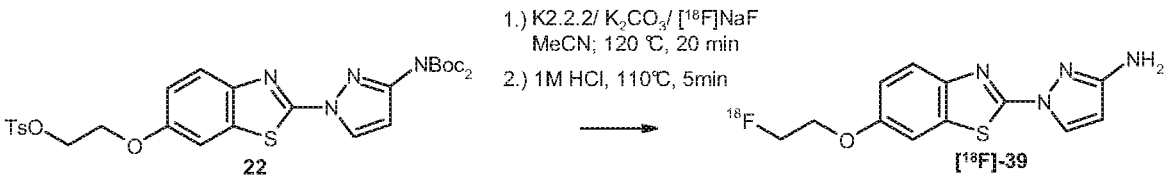
^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.03 (d, 1H), 8.1 1 - 8.13 (d, 1H) ppm.

2-Chloro-6-iodothiazolo[5,4-b]pyridine (52 mg, 0.18 mmoi) in DMF (1.1 mL) and acetonitrile (1.1 mL) was added to a stirred suspension of caesium carbonate (36 mg, 0.26 mmol) and 1H-pyrazol-3-amine (16 mg, 019 mmol) in DMF (0.6 mL) and acetonitrile (0.6 mL) and heated to 70℃ for 1.2 ho urs, while additional portions of caesium carbonate (40 mg, 0.9 mmol) were added after 10, 20, 30, 40, 50 and 60 minutes. The mixture was poured into ice water and stirred for 10 minutes. The forming precipitate was collected by filtration and washed with water. The precipitate was triturated with dichloromethane and additionally purified by preparative thin layer chromatography on silica gel (ethyl acetate in dichloromethane 30% + 1% triethylamine) to yield 10 mg of the title compound.

^{1}H-NMR (300 MHz, DMSG-d $_6$) δ = 5.90 (s, 2H), 6.03 (d, 1H), 7.69 (d, 1H), 8.05 (d, 1H), 8.28 (d, 1H) ppm, LC/MS ES÷ m/z 344.02 (M+1).

Radiochemistry

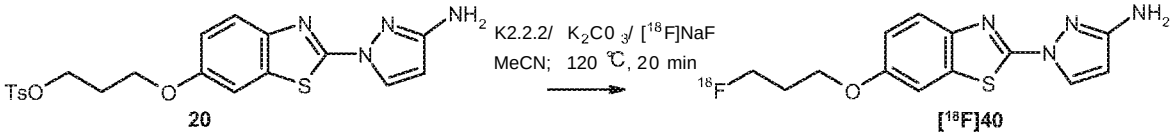
1-{6-[2-[^{18}F]fluoroethoxy]-1 ,3-benzothiazoi-2-yl}-1 H-pyrazoi-3-amine [^{18}F]-39



[^{18}F]fluoride (7.4 GBq) was trapped on a preconditioned QMA cartridge (Waters). The activity was eluted using 1.5 mL kryptofix solution (5 mg $_{K222}$, 1 mg K_2C0_3, 1.25 mL MeCN, 0.25 mL water) and the solvent was removed at 120 °C under gentle nitrogen steam and more MeCN (2 x 1 mL) was added and evaporated as before. The precursor 22 (1.5 mg in 150 µi. DMSO + 100 µi MeCN) was added and the resulting solution was stirred for 10 min at 120 °C. Aqueous HCl (1M, 1 mL) was added to the mixture and stirred for additional 5 min at 110 °C. After cleavage of the protective groups the solution was diluted with water to a total volume of appr. 20 mL and passed through a preconditioned tC1 8 plus cartridge (Waters). This cartridge was washed with water (10 mL) and eluted with 2 mL MeCN to deliver 1.125 GBq of pre-purified product (19 % corrected for decay), which was diluted with 2.5 mL water (+0.1 % TFA) and purified by preparative HPLC (ACE 5 C18-HL; 250*10mm; 5µm; Advanced Chromatography Technologies, A: water (+0.1 % TFA); B: MeCN (+0.1 % TFA) isocratic, 45 % B, 2 ml/min, t_R=9.5 min). The collected HPLC fraction was diluted with 50 mL water, passed through a preconditioned tC1 8 plus cartridge. The cartridge was washed with 5 mL water and eluted with 2 mL EtOH to deliver 716 MBq of the final product [^{18}F]-39 (14%, corrected for decay, radiochemical purity > 98%) after an aliover synthesis time of 63 min. The identity of the product was confirmed by co-injection with the non-radioactive F-19 fluoro standard 13 on the analytical HPLC: ACE3-C1 8 50 mm x 4,6 mm; solvent gradient: start 5%acetonitril - 95%acetonitrii in 0.1% trifluoroacetic acid in 7 min., flow: 2m!/min, t_R=4.1 min.

HPLC chromatograms of [^{18}F]-39 are shown in Fig. 2.

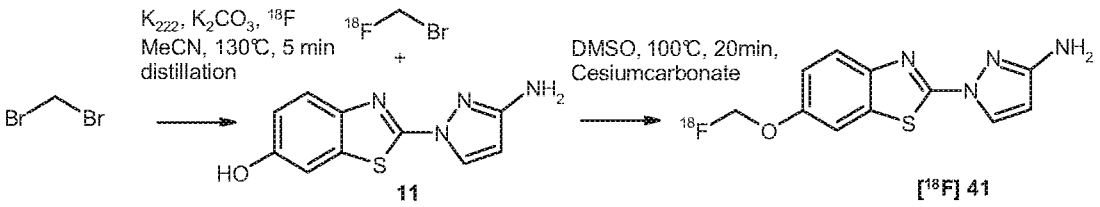
1-{6-[3-[^{18}FJfiuoropropoxyJ-1 ,3-benzothiazoi-2-yi}-1 H-pyrazol-3-amine [^{18}F]-40



Aqueous [18FJF!uoride (8.1 GBq) was trapped on a QMA cartridge (Waters) and eluted with 5 mg K2.2.2 in 0,95ml MeCN +1mg K_2C0_3 in 50µI water into a reaction vessel. The solvent was removed by heating at 120℃ for 10 min under a stream of nitrogen. Anhydrous MeCN (1 ml) was added and evaporated as before. A solution of starting material 20 (2 mg) in 500 µI anhydrous MeCN was added. After heating at 120℃ for 20 min the crude reaction mixture was analyzed using analytical HPLC: ACE3-C18 50 mm x 4,6 mm; solvent gradient: start 5%acetonitril - 95%acetonitrii in 0.1% trifluoroacetic acid in 7 min., flow: 2 mL/min. The desired F-18 labeled product was confirmed by co-injection with the corresponding non-radioactive F-19 fluoro-standard on the analytical HPLC (t_R=4.3min). The crude product was purified by preparative HPLC: ACE 5-C18-HL 250mmx10rnrn; isocratic, 48% acetonitrile in 0.1% trifluoroacetic acid, flow: 4 ml/min; t_R~15 min. The desired product **[18F]-40** was obtained (500 MBq) as reconfirmed by co-injection with the non-radioactive F-19 fiuoro standard 16 (t_R=4.1 min) on the analytical HPLC. The collected HPLC fraction was diluted with 40 mL water and immobilized on a Sep-Pak light C18 cartridge (Waters), which was washed with 5 mL water and eluted with 1 mL ethanoi to deliver 471 MBq product (11 %, corrected for decay; radiochemical purify >97.5 %) in 1000µI EtOH in a overall synthesis time of 60 min.

HPLC chromatograms of [18F]-40 are shown in Fig. 3.

1-{6-[[18F]Fiuoromethoxy]-1 ,3-benzothiazol-2-yl}-1H-pyrazoi-3-amine [18F]41

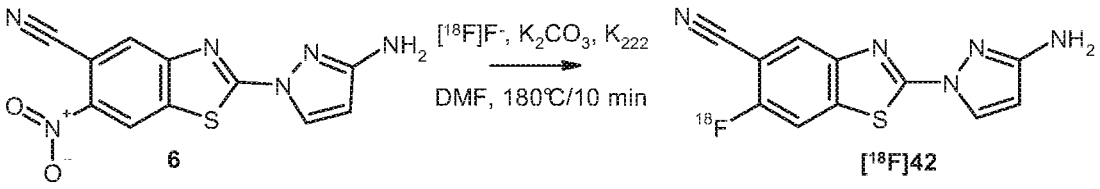


Aqueous [18F]Fiuoride (3 GBq) was trapped on a QMA cartridge (Waters) and eluted with 15mg K2.2.2 in 0.95 mL MeCN / 2.7mg K_2C0_3 in 50µL water into the reaction

vessel. The solvent was removed by heating at 140°C for 10 min under a stream of nitrogen. Anhydrous MeCN (1 mL) was added and evaporated as before. A solution of dibromo-methane (100µL) in 1000 µlLanhydrous MeCN was added. After heating at 130 ℃ for 5 min the crude reaction mixture was allowed to cool down to room temperature. By bubbling a stream of nitrogen through the reaction mixture. [^{18}F]Bromo-fluoro-methane was purified by distillation through several SepPak Silica Plus cartridges (Waters) and trapped in 800 µL DMSO in 5 mL Weaton V-vial. The intermediate was analyzed using analytical HPLC: ACE3-C18 50 mm x 4,6 mm; isocratic: start 10% acetonitrile in 0.1% trifluoroacetic acid for 5 min., flow: 2 mL/min; t_R=1.3 min. in a second step 3mg of 11 and 6 mg Cs_2C0_3 were added sequentially and heated at 100 ℃ for 20 min. The reaction mixture was diluted with 4 mL H_20/MeCN (+0, 1% TFA) 65:35 and eventually purified by preparative HPLC: ACE 5-C18-HL 25Qmmx10mm; isocratic, 35% acetonitrile in 0.1% trifluoroacetic acid, flow: 4 mL/min; t_R~20 min. The desired product [^{18}F]-41 was obtained (243 MBq) (t_R= 3.9 min) and reconfirmed by co-injection with the non-radioactive F-19 fluoro standard 15 (t_R= 3.8 min) on the analytical HPLC: ACE3-C18 50 mm x 4.6 mm; solvent gradient: start 5%acetonitril - 95%acetonitril in 0.1% trifluoroacetic acid in 7 min., flow: 2ml/min. The collected HPLC fraction was diluted with 40ml water and immobilized on a Sep-Pak light C18 cartridge (Waters), which was washed with 5 mL water and eluted with 1 mL ethanoi to deliver 220 MBq product (16%, corrected for decay; radiochemical purify >99%) in 1000 µL EtOH in a overall synthesis time of 110 min.

HPLC chromatograms of [^{18}F]41 are shown in Fig. 4.

