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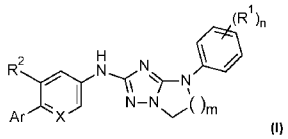
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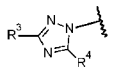
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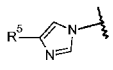
(54) Title: BICYCLIC HETEROARYL DERIVATIVES



(I)



(A)



(B)



(C)



(D)



(E)



(F)

(57) Abstract: The present invention relates to a compound of formula (I), wherein R^1 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy or lower alkoxy substituted by halogen; and R^1 may be different if n is 2 or 3; R^2 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, CN, lower alkoxy or lower alkoxy substituted by halogen; X is CH or N; m is 1, 2 or 3; -( )$_m$ is $-(CH_2)_m-$; n is 1, 2 or 3; Ar is a five membered heteroaryl group, selected from formula (A), (B), (C), (D), (E) or (F), wherein R^3 is hydrogen, methyl or chloro; R^4 is hydrogen or methyl; R^5 is F, Cl, CHF_2 or CF_3; or to pharmaceutically active acid addition salts thereof. The compounds may be used for the treatment of Alzheimer's disease, cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis, Dutch-type (HCHWA-D), multi-infarct dementia, dementia pugilistica or Down syndrome.

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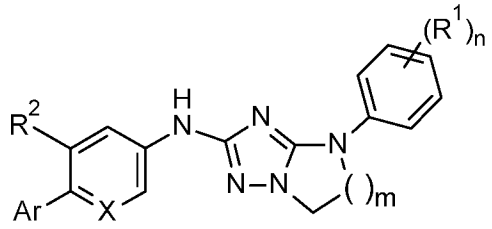
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Bicyclic heteroaryl derivatives

The present invention relates to a compound of formula I,



I

wherein

R^1 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy or lower alkoxy substituted by halogen;
and R^1 may be different if n is 2 or 3;

R^2 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, CN, lower alkoxy or lower alkoxy substituted by halogen;

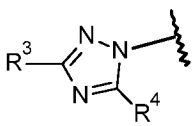
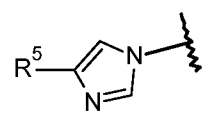
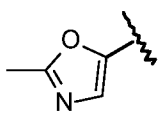
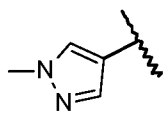
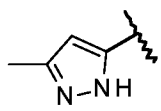
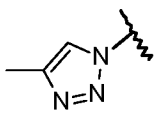
X is CH or N;

m is 1, 2 or 3;

n is 1, 2 or 3;

-( )$_m$ is $-(CH_2)_m-$;

Ar is a five membered heteroaryl group, selected from


,

,

,

,

or

,

wherein

R^3 is hydrogen, methyl or chloro;

R^4 is hydrogen or methyl;

R^5 is F, Cl, CHF_2 or CF_3;

or to pharmaceutically active acid addition salts thereof.

Now it has been found that the present compounds of formula I are modulators of γ-secretase, they may be useful for the treatment or prevention of a disease associated with the deposition of β-amyloid in the brain, in particular Alzheimer's disease, and other diseases such as cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis, Dutch-type (HCHWA-D), multi-infarct dementia, dementia pugilistica and Down syndrome.

Alzheimer's disease (AD) is the most common cause of dementia in later life. Pathologically, AD is characterized by the deposition of amyloid in extracellular plaques and intracellular neurofibrillary tangles in the brain. The amyloid plaques are mainly composed of amyloid peptides (Aβ peptides) which originate from the β-Amyloid Precursor Protein (APP) by a series of proteolytic cleavage steps. Several forms of APP have been identified of which the most abundant are proteins of 695, 751 and 770 amino acids length. They all arise from a single gene through differential splicing. The Aβ peptides are derived from the same domain of the APP.

Aβ peptides are produced from APP through the sequential action of two proteolytic enzymes termed β- and γ-secretase. β-Secretase cleaves first in the extracellular domain of APP just outside of the trans-membrane domain (TM) to produce a C-terminal fragment of APP (CTFβ) containing the TM- and cytoplasmatic domain. CTFβ is the substrate for γ-secretase which cleaves at several adjacent positions within the TM to produce the Aβ peptides and the cytoplasmic fragment. Various proteolytic cleavages mediated by γ-secretase result in Aβ peptides of different chain length, e.g. Aβ38, Aβ40 and Aβ42. The latter one is regarded to be the more pathogenic amyloid peptide because of its strong tendency to form neurotoxic aggregates.

The β-secretase is a typical aspartyl protease. The γ-secretase is a high molecular weight complex that consists of four essential subunits: Presenilin (PS, including PS1 and PS2), nicastrin, anterior pharynx defective 1 (APH-1), and presenilin enhancer 2 (PEN-2). The atomic structure of human γ-secretase at 3.4 Å resolution has been published (X. Bai, C. Yan, G. Yang, P. Lu, D. Ma, L. Sun, R. Zhou, S. H. W. Scheres, Y. Shi, Nature 2015, 525, pages 212 – 217. The presenilins are bearing the catalytic site and represent a group of atypical aspartyl proteases which cleave their substrates within the TM of and which are themselves polytopic membrane proteins. The other essential components of γ-secretase , nicastrin and the products of the aph1

and pen-2 genes are believed to be responsible for substrate recognition and recruitment. Proven substrates for γ-secretase are APP and the proteins of the Notch receptor family, however, γ-secretase has a loose substrate specificity and many further membrane proteins unrelated to APP and Notch have been reported to be cleaved by the γ-secretase in vitro.