2-(3-amino-1 H-pyrazol-1 -yl)-6-[^{18}F]fiuoro-1 ,3-benzothiazoie-5-carbonitriie [^{18}F]42

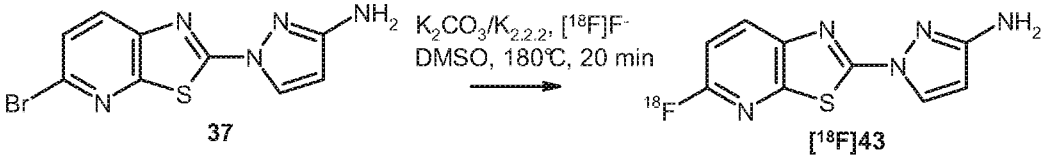


Aqueous [^{18}FjFluoride (1.8 GBq) was trapped on a QMA cartridge (Waters, Sep Pak Light QMA Part.No.: WAT023525) and eluted with 1.5 mL K_{222}/K_2C0_3 solution (5 mg K_{222} in 0.95 mL MeCN, 1 mg K_2C0_3 in 0.05 mL water) into the reaction vessel. The solvent was removed by heating at 120℃ for 10 min under a stream of nitrogen. Anhydrous MeCN (1 mL) was added and evaporated as before. A solution of precursor 6 (2.5 mg) in 500 µL anhydrous DMF was added. After heating at 18013 for 10 min the

crude reaction mixture was allowed to cool down to room temperature and diluted with water to a total volume of 5 mL and purified by preparative HPLC: Sepserv UltraSep ES, Amid H RP18P 5 µm, 250 x 8 mm; isocratic, 10% acetonitrile -> 70% acetonitrile in 0.1% trifluoroacetic acid in 30 min, 3 mL/min flow; t_R=22 min. The collected HPLC fraction was diluted with 40mL water and immobilized on a Sep-Pak light C18 cartridge (Waters, WATQ235Q1), which was washed with 5mL water and eiuted with 1mL ethanol to deliver 220 MBq of the product [^{18}F]-42 (t_R=3.9 min, RCP: >99 %) (20%, corrected for decay) which was characterized and reconfirmed by co-injection with the non-radioactive F-19 fluoro standard 4, (t_R=3.7 min) using analytical HPLC: ACE 3 C18 S/N-A56904, 50 x 4.6 mm; 3 µm, ACE-1 11-, A): Wafer + 0,1% TFA, B): MeCN + 0,1% TFA, 0 to 7 min, 5 to 95% B;7 to 7.10 min, 95 to 100% B; 7.1 to 9 min, 100% B; 9 to 9.10 min 100%B to 5 % B; 9.10 to 12 min, 5% B; 2mb'min.

HPLC chromatograms of [^{18}F]-42 are shown in Fig. 5.

1-[6-[^{18}F]fluorothiazolo[5,4-bjpyridin-2-yl]-1 H-pyrazoi-3-amine [^{18}F]43



Aqueous [^{18}F]Fiuoride 8.5 GBq was trapped on a QMA cartridge (Waters) and eiuted with 1.5 mL K222/K2CO3 solution (5 mg K_{222} in 0.95 mL MeCN, 1 mg K_2C0_3 in 0.05 rnL! water) into the reactor. The solvent was removed by heating at 120X for 10 min under a stream of nitrogen. Anhydrous MeCN (1 mL) was added and evaporated as before. A solution of precursor 37 (5 mg) in 500 µL anhydrous DMSO was added. After heating at 180 °C for 20 min the crude reaction mixture was diluted with 4 mL water/MeCN (3:1) and purified by preparative HPLC: ACE 5 C18 HL, 30% MeCN/ 70% 0.1 M ammonium formiate; isocratic, 4 mL/min ; t_R~20 min. The collected HPLC fraction was diluted with 40mL water and immobilized on a Sep-Pak tC18 plus short: Waters; Part.No.: WAT03881 0, which was washed with 5 mL water and eiuted with 1 mL ethanol to deliver the 650 MBq of the F-18 labeled product (13 % rc. yield, corrected for decay; >99% HPLC) in 1000µI EtOH in a overall synthesis time of -80 min. The desired F-18 labeled product [^{18}F]-43 (t_R=3.4 min) was analyzed using analytical HPLC: ACE3-C18 50 mm x 4,6 mm; solvent gradient: start 5 % acetonitrile - 95 % acetonitrile in 0.1% trifluoroacetic acid in 7 min., flow: 2mL/min and confirmed by co-injection with the corresponding non-radioactive F-19 fluoro-standard 36 on the analytical HPLC (t_R=3.3 min).

HPLC chrornatograms of [^{18}F]-43 are shown in Fig. 6.

Biological data

Examples

The methods for making and labeling these compositions are more fully illustrated in the following Examples. These Examples illustrate certain aspects of the above-described method and advantageous results. These Examples are shown by way of illustration and not by way of limitation.

Binding studies using human brain homogenate

A competition assay with a tritiated amyloid ligand was performed in 96-weli plates (Greiner bio-one; Cat. 651 201 ; Lot. 062601 30) using brain homogenate from AD patients.

Homogenates were prepared by homogenizing (Ultra-Turrax, setting 2, 30 s, 24000 rpm) dissected frontal cortex containing grey matter and white matter from AD patients in phosphate buffered saline (PBS, pH 7.4). The homogenate with a concentration of 100 mg wet tissue/mi was divided into aliquots of 300 µl and stored at -80°C.

Varying concentrations of the unlabeled test substances were incubated with 100 µg/ml homogenate and 10 nM of the tritiated ligand in PBS, 0.1% BSA (final volume 200 µl) for 3 h at room temperature. Subsequently the binding mixture was filtered through Whatman GF/B filters (wetted with PBS, 0.1% BSA) using a Fiitermate 196 harvester (Packard). Filters were then washed twice with PBS, 0.1%BSA and 40 µl scintillator was added to each well before the bound radioactivity was measured in a TopCount devise (Perkin Elmer). Non-specific binding was assessed by adding an excess of the cold reference ligand to the reaction mixture. Finally IC50 values were calculated with the help of appropriate analysis software.

Table 1: Binding affinity of compounds towards human AD brain homogenate

Compound	IC50 human ADH [nM]
1	9
2	15
4	51
12	142
13	27
14	227

15	7
16	26
17	69
26	163
27	>400
34	367
36	57

Autoradiographical analysis

Fresh frozen as well as paraffin embedded sections of the frontal lobe from Alzheimer's dementia patients, frontotemporal dementia patients and age matched controls were used for the study.

Frozen sections, sliced at 18 µm thickness on a cryostate (Leica, Germany) and paraffin sections, sliced on a sliding microtom (Leica) at a thickness of 6 µm, were mounted onto glass slides (Superfrost Plus, Fa.Menzei, Braunschweig Germany). Frozen sections were allowed to adhere to the slides for several nights at -20°C. The paraffin sections were deparaffinized using routine histological methods. For binding studies sections were incubated with the F-18 labeled test compound at 10 Bq/µl diluted in 25mM Hepes buffer, pH 7.4, 0,1% BSA (200-300 µl/slide) for 1,5 hour at room temperature in a humidified chamber. For blocking experiments an excess of the unlabeled test substance was added to the incubation mixture. After hybridization, sections were washed four times with Hepes buffer, 0.1% BSA (or alternatively two times with 40% ethanol) and finally dipped two times into A. dest. for 10 sec. The air-dried sections were exposed to imaging plates and signals were detected by a phosphoimager device (Fuji BAS5000).

^{18}F-39

The autoradiography of post-mortem AD brain sections of ^{18}F-39 confirmed the specific binding related to the presence of Aβ plaques.

Results are shown by Fig. 7.

^{18}F-40

The autoradiography of post-mortem AD brain sections of ^{18}F-4D confirmed the specific binding related to the presence of Aβ plaques.

Results are shown in Fig. 8

^{18}F-41

The autoradiography of post-mortem AD brain sections of ^{18}F-41 confirmed the specific binding related to the presence of Aβ plaques.

Results are shown by Fig. 9.

^{18}F-43

The autoradiography of post-mortem AD brain sections of ^{18}F-43 confirmed the specific binding related to the presence of Aβ plaques.

Results are shown in Fig. 10.

Biodistribution

Biodistribution and excretion studies were performed in male NMRi mice (body weight app. 30 g; 3 animals per time point). The animals were kept under normal laboratory conditions at a temperature of 22 ± 2℃ and a dark/ light rhythm of 12 hours. Food and water were provided ad iibitium. During an acclimation period of at least 3 days before the beginning of the study animals were clinically examined to ascertain the absence of abnormal clinical signs.

At 2, 5, 30, 60, 240 min post intravenous injection via the tail vein of ca. 150 kBq in 100 µl of the test compound, urine and feces were quantitatively collected. At the same time points, animals were sacrificed by decapitation under isoflurane anaesthesia and organs and tissues of interest were removed for the determination of radioactivity using a gamma-counter. For analysis the decay corrected percentage of the injected dose per tissue weight (%ID/g ± standard deviation) was calculated.

Tabei 2: Brain uptake and brain wash-out of compounds expressed as percentage of injected dose per gram tissue [%I D/g]. The F-18 signal was detected at 2 min and 30 min after compound administration to mice. Note the favourable high brain uptake and fast wash-out from healthy mouse brain, which is devoid of plaques.

Compound	Brain uptake at 2 min [%iO/g]	Brain uptake at 30 min [%ID/g]	Brain wash-out ratio [%ID/g at 2min] / [%ID/g at 30min]
^{18}F-33	5.14	2.45	2.1
^{18}F-40	4.85	0.82	5.9
^{18}F-41	3.91	1.59	2.6
^{18}F-43	5.36	0.43	12.5

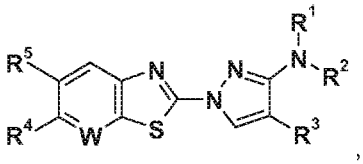
The tracers ^{18}F-40 and ^{18}F-43 show an advantageous rapid eiimination of the unspecific radioactive signal from the brain.

5

The studies described above indicate that compounds of formula I are useful as imaging agents for amyloid plaques. They can penetrate the intact blood-brain barrier and specifically bind amyloid deposits.

Claims

1. A compound of formula I



I

wherein

- R^1 is selected from the group consisting of H, C(0)CH_3, C(0)$(CH_2)_nCH_2X$, C(0)CF_3, C(0)$OC(CH_3)_3$, C(0)C_6H_4X, C(0)C_6H_3XZ, C(0)heteroraryl, substituted C(0)heteroraryl;

- R^2 is selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, $(CH_2)_nCH_2X$, R^1;

- R^3 is selected from the group consisting of H, C(0)OH, C(0)0$(CH_2)_nCH_3$, C(0)0 $(CH_2)mCH_2X$, $C(0)NH_2$, C(0)NH$(CH_2)_nCH_3$, C(0)NH$(CH_2)_mCH_2X$;

- R^4 and R^5 are independently selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, $(CH_2)_nCH_2X$, OH, OCH_3, O$(CH_2)_nCH_3$, 0$(CH_2)_nCH_2X$, O-cyciobutyl-X, O-cyclopentyi-X, O-cyclohexyl-X, O$(CH_2CH_20)_nCH_2CH_2X$, SH, SCH_3, $S(CH_2)_nCH_3$, $S(CH_2)_nCH_2X$, NH_2, $NHCH_3$, $N(CH_3)_2$, NH$(CH_2)_nCH_3$, NH$(CH_2)_mCH_2X$, $NCH_3(CH_2)_mCH_2X$, X, Z;

- W is selected from CH or N

- X is selected from the group consisting of F, ^{18}F, I, ^{125}I, ^{123}I;

- Z is selected from the group consisting of H, CF_3, CN, C(0)H, C(0)CH_3, C(0)0$(CH_2)_nCH_3$;
- m has the meaning of 1-4;
and n has the meaning of 0-4;

including ail isomeric forms of said compound, including enantiomers and diasteromers as well as racemic mixtures,

and any pharmaceutically acceptable salt, ester, amide, complex or prodrug thereof, wherein the formula comprises only one X.

2. A compound according to claim 1, wherein

- R^1 is selected from the group consisting of H, C(0)CH_3, C(0)$(CH_2)_nCH_2X$, CfO)CF_3, C(0)OC$(CH_3)_3$, C(0)C_6H_4X, C(0)C_6H_3XZ, C(0)heteroraryi , substituted C(0)heteroraryi;

- R^2 is selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, $(CH_2)_mCH_2X$, R^1;

- R^3 is selected from the group consisting of H, C(0)OH, C(0)0$(CH_2)_nCH_3$, C(0)0$(CH_2)mCH_2X$, C(0)NH_2, C(0)NH$(CH_2)_nCH_3$, C(0)NH$(CH_2)_mCH_2X$;

- R^4 and R^5 are independently selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, $(CH_2)_nCH_2X$, OH, OCH_3, 0$(CH_2)_nCH_3$, 0$(CH_2)_nCH_2X$, O-cyclobutyl-X, O-cyclopentyi-X, 0$(CH_2CH_20)_nCH_2CH_2X$, NH_2, $NHCH_3$, $N(CH_3)_2$, $NH(CH_2)_nCH_3$, $NH(CH_2)_mCH_2X$, $NCH_3(CH_2)_mCH_2X$, X, Z;

- **W** is selected from CH or N

- **X** is selected from the group consisting of F, ^{18}F, I, ^{125}I, ^{123}I;

- Z is selected from the group consisting of H, CF_3, CN, C(0)H, C(G)CH_3;
- m has the meaning of 1-3;
and n has the meaning of 0-3;

including ail isomeric forms of said compound, including **enantiomers** and diasteromers as well as racemic mixtures,

and any pharmaceutically acceptable salt, ester, amide, complex or prodrug thereof,

wherein the formula comprises only one X.

3. A compound according to claim 1 or 2, wherein

- R^1 is selected from the group consisting of H, C(0)CH_3, C(0)$(CH_2)_nCH_2X$, C(0)CF_3, C(0)OC$(CH_3)_3$, C(0)C_6H_4X, C(0)C_6H_3XZ;

- R^2 is selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, R^1;

- R^3 is selected from the group consisting of H, C(0)OH, $C(0)0(CH_2)nCH_3$, $C(0)0(CH_2)_mCH_2X$;

- R^4 and R^5 are independently selected from the group consisting of H, $(CH_2)_nCH_2X$, OH, OCH_3, $0(CH_2)_nCH_2X$, 0-cyclobutyi~X, $0(CH_2CH_20)„CH_2CH_2X$, X, Z;

- W is selected from CH or N

- X is selected from the group consisting of F, ^{18}F;

- Z is selected from the group consisting of H, CF_3, CN, C(0)H;
- m has the meaning of 1-2;
and n has the meaning of 0-2,

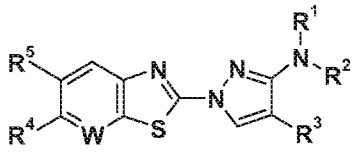
including all isomeric forms of said compound, including enantiomers and diasteromers as well as racemic mixtures,

and any pharmaceutically acceptable salt, ester, amide, complex or prodrug thereof,

wherein the formula comprises only one X.

4. A compound according to claims 1, 2 or 3, wherein X is ^{18}F.

5. A compound of formula I



I

wherein

- R^1 is selected from the group consisting of H, $C(0)CH_3$, $C(0)(CH_2)nCH_2X$, $C(0)CF_3$, $C(0)OC(CH_3)_3$, $C(0)C_6H_4X$, $C(0)C_6H_3YZ$, $C(0)C_6H_3XZ$, C(0)heteroraryl, substituted C(0)heteroraryl, $C(0)OCH_3$, $C(0)OCH_2CH_3$, $C(0)OCH_2C_6H_5$, $C(0)OCH_2CH=CH_2$, Fmoc, $C(0)OCH_2CH_2Si(CH_3)_3$, $C(0)OCH_2CCl_3$;

- R^2 is selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, $(CH_2)_mCH_2X$, R^1;

- R^3 is selected from the group consisting of H, C(0)OH, $C(0)0(CH_2)_nCH_3$, $C(0)0(CH_2)_mCH_2X$, $C(0)NH_2$, $C(0)NH(CH_2)_nCH_3$, $C(0)NH(CH_2)_mCH_2X$;

- R^4 and R^5 are independently selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, $(CH_2)_nCH_2X$, OH, OCH_3, $0(CH_2)_nCH_3$, $0(CH_2)_nCH_2X$, O-cyclobutyl-X, O-cyciopentyl-X, O-cyclohexyl-X, $0(CH_2CH_20)_nCH_2CH_2X$, SH, SCH_3, $S(CH_2)nCH_3$, $S(CH_2)_nCH_2X$, NH_2, $NHCH_3$, $N(CH_3)_2$, $NH(CH_2)_nCH_3$, $NH(CH_2)_mCH_2X$, $NCH_3(CH_2)_mCH_2X$, X, Y, Z;

- W is selected from CH or N

- X is selected from the group consisting of F, Cl, Br, I, $OS0_2CH_3$, $OS0_2CF_3$, $OS0_2C_4F_9$, $OS0_2C_6H_5$, $OS0_2C_6H_4CH_3$, $OS0_2C_6H_4N0_2$, $OS0_2C_6H_4Br$, $OS0_2C_6H_2(CH(CH_3)_2)_3$, $OS0_2C_6H_3(OCH_3)_2$;

- Y is selected from the group consisting of $N0_2$, N^+Me_3, I^+aryl, S^+aryl_2;

- Z is selected from the group consisting of H, CF_3, CN, C(0)H, $C(0)CH_3$, $C(0)0(CH_2)_nCH_3$;

- m has the meaning of 1-4;
and n has the meaning of 0-4;

including ail isomeric forms of said compound, including enantiomers and diasteromers as well as racemic mixtures,

and any pharmaceutically acceptable salt, ester, amide, complex or prodrug thereof,

wherein the formula comprises only one X,
and wherein the formula comprises only one Y.

6. A compound according to claim 5, wherein

- R^1 is selected from the group consisting of H, $C(0)CH_3$, $C(0)(CH_2)_nCH_2X$, $C(0)CF_3$, $C(0)0C(CH_3)_3$, $C(0)C_6H_4X$, $C(0)C_6H_3YZ$, $C(0)C_6H_3XZ$, $C(0)C_6H_4Y$, C(0)heteroraryl, substituted C(0)heteroraryl , $C(0)0CH_2C_6H_5$, $C(0)0CH_2CH=CH_2$, Fmoc;

- R^2 is selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, $(CH_2)_mCH_2X$, R^1;

- R^3 is selected from the group consisting of H, C(0)OH, $C(0)0(CH_2)_nCH_3$, $C(0)0(CH_2)_mCH_2X$, $C(0)NH_2$, $C(0)NH(CH_2)_nCH_3$, $C(0)NH(CH_2)_mCH_2X$;

- R^4 and R^5 are independently selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, $(CH_2)_nCH_2X$, OH, OCH_3, $0(CH_2)_nCH_3$, $0(CH_2)_nCH_2X$, O-cyclobutyl-X, O-cyclopentyi-X, $0(CH_2CH_20)_nCH_2CH_2X$, NH_2, $NHCH_3$, $N(CH_3)_2$, $NH(CH_2)_nCH_3$, $NH(CH_2)_mCH_2X$, $NCH_3(CH_2)_mCH_2X$, X, Y, Z;

- W is selected from CH or N

- X is selected from the group consisting of F, Cl, Br, I, $OS0_2CH_3$, $OS0_2CF_3$, $OS0_2C_4F_9$, $OS0_2C_6H_5$, $OS0_2C_6H_4CH_3$, $OS0_2C_6H_4N0_2$, $0S0_2C_6H_4Br$, $OS0_2C_6H_3(OCH_3)_2$;

- Y is selected from the group consisting of $N0_2$, N^+Me_3, I^+aryl, S^+aryl_2;

- Z is selected from the group consisting of H, CF_3, CN, C(0)H, $C(0)CH_3$;

- m has the meaning of 1-3;
and n has the meaning of 0-3;

including all isomeric forms of said compound, including enantiomers and diasteromers as well as racemic mixtures,

and any pharmaceutically acceptable salt, ester, amide, complex or prodrug thereof

wherein the formula comprises only one X,
and wherein the formula comprises only one Y.

7. A compound according to claim 5 or 6, wherein

- R^1 is selected from the group consisting of H, $C(0)CH_3$, $C(0)(CH_2)_nCH_2X$, $C(0)CF_3$, $C(0)0C(CH_3)_3$, $C(0)C_6H_4X$, $C(0)C_6H_3YZ$, $C(0)C_6H_3XZ$, $C(0)OCH_3$, $C(0)OCH_2CH_3$, $C(0)0CH_2C_6H_5$, **Fmoc**;

- R^2 is selected from the group consisting of H, CH_3, $(CH_2)_nCH_3$, R^1;

- R^3 is selected from the group consisting of H, C(0)OH, $C(0)0(CH_2)nCH_3$, $C(0)0(CH_2)_mCH_2X$;

- R^4 and R^5 are independently selected from the group consisting of H, $(CH_2)_nCH_2X$, OH, OCH_3, $0(CH_2)_nCH_2X$, 0-cyclobutyl~X, $0(CH_2CH_20)_nCH_2CH_2X$, X, Y, Z;

- W is selected from CH or N

- X is selected from the group consisting of F, Cl, Br, I, $0S0_2CH_3$, $OS0_2CF_3$, $OS0_2C_4F_9$, $0S0_2CsH5$, $OSO_2C_6H_4CH3$;

- Y is selected from the group consisting of $N0_2$, N^+Me_3, I^+aryl, S^+aryl_2;

- Z is selected from the group consisting of H, CF_3, CN, C(0)H;
- m has the meaning of 1-2;
and n has the meaning of 0-2,

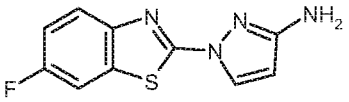
including all isomeric forms of said compound, including enantiomers and diasteromers as well as racemic mixtures,

and any pharmaceutically acceptable salt, ester, amide, complex or prodrug thereof,

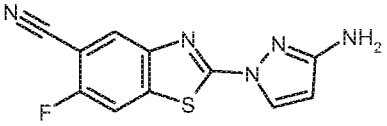
wherein the formula comprises only one X,
and wherein the formula comprises only one Y.