The γ-secretase activity is absolutely required for the production of Aβ peptides. This has been shown both by genetic means, i.e., ablation of the presenilin genes and by low-molecular-weight inhibitory compounds. According to the amyloid cascade hypothesis for AD the production and deposition of Aβ is the ultimate cause for the disease. Therefore, it was believed that selective and potent inhibition of γ-secretase might be useful for the prevention and treatment of AD.

An alternative mode of treatment is the modulation of the γ-secretase activity which results in a selective reduction of the Aβ42 production. This will lead in an increase of shorter Aβ isoforms, such as Aβ38, Aβ37 or others, which have no or reduced capability for aggregation and plaque formation, and are not or less neurotoxic. Compounds which show this effect on modulating γ-secretase activity include certain non-steroidal anti-inflammatory drugs (NSAIDs) and related analogues (Weggen et al., Nature, 414 (2001) 212-16).

Thus, the compounds of this invention will be useful for the treatment or prevention of a disease associated with the deposition of β-amyloid in the brain, in particular Alzheimer's disease, and other diseases such as cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis, Dutch-type (HCHWA-D), multi-infarct dementia, dementia pugilistica and Down syndrome.

Numerous documents describe the current knowledge on γ-secretase modulation, for example the following publications:

Morihara et al, J. Neurochem., 83 (2002) 1009-12

Jantzen et al, J.Neuroscience, 22 (2002) 226-54

Takahashi et al, J. Biol. Chem., 278 (2003) 18644-70

Beher et al, J. Biol. Chem. 279 (2004) 43419-26

Lleo et al, Nature Med. 10 (2004) 1065-6

Kukar et al, Nature Med. 11 (2005) 545-50

Perretto et al, J. Med. Chem. 48 (2005) 5705-20

Clarke et al, J. Biol. Chem. 281 (2006) 31279-89

Stock et al, Bioorg. Med. Chem. Lett. 16 (2006) 2219–2223

Narlawar et al, J. Med. Chem. 49 (2006) 7588-91

Ebke et al, J. Biol. Chem., 286 (2011) 37181-86

Oehlich, Gijsen et al, J. Med. Chem., 54 (2011), 669 – 698

Li et al., Biochemistry, 52, (2013), 3197 - 3216

Hall et al, Progress in Med. Chem., 53 (2014) 101-145

Bursavich et al, J. Med. Chem., 59 (2016) DOI: 10.1021/acs.jmedchem.5b01960

The following definitions for compounds of formula I are used:

As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain group containing from 1 to 7 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred alkyl groups are groups with 1 - 4 carbon atoms.

As used herein, the term "lower alkyl substituted by halogen" denotes an alkyl group as defined above, wherein at least one hydrogen atom is replaced by halogen, for example CF_3, CHF_2, CH_2F, $CHFCF_3$, CH_2CHF_2, CH_2CH_2F, $CH_2C(CH_3)_2CF_3$, $CH_2CF_2CF_3$, $CH(CF_3)_2$, CH_2CF_3, $(CH_2)_2CF_3$, $(CH_2)_3CF_3$, $CH(CH_3)CF_3$, CF_2CF_3, and the like. The preferred group is CF_3.

The term “lower alkoxy” denotes a lower alkyl group as defined above, which group is connected via an O atom.

The term “lower alkoxy substituted by halogen” denotes a lower alkoxy group as defined above, wherein at least one hydrogen atom is replaced by halogen.

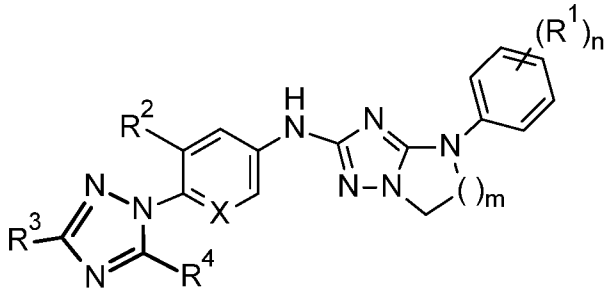
The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

Objects of the present invention are compounds of formula I, the use of such compounds for the preparation of medicaments for the treatment of Alzheimer’s disease, cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis, Dutch-type (HCHWA-D), multi-infarct dementia, dementia pugilistica or Down syndrome, their manufacture and medicaments based on a compound of formula I in accordance with the invention.

Further objects of the present invention are all forms of optically pure enantiomers, racemates or diastereometric mixtures for compounds of formula I.