8. A compound selected from the group consisting of

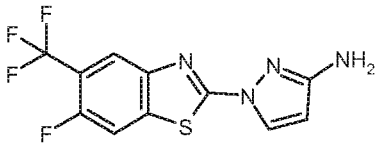
1-(6-Fluorobenzothiazol-2-yl)-1H-pyrazol-3-ylamine 2



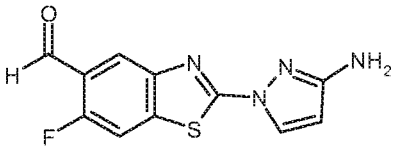
2-(3-Aminopyrazol-1-yl)-6-fluoro-benzothiazole-5-carbonitrile 4



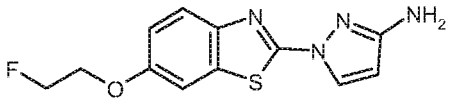
1-(6-Fluoro-5-irifluoromethylbenzothiazo!-2-yl)-1H-pyrazoi-3-ylarnine 5



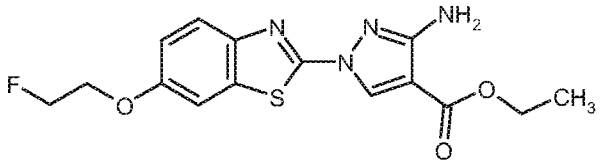
2-(3-Aminopyrazol-1-yi)-8-fluorober!zothiazole-5-carba!dehyde 9



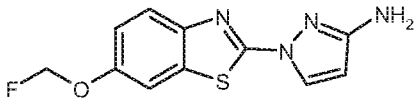
1-[6-(2-Fluoroethoxy)benzothiazol-2 -yl]-1H-pyrazol-3-ylamine 13



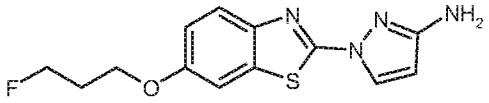
3-Amino-1-[6-(2~fluoroeihoxy)benzothiazoi-2~yl]-1H~pyrazo!e~4-carboxylic acid etby! ester 14



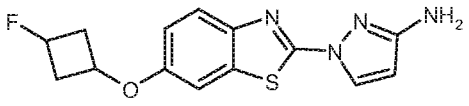
1-[6-(Fluorornethoxy)benzoihiazo!-2-yl]-1H-pyrazol-3-y!amine 15



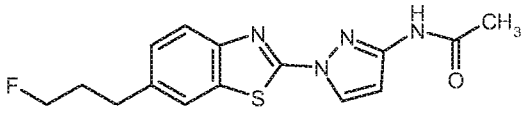
1-[6-(3-Fluoropropoxy)benzothiazol-2-y!]-1H-pyrazoi-3-ylarnine 16



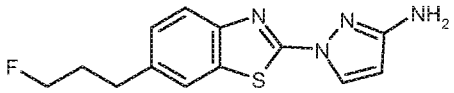
1-[6-(3-Fluorocyclobuioxy)benzothiazol-2-y!]-1H~pyrazoi-3-ylarnine 17



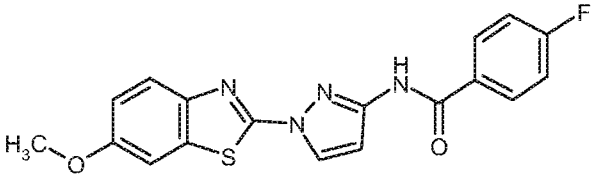
N-{1-[6-(3-Fluoropropyl)benzothiazol-2-yl]-1H-pyrazol-3-yi}acetamide 25



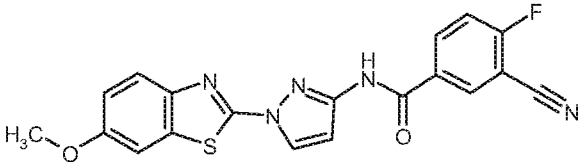
1-[6-(3-F!uoropropyl)benzothiazol-2-y!]-1 H-pyrazol-3-ylarnine 28



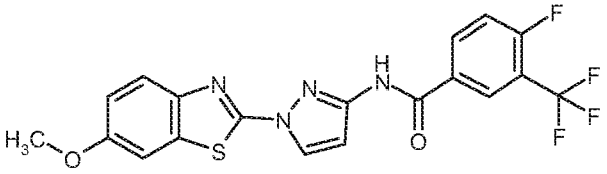
4-Fluoro-N-[1-(6-rneihoxybenzothiazol-2-yl)-1 H-pyrazol-3-y!]benzamide *27*



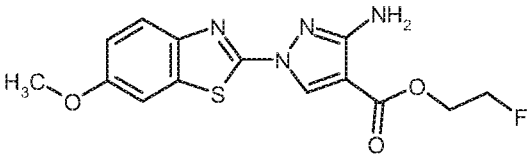
3-Cyano-4-fluoro-N-[1-(6-methoxybenzothiazol-2-yl)-1H-pyrazol-3-yi]benzamide 28



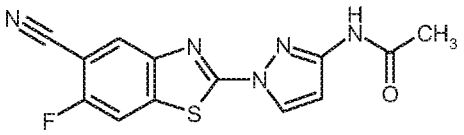
4-Fluoro-N-[1 -(6-methoxybenzoihiazoi-2-yl)-1 H-pyrazol-3-ylj-3-(trifluoromethyl)benzamide **29**



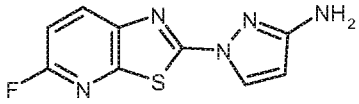
3-Arnino-1 -(6-mei:hoxybenzothiazo!-2-yl)-1 H-pyrazoie-4-carboxylic acid 2-f!uoroethyl ester 34



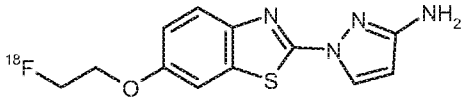
N-[1-(5-Cyano-6-fluorobenzothiazol-2-yl)-1H-pyrazol-3-yl]**aceiaiT**!ide 35



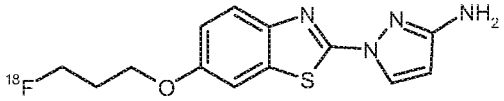
1~(6-F!uorothiazo!o[5,4~b]pyridin-2~yl)-1H-pyrazoi-3-amine 36



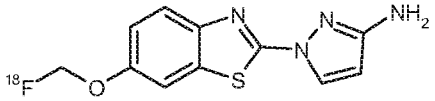
1-[6-(2-[^{18}F]Fluoroeihoxy)benzothiazol-2-yi]-1H-pyrazol-3-ylamine [18FJ-39



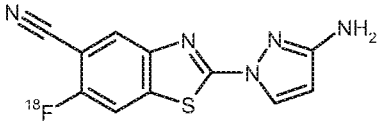
1-[6-(3-[^{18}F]Fluoropropoxy)benzotbiazol-2-yl]-1H-pyrazol-3-ylamirse [18FJ-40



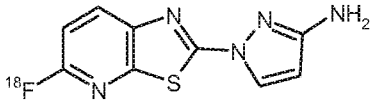
1-[6-([^{18}F]FlLioromethoxy)benzoihiazol-2-ylj-1H-pyrazoi-3-ylamine [18FJ-41



2-(3-Aminopyrazol-1-yl)-6-[^{18}F]fluoro-berszothiazole-5-carbonitriie **[18F]-42**

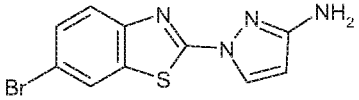


1-(6-[^{18}F]Fluorothiazolo[5,4-bjpyridin-2-yl)-1H-pyrazol-3-amine [18FJ-43

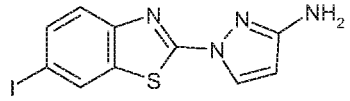


9. A compound selected from the group consisting of

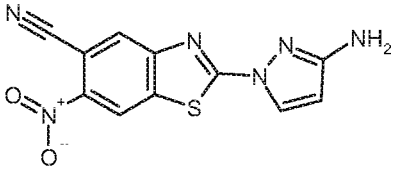
1-(6-Bromobenzothiazoi-2-yl)-1H-pyrazoi-3-ylamine **1**



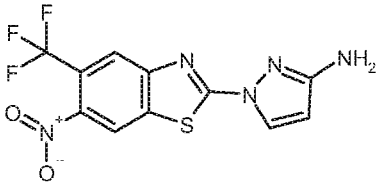
1-(6-iodobenzothiazol-2-y!)-1H-pyrazol-3-y!amine 3



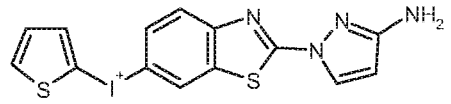
2-(3-Aminopyrazol-1-yl)-6-nitrobenzothiazoie-5-carbonitriie 6



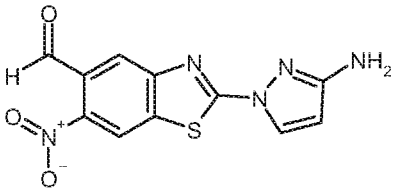
1-(6-Nitro-5-trifluoromethylbenzothiazoi-2-yl)-1H-pyrazoi-3-ylamine *7*



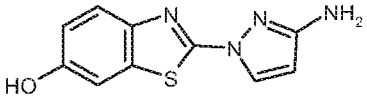
[2-(3-Aminopyrazo!-1-yi)-benzothiazoi-8-yl]thien-2-yi-iodonium 8



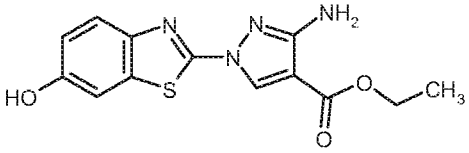
2-(3-Aminopyrazoi-1-y!)-6-nitrobenzothiazole-5-carbaidehyde **10**



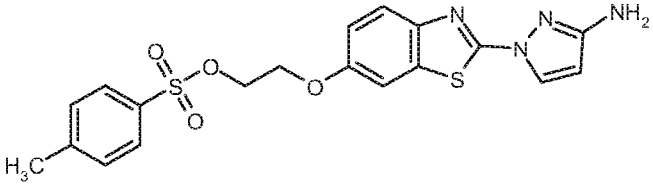
2-(3-Aminopyrazoi-1-yl)-benzothiazol-6-ol 11



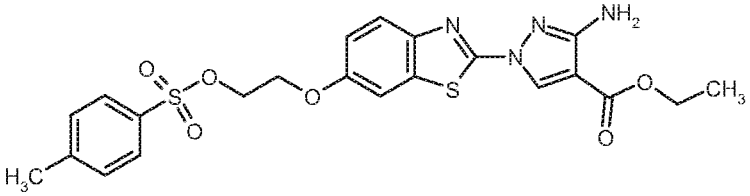
3-Amino-1-(6-hydroxybenzothiazol-2-yl)-1H-pyrazole-4-carboxylic acid ethyl ester 12



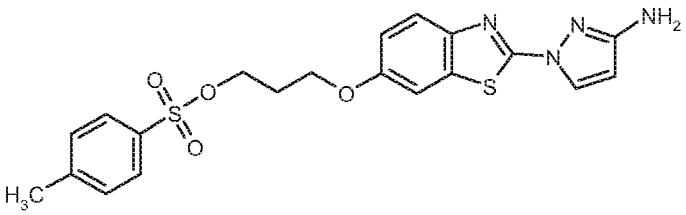
Toluene-4-sulfonic acid 2-[2-(3-amino-pyrazol-1-yl)benzoth!azo!-6-yloxy] ethyi ester 18



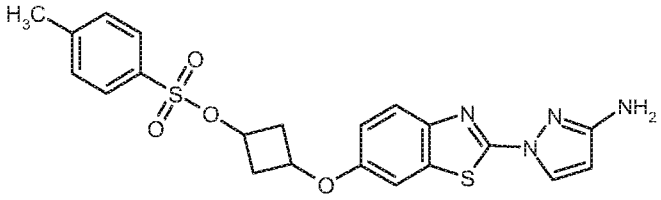
3-Arnino-1-{6-[2-(toiuene-4-sulfony!oxy)ethoxy]benzoth!azo!-2-yl}-1H-pyrazo!e-4-carboxylic acid ethyl ester **19**



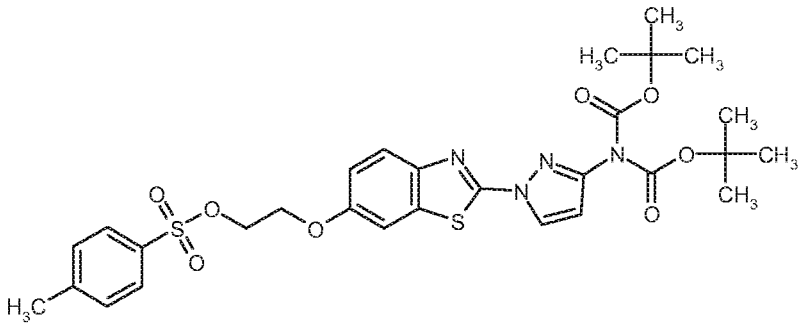
To!uene-4-suifonic acid 3-[2-(3-arnino-pyrazol-1-yi)ber!zothiazol-6-yloxy] propyl ester 20