One object of the present invention is a compound of formula I-1,



I-1,

wherein

R^1 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy or lower alkoxy substituted by halogen;
and R^1 may be different if n is 2 or 3;

R^2 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, CN, lower alkoxy or lower alkoxy substituted by halogen;

X is CH or N;

m is 1, 2 or 3;

n is 1, 2 or 3;

R^3 is hydrogen, methyl or chloro;

R^4 is hydrogen or methyl;

$-(\ )_m$ is $-(CH_2)_m-$;

or a pharmaceutically active acid addition salt thereof, for example the following compounds

N-[3-(difluoromethoxy)-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

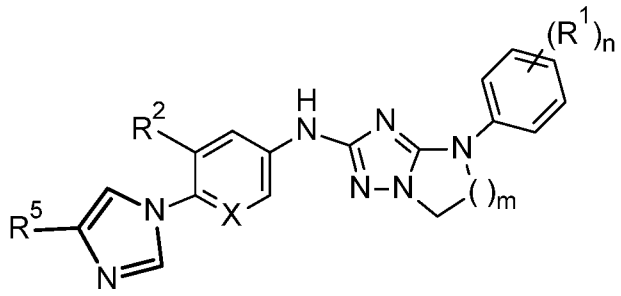
4-(3,4-difluorophenyl)-N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

4-(3,4-difluorophenyl)-N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepin-2-amine

4-(3,4-difluorophenyl)-N-[3-fluoro-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-

[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
N-[4-(3-chloro-1,2,4-triazol-1-yl)-3-methoxy-phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
4-(3,4-difluorophenyl)-N-[3-fluoro-4-(5-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
4-(3,4-difluorophenyl)-N-[3-fluoro-4-(1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-4-(2,3,4-trifluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
N-[4-(3-chloro-1,2,4-triazol-1-yl)-3-fluoro-phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
4-(3,4-difluorophenyl)-N-[4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
5-[[4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]amino]-2-(3-methyl-1,2,4-triazol-1-yl)benzonitrile
4-(3-fluorophenyl)-N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
4-(4-fluorophenyl)-N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
N-[3-(difluoromethoxy)-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
4-(3,5-difluorophenyl)-N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine or
N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-4-phenyl-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine.

One further object of the present invention is a compound of formula I-2,



I-2,

wherein

R^1 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy or lower alkoxy substituted by halogen;
and R^1 may be different if n is 2 or 3;

R^2 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, CN, lower alkoxy or lower alkoxy substituted by halogen;

X is CH or N;

m is 1, 2 or 3;

n is 1, 2 or 3;

R^5 is F, Cl, CHF_2 or CF_3;

$-(\ )_m$ is $-(CH_2)_m-$;

or a pharmaceutically active acid addition salt thereof, for example the following compounds

4-(3,4-difluorophenyl)-N-[3-methoxy-4-[4-(trifluoromethyl)imidazol-1-yl]phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

N-[6-(4-chloroimidazol-1-yl)-5-methoxy-3-pyridyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(3,4-difluorophenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepin-2-amine

4-(3,4-difluorophenyl)-N-[3-methoxy-4-[4-(trifluoromethyl)imidazol-1-yl]phenyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepin-2-amine

N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(2,3,4-trifluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

N-[4-(4-chloroimidazol-1-yl)-3-fluoro-phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

N-[4-(4-chloroimidazol-1-yl)phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

2-(4-chloroimidazol-1-yl)-5-[[4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]amino]benzonitrile

2-[4-(difluoromethyl)imidazol-1-yl]-5-[[4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]amino]benzonitrile

N-[3-chloro-4-(4-chloroimidazol-1-yl)phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(3-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

2-(4-chloroimidazol-1-yl)-5-[[4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]amino]benzonitrile

N-[4-(4-chloroimidazol-1-yl)-3-fluoro-phenyl]-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

N-[6-(4-chloroimidazol-1-yl)-5-methoxy-3-pyridyl]-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

4-(3,4-difluorophenyl)-N-[4-(4-fluoroimidazol-1-yl)-3-methoxy-phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

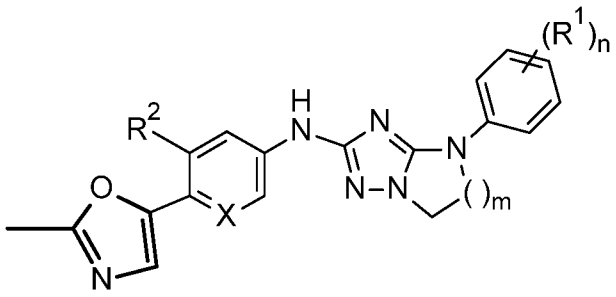
N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(3,5-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-[4-(trifluoromethyl)phenyl]-5,6-dihydroimidazo[1,2-b][1,2,4]triazol-2-amine

N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(2,3,4-trifluorophenyl)-5,6-dihydroimidazo[1,2-b][1,2,4]triazol-2-amine or

N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(3,4-difluorophenyl)-5,6-dihydroimidazo[1,2-b][1,2,4]triazol-2-amine.

One object of the present invention is a compound of formula I-3,



I-3,

wherein

R^1 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy or lower alkoxy substituted by halogen;
and R^1 may be different if n is 2 or 3;

R^2 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, CN, lower alkoxy or lower alkoxy substituted by halogen;

X is CH or N;

m is 1, 2 or 3;

n is 1, 2 or 3;

$-(\ )_m$ is $-(CH_2)_m-$

or a pharmaceutically active acid addition salt thereof, for example the following compounds

4-(3,4-difluorophenyl)-N-[3-methoxy-4-(2-methyloxazol-5-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

4-(3,4-difluorophenyl)-N-[3-methoxy-4-(2-methyloxazol-5-yl)phenyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepin-2-amine

N-[3-methoxy-4-(2-methyloxazol-5-yl)phenyl]-4-(2,3,4-trifluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

4-(3,4-difluorophenyl)-N-[3-fluoro-4-(2-methyloxazol-5-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

4-(3,4-difluorophenyl)-N-[4-(2-methyloxazol-5-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

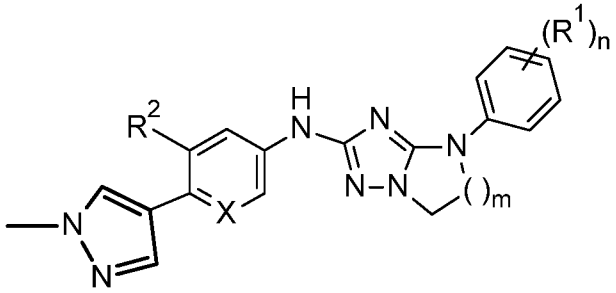
5-[[4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]amino]-2-(2-

methyloxazol-5-yl)benzonitrile

N-[5-fluoro-6-(2-methyloxazol-5-yl)-3-pyridyl]-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine or

4-(4-fluorophenyl)-N-[3-methoxy-4-(2-methyloxazol-5-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine.

One object of the present invention is a compound of formula I-4,



I-4,

wherein

R^1 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy or lower alkoxy substituted by halogen;
and R^1 may be different if n is 2 or 3;

R^2 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, CN, lower alkoxy or lower alkoxy substituted by halogen;

X is CH or N;

m is 1, 2 or 3;

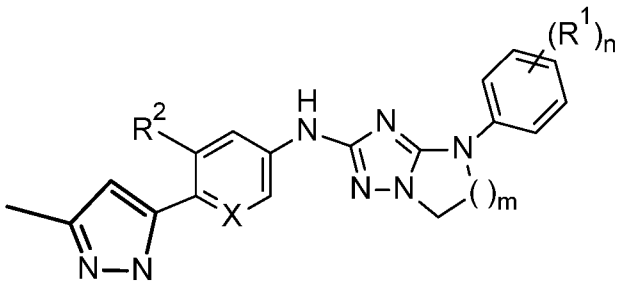
n is 1, 2 or 3;

$-(\ )_m$ is $-(CH_2)_m-$

or a pharmaceutically active acid addition salt thereof, for example the following compound

4-(3,4-difluorophenyl)-N-[3-methoxy-4-(1-methylpyrazol-4-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine.

One object of the present invention is a compound of formula I-5,



I-5,

wherein

R^1 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy or lower alkoxy substituted by halogen;
and R^1 may be different if n is 2 or 3;

R^2 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, CN, lower alkoxy or lower alkoxy substituted by halogen;

X is CH or N;

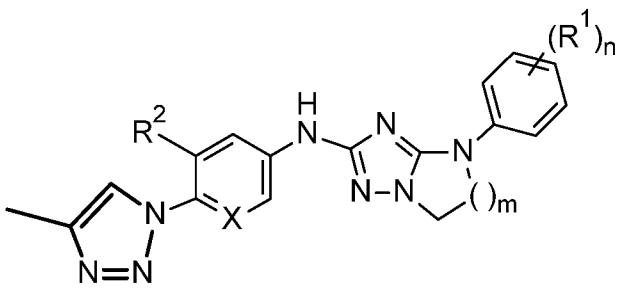
m is 1, 2 or 3;

n is 1, 2 or 3;

$-(\,)_m$ is $-(CH_2)_m-$

or a pharmaceutically active acid addition salt thereof, for example the following compound 4-(3,4-difluorophenyl)-N-[3-methoxy-4-(3-methyl-1H-pyrazol-5-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine.

One object of the present invention is a compound of formula I-6,



I-6,

wherein

R^1 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy or lower alkoxy substituted by halogen;
and R^1 may be different if n is 2 or 3;

R^2 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, CN, lower alkoxy or lower alkoxy substituted by halogen;

X is CH or N;

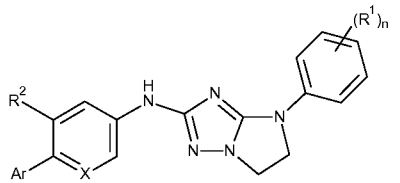
m is 1, 2 or 3;

n is 1, 2 or 3;

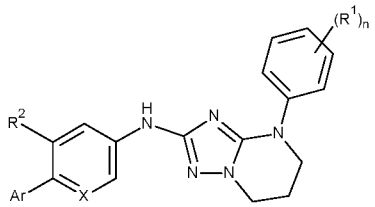
$-(\ )_m$ is $-(CH_2)_m-$

or a pharmaceutically active acid addition salt thereof, for example the following compound 4-(3,4-difluorophenyl)-N-[4-(4-methyltriazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine.