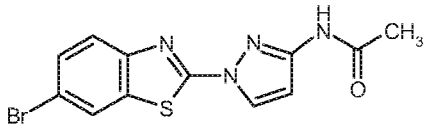
ToiLiene-4-sulfonic acid 3-[2-(3-amirso-pyrazol-1-yl)benzothiazol-8-yloxy] cyclobutyl ester 21



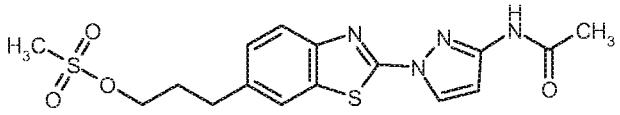
Toiuene-4-su!fonic acid 2-[2-(3-di-tert-buioxycarbonyiam!r!opyrazoi-1-yl)benzothiazol-6-yioxy] ethyl ester 22



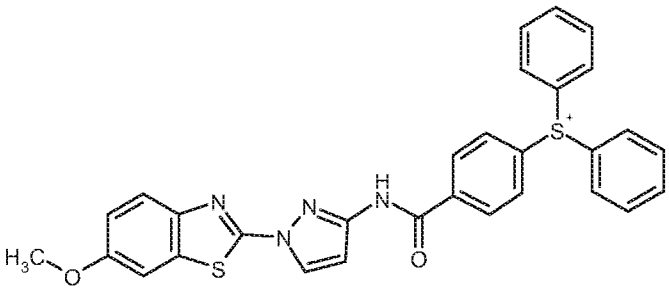
N-[1-(6-Brorriobenzothiazoi-2-yl)-1H-pyrazol-3-yl]acetamide 23



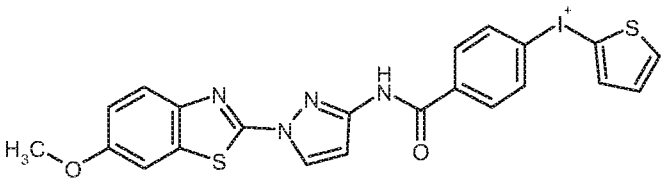
Methane sulfonic acid 3-[2-(3-aminopyrazol-1-yl)benzothiazol-8-yl]propyl ester 24



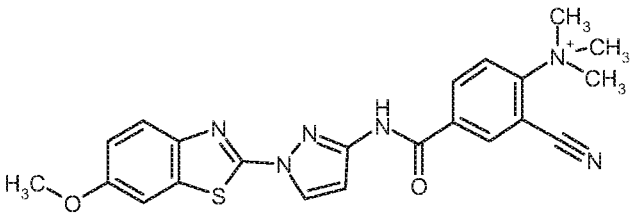
{4-[1-(6-Methoxybenzothiazol-2-yl)-1H-pyrazol-3-ylcarbarrioyl]-phersyl}diphenyl-· suifonium 30



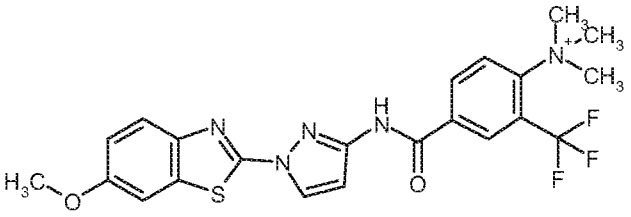
{4-[1-{6-Methoxybenzoihiazoi-2-yl)-1H-pyrazol-3-y!carbamoyl]phenyi}ihien-2-yl-iodorsium 31



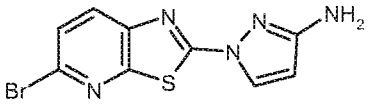
{2-Cyano-4-[1-(6-rrseihoxybenzothiazol-2-yr)-1H-pyrazoi-3-ylcarbamoy[ ]-phenyl}trimethyl-ammonium **32**



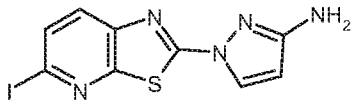
{4-[1-{6-Methoxybenzoihiazoi-2-yl)-1H-pyrazol-3-y!carbamoyl]-2-irifiuoromethyl-phenyl}trimethyl-ammonium **33**



1-(6-Bromoihiazolo[5,4-b]pyridin-2-yi)-1H-pyrazol-3-amine 37

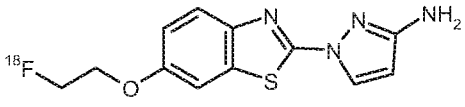


1-(6-Iodothiazolo[5,4-b]pyridin-2-yl)-1 H-pyrazol-3-amine 38

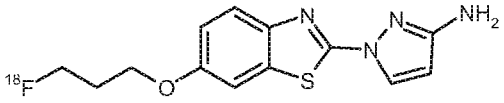


10. A compound selected from the group consisting of

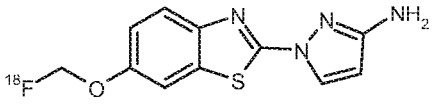
1-[6-(2-[^{18}F]Fluoroethoxy)benzothiazoi-2-yl]-1 H-pyrazo!-3-yiam ine [18FJ-39



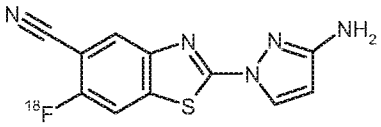
1-[6-(3-[^{18}F]Fiuoropropoxy)benzothiazoi-2-y!]-1 H-pyrazoi-3-ylamine [18F]-40



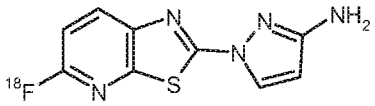
1-[6-([^{18}FjFluoromethoxy)benzothiazol-2-yl]-1 H-pyrazol-3-yiamine [18F]-41



2-(3-Aminopyrazoi-1 -yl)-8-[^{18}F]fluoro-benzofhiazole-5-carbonitrile **[18F]-42**



1-(6-[^{18}F] FiLiorothiazoio[5,4-b]pyridin-2-yi)-1 H-pyrazol-3-amine [18F]-43



11. **A** compound according to claim 8, wherein F has the meaning of ^{18}F when F is not part of a -CF_3-group.

12. An ^{18}F-radioactively labelled compound according to claims 1 - 4, 10 or 11 as a compound for diagnostic imaging.

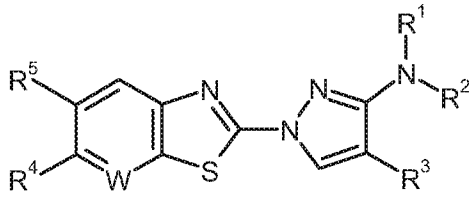
13. A compound according to claim 12 as a compound for diagnostic imaging of a disease selected from the group of diseases comprising Alzheimer's disease, a neurodegenerative disorder, or an amyloidosis.

14. A pharmaceutical or diagnostic composition comprising a ^{18}F radioactively labelled compound according to claims 1 - 4, 10 or 11 and a pharmaceutically acceptable carrier.

15. A method for the preparation of a ^{18}F radiofluorinated compound according to claims 1 - 4, 10 or 11, the method comprising reacting a suitable precursor molecule of claims 5 - 7, or 9 with a radiofluorinating agent.

Figures

Fig.1



Nr.	R1	R2	R3	R4	R5	W	X	Y	Z
1	H	H	H	X	H	CH	Br		
2	H	H	H	X	H	CH	F		
3	H	H	H	X	H	CH	I		
4	H	H	H	X	Z	CH	F		CN
5	H	H	H	X	Z	CH	F		CF_3
6	H	H	H	Y	Z	CH		NO_2	CN
9	H	H	H	X	Z	CH	F		C(O)H
11	H	H	H	OH	H	CH			
12	H	H	$C(O)OCH_2CH_3$	OH	H	CH			
13	H	H	H	OCH_2CH_2X	H	CH	F		
14	H	H	$C(O)OCH_2CH_3$	OCH_2CH_2X	H	CH	F		
15	H	H	H	OCH_2X	H	CH	F		
16	H	H	H	$OCH_2CH_2CH_2X$	H	CH	F		

Fig. 1 continued

Nr.	R1	R2	R3	R4	R5	W	X	Y	Z
17	H	H	H	O-cyclobutyl-X	H	CH	F		
18	H	H	H	OCH_2CH_2X	H	CH	$OSO_2C_6H_4CH_3$		
20	H	H	H	$OCH_2CH_2CH_2X$	H	CH	$OSO_2C_6H_4CH_3$		
21	H	H	H	O-cyclobuty-X	H	CH	$OSO_2C_6H_4CH_3$		
22	$C(O)OC(CH_3)_3$	$C(O)OC(CH_3)_3$	H	OCH_2CH_2X	H	CH	$OSO_2C_6H_4CH_3$		
23	$C(O)CH_3$	H	H	X	H	CH	Br		
24	$C(O)CH_3$	H	H	$CH_2CH_2CH_2X$	H	CH	$OSO_2C_6H_4CH_3$		
25	$C(O)CH_3$	H	H	$CH_2CH_2CH_2X$	H	CH	F		
26	H	H	H	$CH_2CH_2CH_2X$	H	CH	F		
27	$C(O)C_6H_4X$	H	H	OCH_3	H	CH	F		
34	H	H	$C(O)OCH_2CH_2X$	OCH_3	H	CH	$OSO_2C_6H_4CH_3$		
35	$C(O)CH_3$	H	H	X	Z	CH	F		CN
36	H	H	H	X	H	N	F		
37	H	H	H	X	H	N	Br		
38	H	H	H	X	H	N	I		

[18F]39	H	H	H	OCH_2CH_2X	H	CH	18-F		
[18F]40	H	H	H	$OCH_2CH_2CH_2CH_2X$	H	CH	18-F		
[18F]41	H	H	H	CH_2X	H	CH	18-F		
[18F]42	H	H	H	X	Z	CH	18-F		CN
[18F]43	H	H	H	X	H	N	18-F		