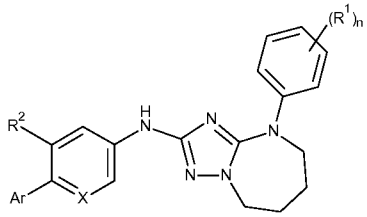
Further objects of the present invention are compounds of formulas



Ia,



Ib or



Ic,

wherein

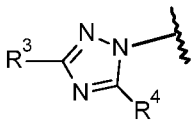
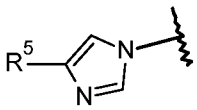
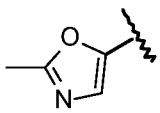
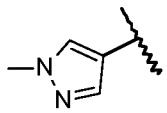
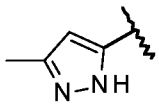
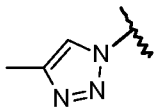
R^1 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy or lower alkoxy substituted by halogen;
and R^1 may be different if n is 2 or 3;

R^2 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, CN, lower alkoxy or lower alkoxy substituted by halogen;

X is CH or N;

n is 1, 2 or 3;

Ar is a five membered heteroaryl group, selected from






or

,

R^3 is hydrogen, methyl or chloro;

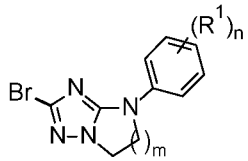
R^4 is hydrogen or methyl;

R^5 is F, Cl, CHF_2 or CF_3;

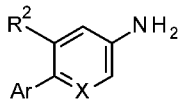
or pharmaceutically active acid addition salts thereof.

The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which processes comprise

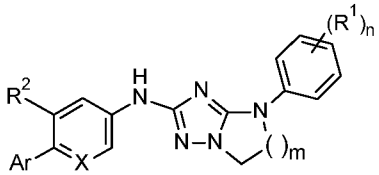
a) reacting a compound of formula 9



with a compound of formula 10-b



to a compound of formula I



wherein the substituents have the meaning as described above, and,

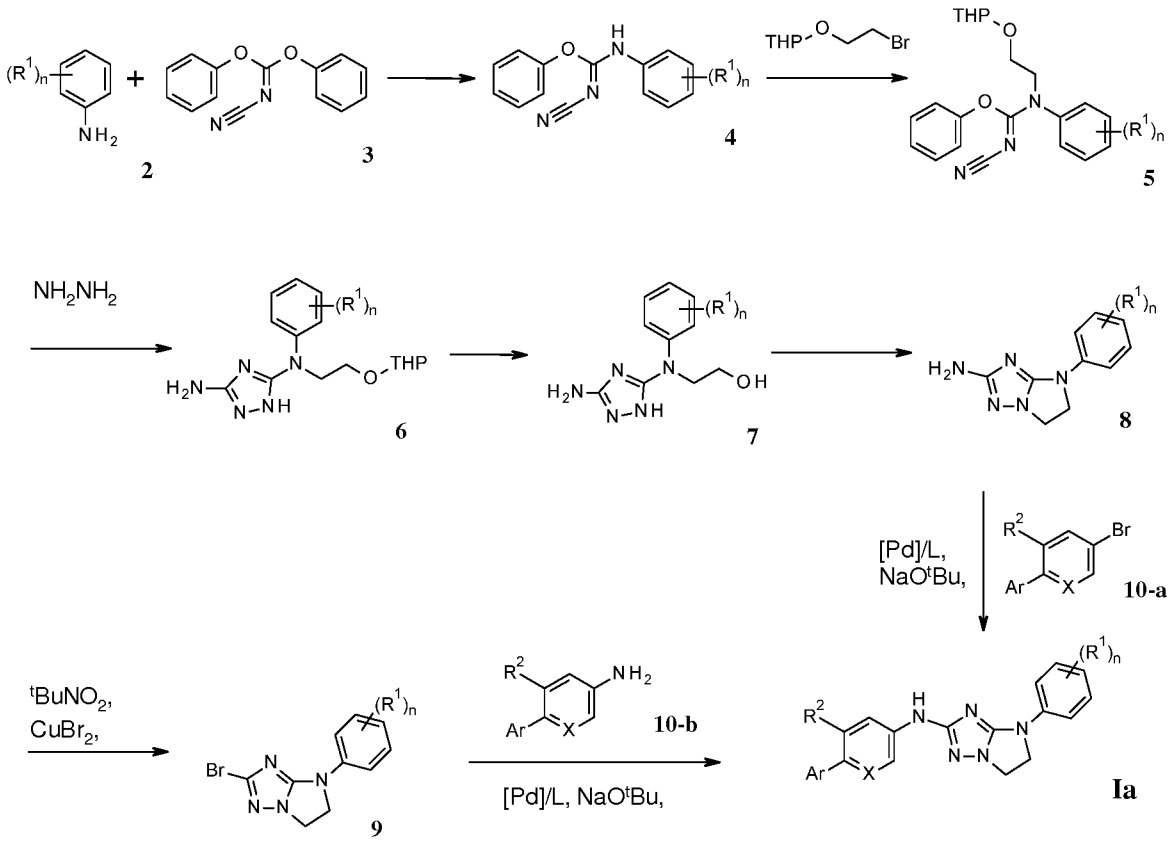
if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts;

In more detail, compounds of formula I and their intermediates may be prepared by schemes 1 – 3 and by the description of 48 specific examples.