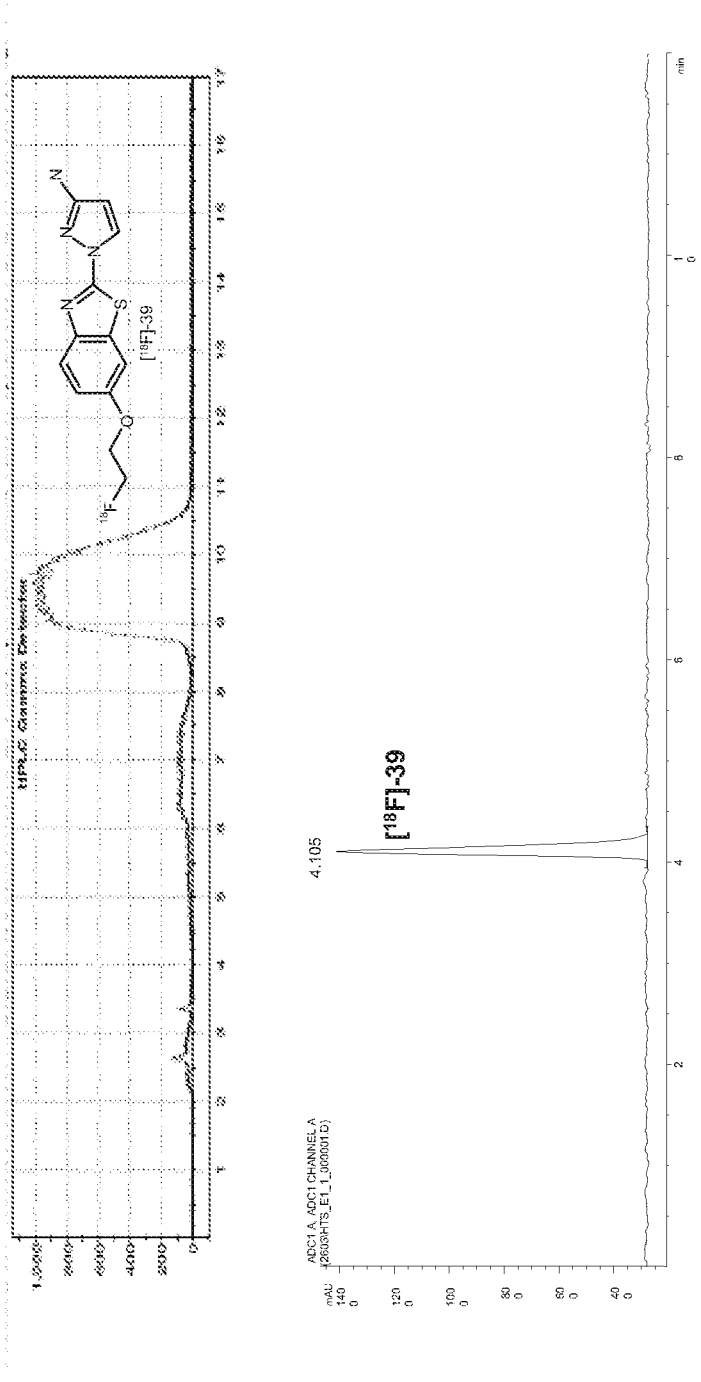
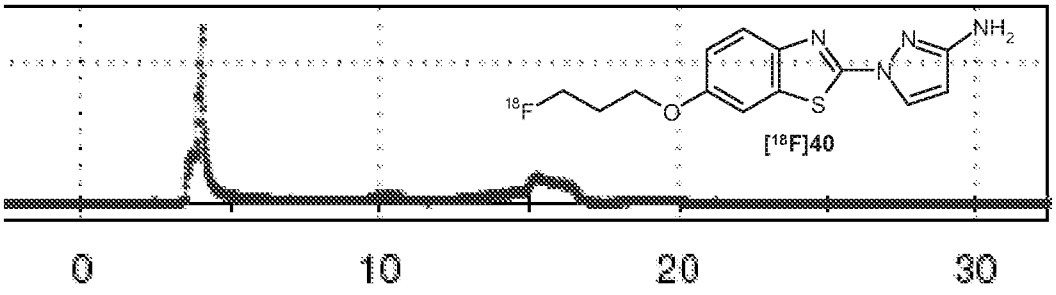
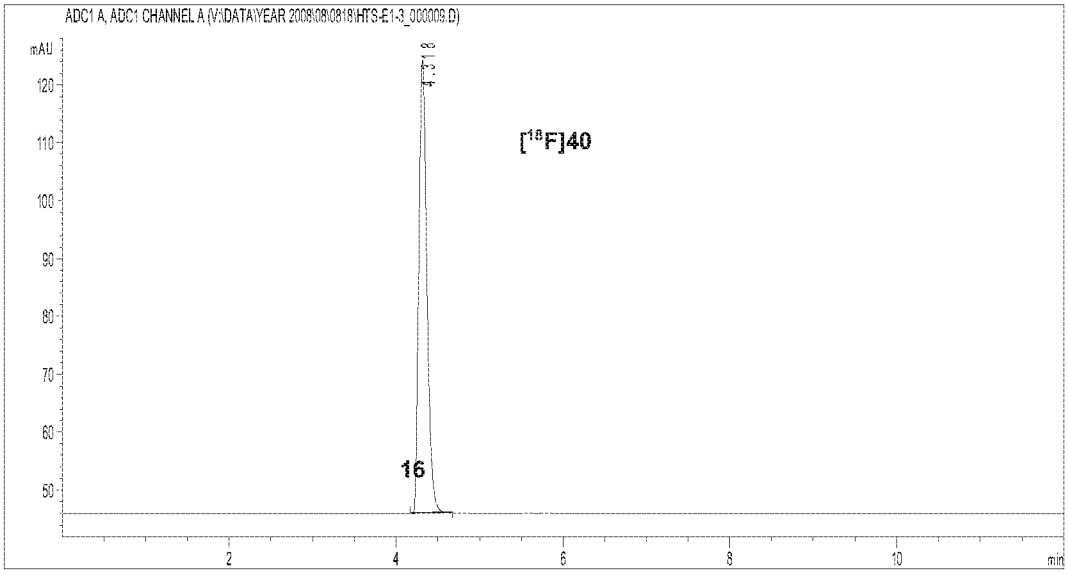


Fig. 2

Fig. 3


^{18}F
O
N
N
S
NH$_2$
[^{18}F]40
0
10
20
30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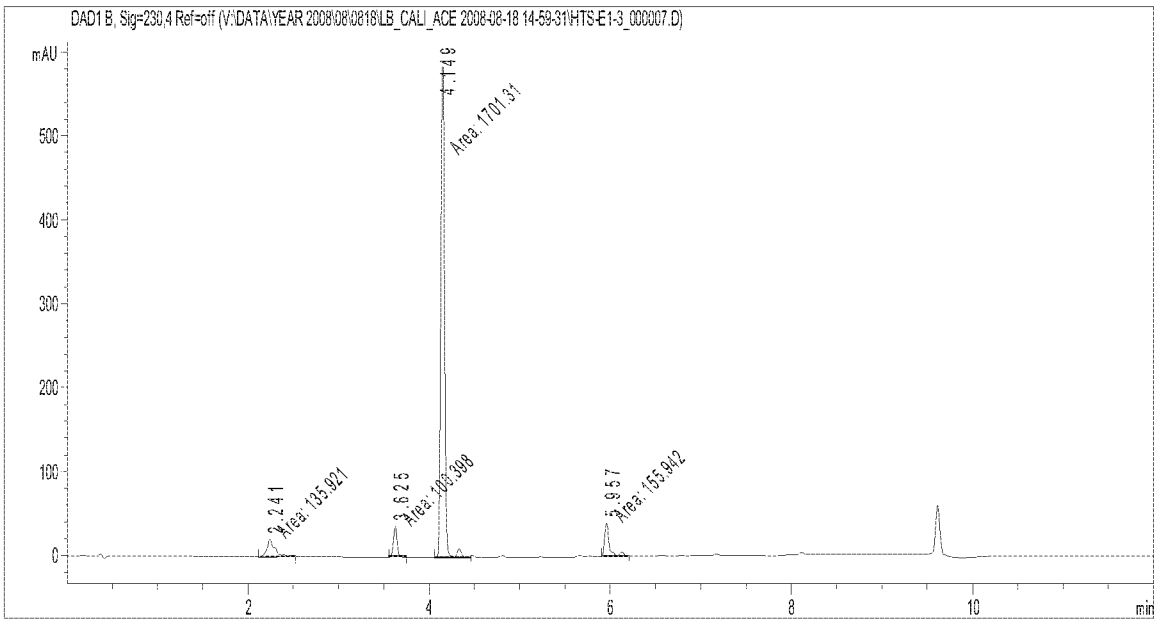
mAU
4.371 8
[^{18}F]40
16
min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mAU
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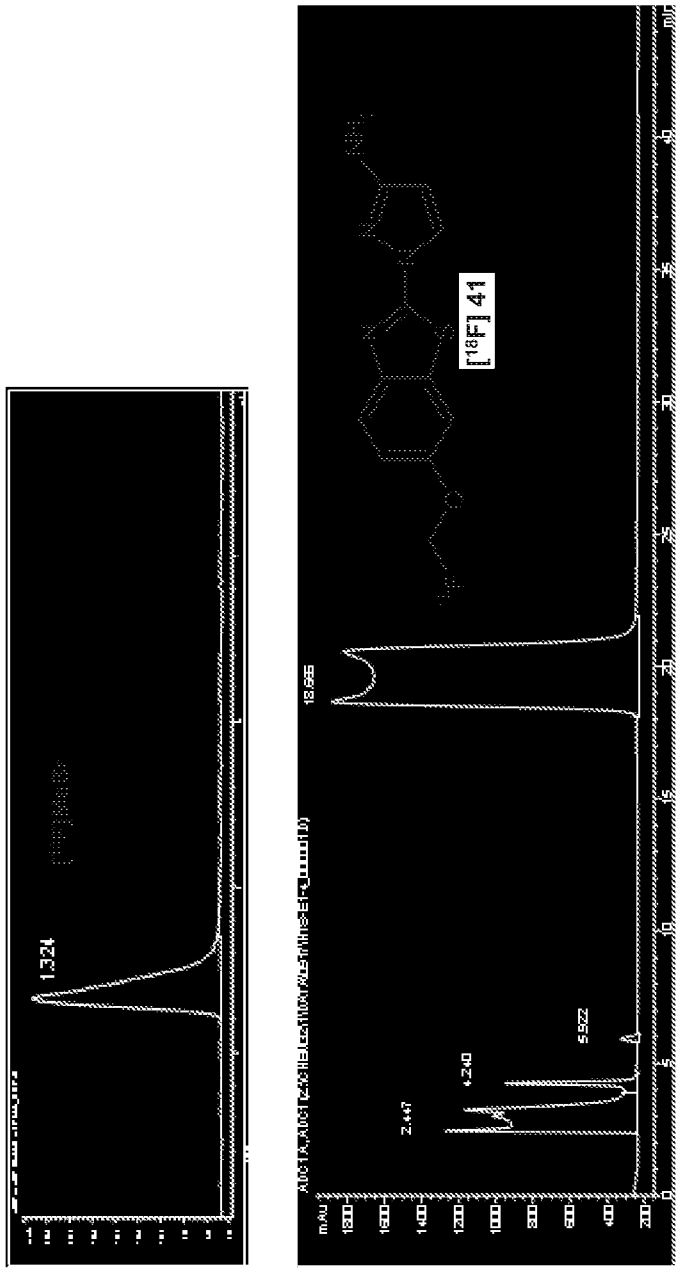
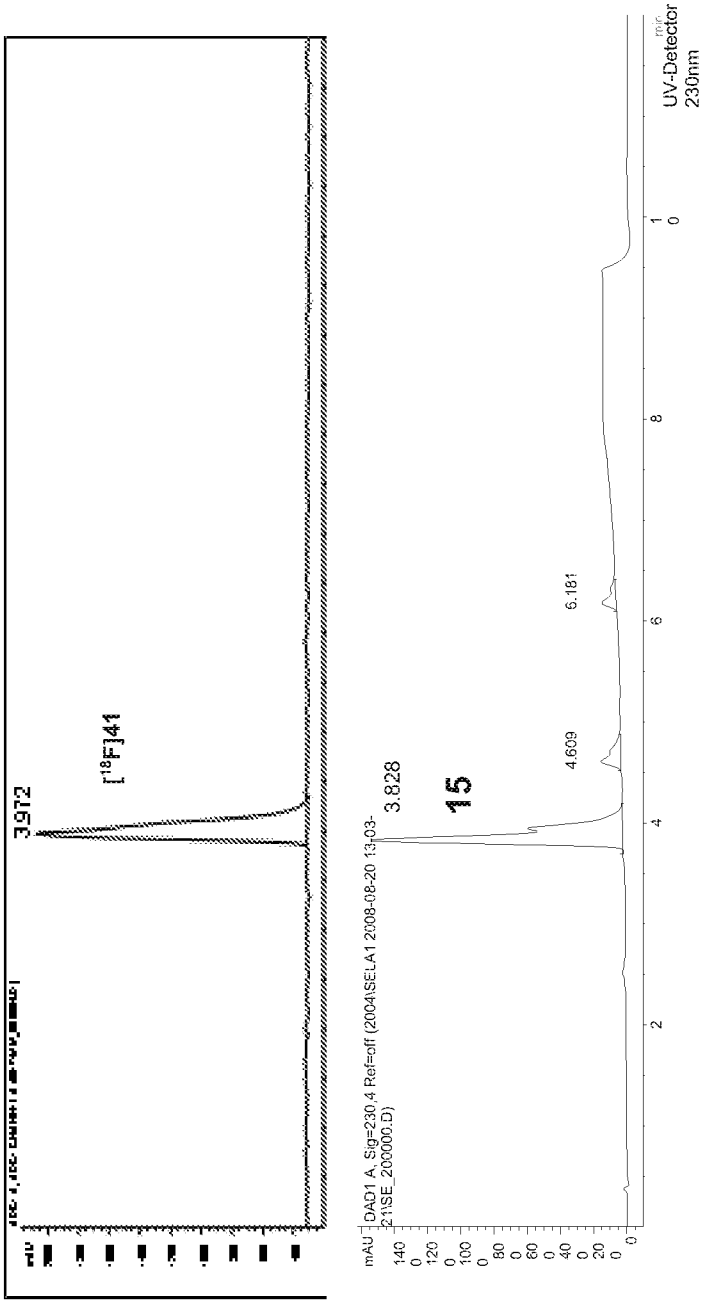
2.241
Area: 135.921
3.625
Area: 103.398
5.957
Area: 155.942
min

Fig. 4




3972
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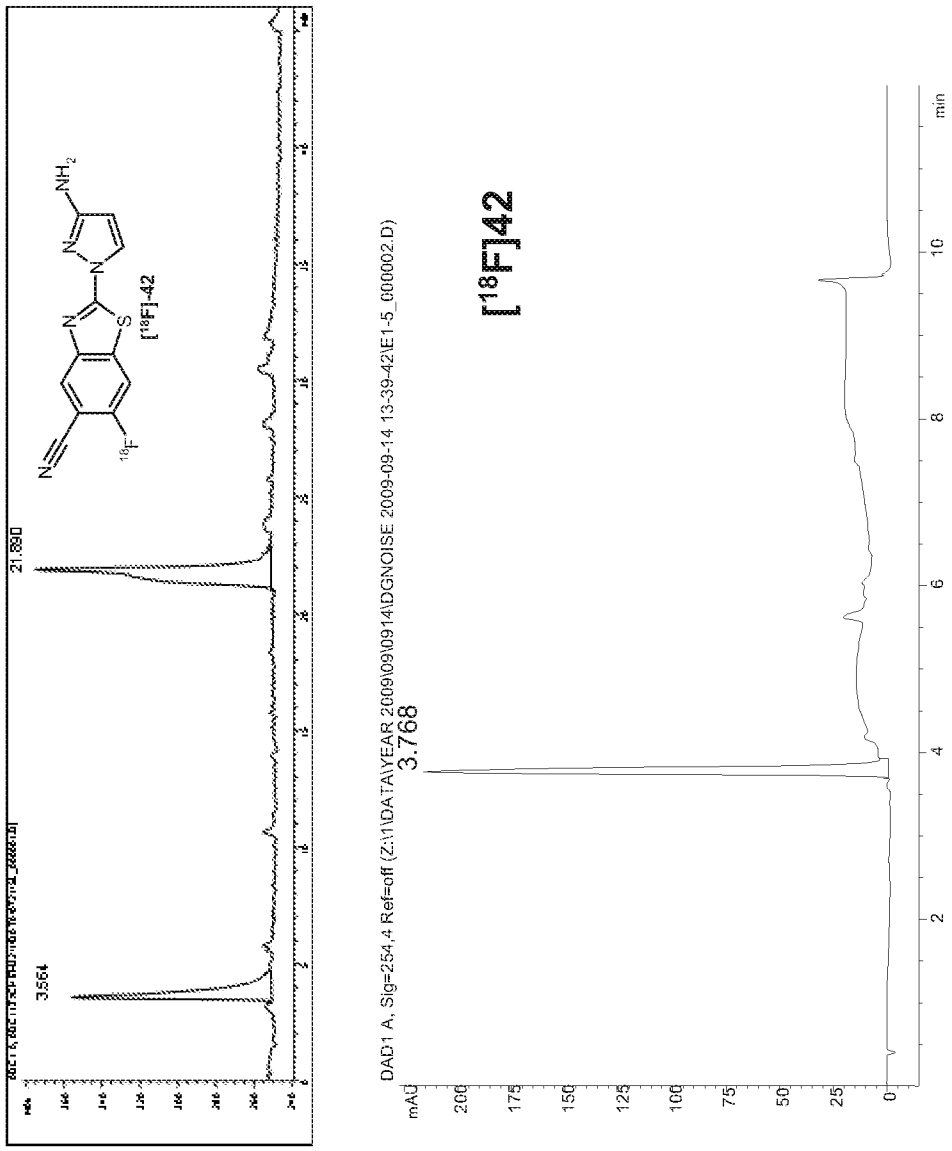
15
3.828
4.609
6.181
mAU
DAD1 A, Sig=230,4 Ref=off (2004\SELA1 2008-08-20 13-03-21\SE_200000.D)
UV-Detector 230nm

Fig. 5

HPLC (preparative)



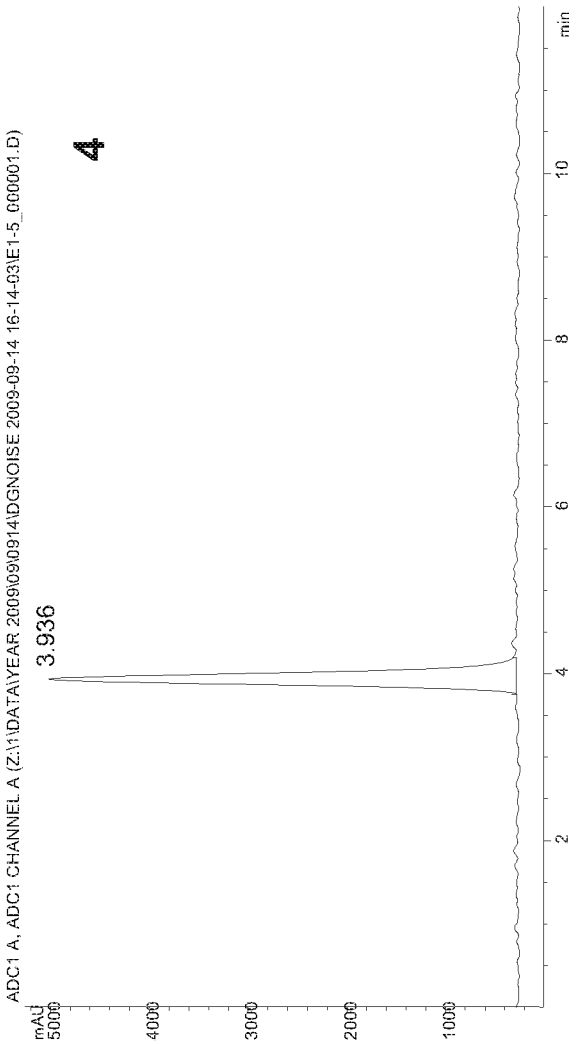
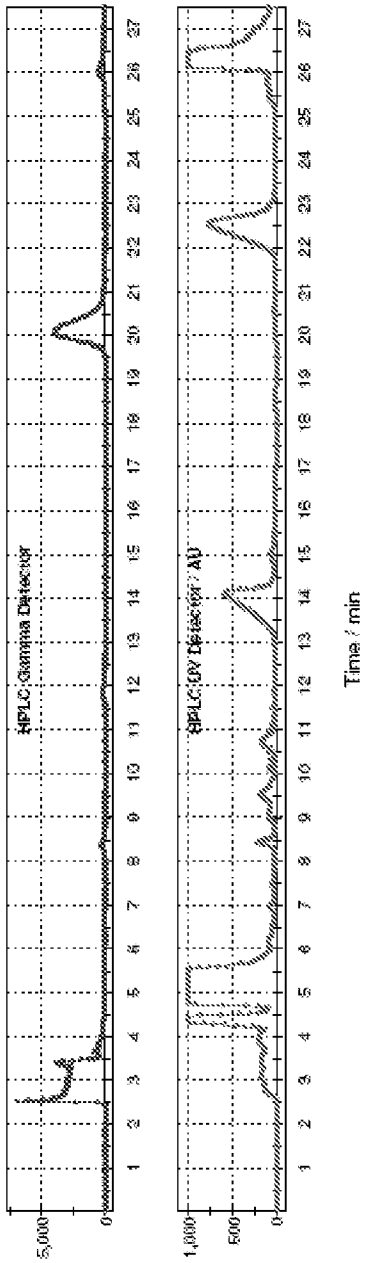
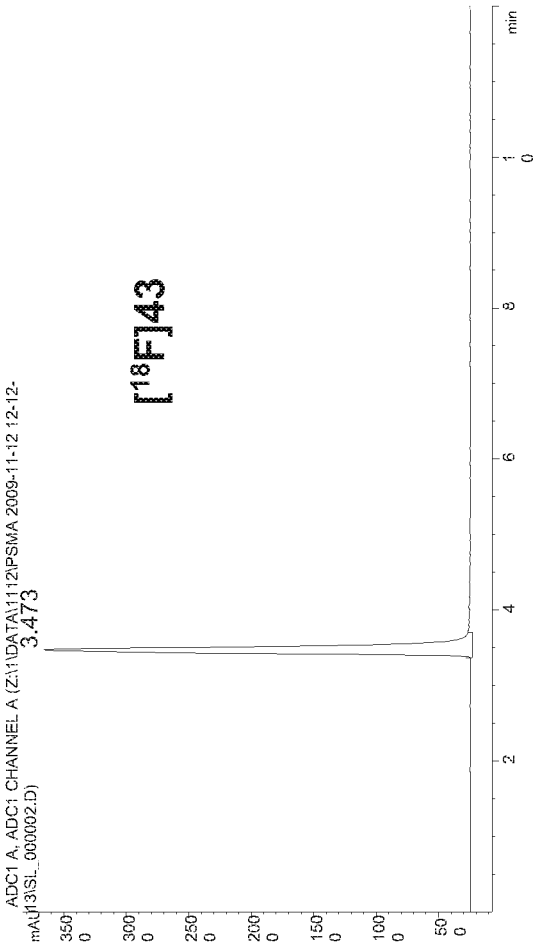
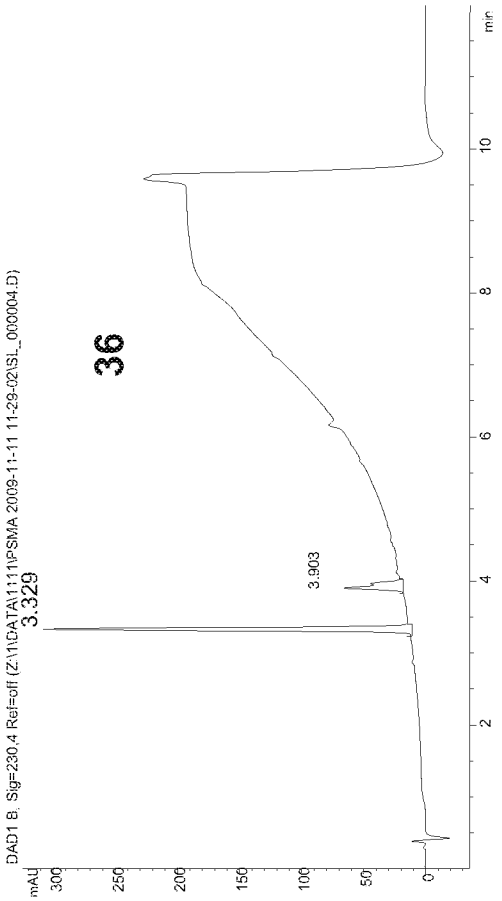