General synthesis schemes

General Synthesis of derivatives of type Ia with m = 1

Scheme 1

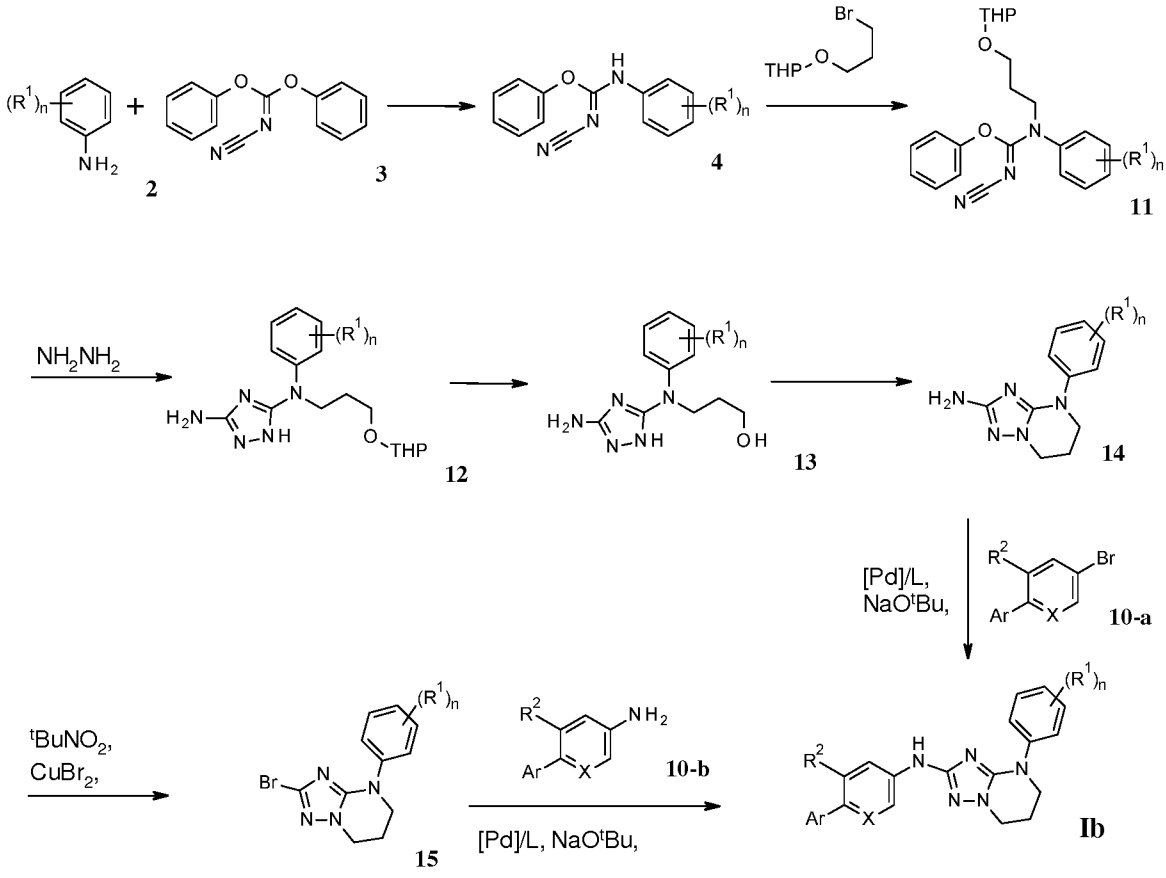


The preparation of derivatives of general formula **Ia** with (m =1), where made according to the scheme 1. The synthesis of target compounds commenced by the nucleophilic addition of a commercially available substituted anilines **2** onto the diphenyl cyanocarbonimidate **3** leading to the intermediates **4** in a good yield. Upon N-alkylation with an electrophile [2-(2-bromoethoxy)tetrahydropyran] containing a protected alcohol moiety the compounds **5** were

obtained. Upon reaction with hydrazine the corresponding triazoles **6** were obtained. Deprotection of the alcohol protected by tetrahydropyran (THP) group under standard acidic conditions afforded **7** in nearly quantitative yield, the alcohol precursor for the Mitsunobu reaction forming **8**. A Buchwald coupling of **8** with a bromo derivatives of formula **10-a** gave final compounds **Ia**. Alternatively, a Sandmeyer reaction with **8** led to the versatiles intermediates bromotriazole **9**, which can easily undergo a Buchwald type reaction with different anilines of type **10-b** affording also final products of formula **Ia**.