ADC1 A, ADC1 CHANNEL A (Z:\1\DATA\YEAR 2009\09\0914\DGNOISE 2009-09-14 16-14-03\E1-5_000001.D)
4
3.936
mAU
5000
4000
3000
2000
1000
2
4
6
8
10
min

Fig. 6


HPLC Gamma Detector
HPLC UV Detector: AU
Time / min


[18F]43
ADC1 A, ADC1 CHANNEL A (Z:\1\DATA\1112\PSMA 2009-11-12 12-12-
3.473
mAU
min


DAD1 B, Sig=230,4 Ref=off (Z:\1\DATA\1\111\PSMA 2009-11-11 11-29-02\SL_000004.D)
mAU
300
250
200
150
100
50
0
3.329
3.903
36
2
4
6
8
10
min

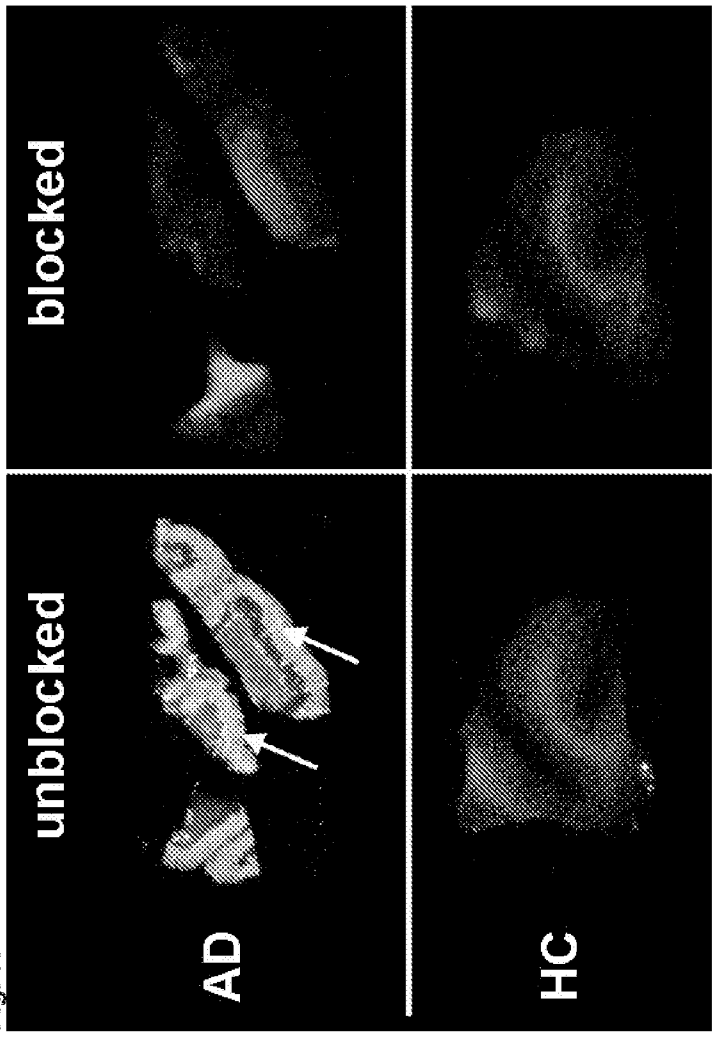


Fig. 7:

Fig. 8:

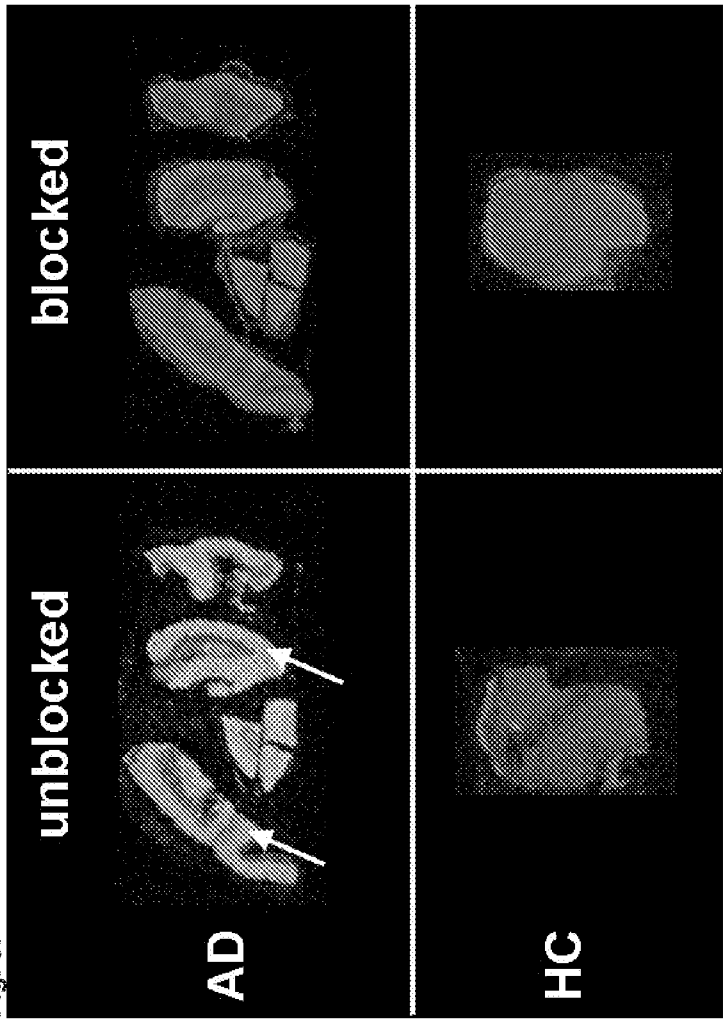
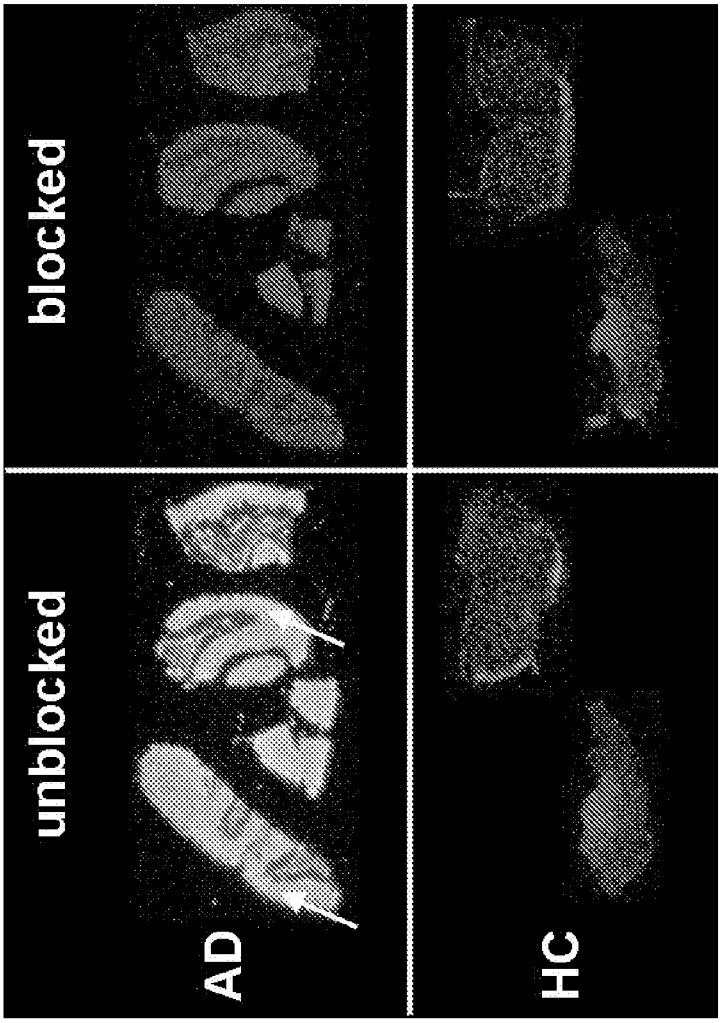


Fig. 9:



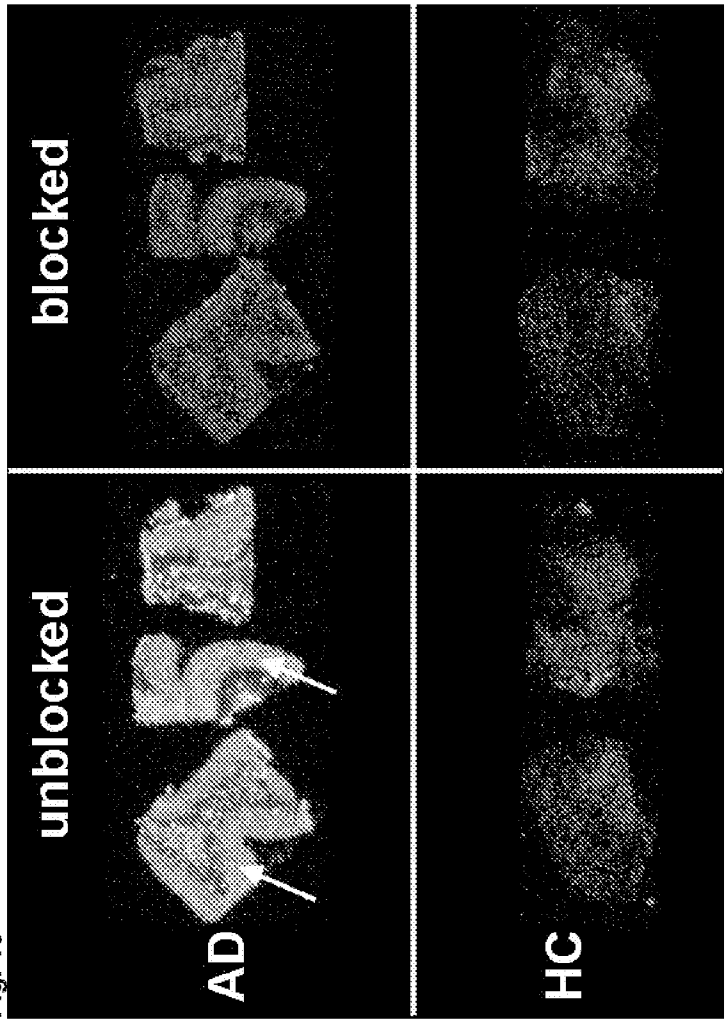


Fig. 10

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/061967

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D417/04 C07D513/04 A61K31/437 A61K31/428 A61K31/431 A61P25/28
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal , WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010/066357 A1 (BAYER SCHERING PHARMA AG [DE] ; HASSFELD JORMA [DE] ; ROEHN ULRIKE [DE] ;) 17 June 2010 (2010-06-17) the whole document	1, 13, 14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu¬ments, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 October 2011	25/10/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	de Nooy, Arjan

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/061967

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010066357 Al	17-06-2010	AR 074593 Al	26-01-2011
		CA 2746433 Al	17-06-2010
		EP 2376463 Al	19-10-2011
		US 2011243846 Al	06-10-2011