General Synthesis of derivatives of type Ib with m = 2

Scheme 2

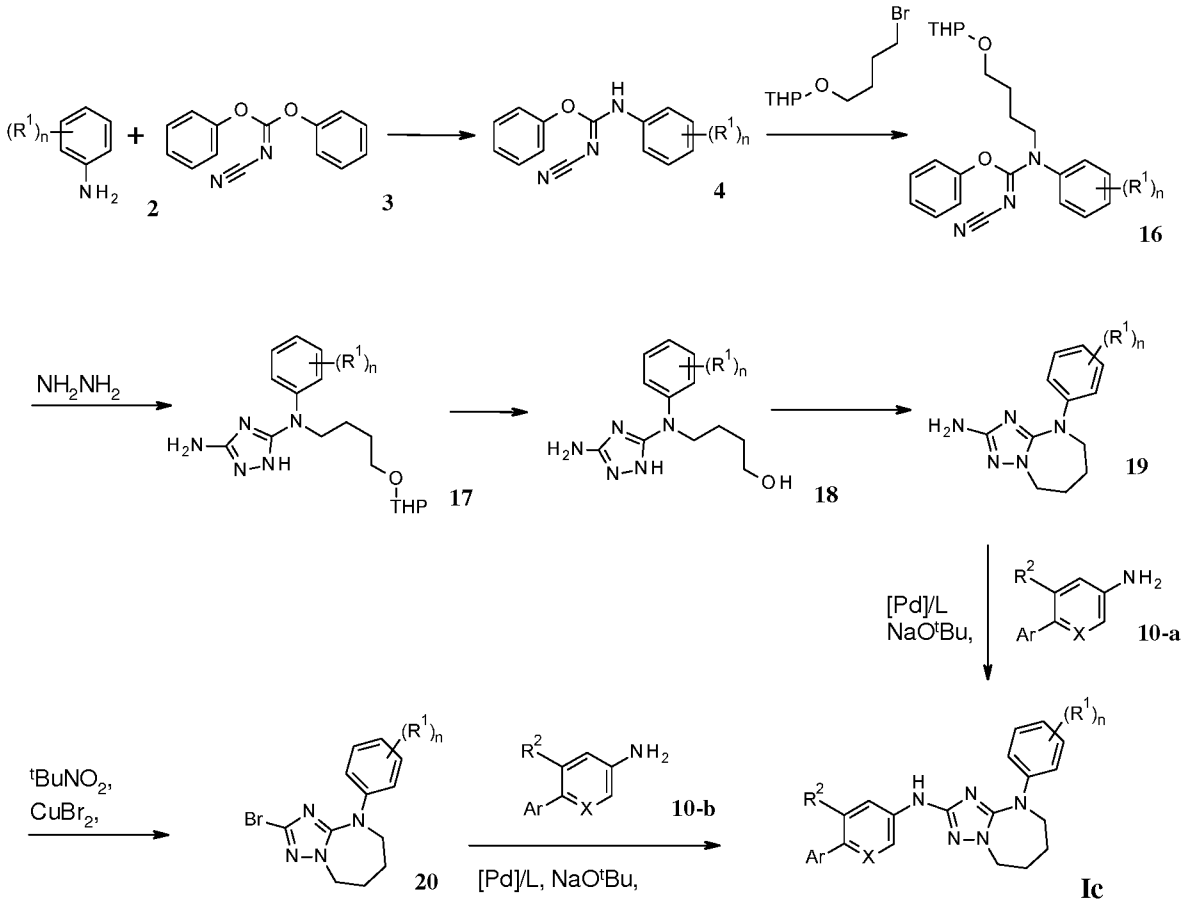


The preparation of derivatives of general formula **Ib** with (m =2), where made according to the scheme 2. The synthesis of target compounds commenced by the nucleophilic addition of a commercially available substituted anilines **2** onto the diphenyl cyanocarbonimidate **3** leading to the intermediates **4** in a good yield. Upon N-alkylation with an electrophile [2-(3-

bromopropoxy)tetrahydropyran] containing a protected alcohol moiety the compounds **11** were obtained. Upon reaction with hydrazine the corresponding triazoles **12** were obtained. Deprotection of the alcohol protected by tetrahydropyran (THP) group under standard acidic conditions afforded **13** in nearly quantitative yield, the alcohol precursor for the Mitsunobu reaction forming **14**. A Buchwald coupling of **14** with a bromo derivatives of formula **10-a** gave final compounds **Ib**. Alternatively, a Sandmeyer reaction of **14** led to the versatiles intermediates bromotriazole **15**, which can easily undergo a Buchwald type reaction with different anilines of type **10-b** affording also final products of formula **Ib**.

General Synthesis of derivatives of type Ic with m = 3

Scheme 3



The preparation of derivatives of general formula **Ic** with (m =3), where made according to the scheme 3. The synthesis of target compounds commenced by the nucleophilic addition of a

commercially available substituted anilines **2** onto the diphenyl cyanocarbonimidate **3** leading to the intermediates **4** in a good yield. Upon N-alkylation with an electrophile [2-(4-bromobutoxy)tetrahydropyran] containing a protected alcohol moiety the compounds **16** were obtained. Upon reaction with hydrazine the corresponding triazoles **17** were obtained. Deprotection of the alcohol protected by tetrahydropyran (THP) group under standard acidic conditions afforded **18** in nearly quantitative yield, the alcohol precursor for the Mitsunobu reaction forming **19**. A Buchwald coupling of **19** with a bromo derivatives of formula **10-a** gave final compounds **Ic**. Alternatively, a Sandmeyer reaction of **19** led to the versatiles intermediates bromotriazole **20**, which can easily undergo a Buchwald type reaction with different anilines of type **10-b** affording final products of formula **Ic**.

The heterocycles halides are either commercial available, known in the literature so they can be prepared by methods known in the art or alternatively could be prepared as described in the specification.

The compounds were investigated in accordance with the test given hereinafter.

Description of γ-secretase assay

Cellular γ-secretase assay

Human neuroglioma H4 cells overexpressing human APP695 with the Swedish double mutation (K595N/M596L) were plated at 30,000 cells/well/100 µl in 96-well plates in IMDM media containing 10% FCS, 0.2 mg/l Hygromycin B and incubated at 37°C, 5% CO_2 .

3-4 hr post plating, compounds are a diluted in media and 50 µl is added as 1.5-fold concentrate to achieve the final concentration. Compound incubation is performed for 24 hr. Final doses typically range from 4 µM down to 0.0013 µM in half-log steps resulting in a eight point dose response curve.

Appropriate controls using vehicle only and reference compound were applied to this assay. The final concentration of Me_2SO was 0.4%.

After incubation at 37°C, 5% CO_2, the supernatant was subjected to quantification of secreted Aβ42 by the means of an AlphaLisa assay kit (Human Amyloid beta 1-42 Kit: Cat# AL203C, Perkin Elmer). 20 µl of the cell culture supernatant was transferred to an assay plate. Then 10 µl of a mixture of the AlphaLisa coupled capture antibody and the biotinylated detection

antibody was added and incubated for 3 hours at room temperature while softly shaking the assay plate. After a further addition of 20 µl of the Donor beads the assay plate was incubated for 30 min at room temperature and constant shaking without exposure to direct light. The assay plate was then read on a Paradigm AlphaLisa Reader using the build-in program with excitation at 680 nm and emission at 570 nm.

The measured signals were then used to calculate IC_{50} values for inhibition of Aβ42 secretion by nonlinear regression fit analysis using XLfit 5.3 software (IDBS).

The table below shows the data for all compounds for the inhibition of Aβ42 secretion (nM):

Example No.	**EC_{50} Aβ42 (uM)**	**Example No.**	**EC_{50} Aβ42 (nM)**
1	0.0166	26	0.0238
2	0.0142	27	0.0202
3	0.0370	28	0.1373
4	0.0143	29	0.0561
5	0.0214	30	0.0251
6	0.0083	31	0.0304
7	0.0132	32	0.0141
8	0.0358	33	0.0352
9	0.0224	34	0.0100
10	0.0619	35	0.0210
11	0.0345	36	0.0399
12	0.0298	37	0.0342
13	0.0248	38	0.0138
14	0.0899	39	0.0175
15	0.0144	40	0.0203
16	0.0329	41	0.0142
17	0.0130	42	0.0074
18	0.0225	43	0.0126

19	0.0204	44	0.0654
20	0.0289	45	0.0300
21	0.1016	46	0.0404
22	0.0198	47	0.0521
23	0.0312	48	0.0947
24	0.009		
25	0.0585		

The compounds of formula I and the pharmaceutically acceptable salts of the compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions.The administration can also be effected topically, e.g. transdermal administration, or in form of eye drops or ear drops.

The compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a

process for their production, which comprises bringing one or more compounds of formula I and/or pharmaceutically acceptable acid addition salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

In accordance with the invention compounds of formula I as well as their pharmaceutically acceptable salts are useful in the control or prevention of illnesses based on the inhibition of Aβ42 secretion, such as of Alzheimer's disease.

The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a compound of general formula I or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

Tablet Formulation (Wet Granulation)

Item	Ingredients	mg/tablet			
		5	25	100	500
1.	Compound of formula I	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

Capsule Formulation

Item	Ingredients	mg/capsule			
		5	25	100	500
1.	Compound of formula I	5	25	100	500
2.	Hydrous Lactose	159	123	148	---
3.	Corn Starch	25	35	40	70
4.	Talc	10	15	10	25
5.	Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

Manufacturing Procedure

1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

Experimental Part

The following examples are provided for illustration of the invention. They should not be considered as limiting the scope of the invention, but merely as being representative thereof.

General

Analytical methods

HPLC (method LCMS_fastgradient)

Column: Agilent Zorbax Eclipse Plus C18, Rapid Resolution HT, 2.1x30 mm, 1.8µm, Part.no. 959731-902

Solvent A: Water 0.01% Formic Acid; Solvent B: acetonitrile (MeCN)

Gradients:

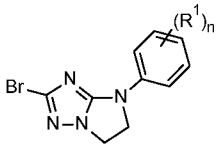
Time [min]	Flow Rate [ml/min]	%A	%B
Initial	0.8	97	3
0.2	1.0	97	3
1.7	1.0	3	97
2.0	1.0	3	97
2.1	1.0	97	3

Abbreviations

The following abbreviations were used in the experimental part:
THF = tetrahydrofurane;
TBME = methyl-tert-butylether;
DMF = dimethylformamide;
TLC = thin layer chromatography;
RT = room temperature, 20-25°C.

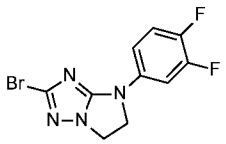
Preparation of intermediates

Intermediates of type 9 (according to scheme 1)



Intermediate **9-1**:

2-bromo-4-(3,4-difluorophenyl)-5,6-dihydroimidazo[1,2-b][1,2,4]triazole



9-1

Step 1: 3,4-Difluoroaniline (3.00 g, 23.20 mmol) and diphenyl cyanocarbonimidate (5.53 g, 23.20 mmol) were dissolved in 2-propanol (64.00 mL). The reaction mixture was stirred at RT overnight. The crude was evaporated *in vacuo* and purified by column chromatography (Hept:EtOAc 100:0 to 50:50) to afford (Z)-phenyl N'-cyano-N-(3,4-difluorophenyl) carbamimidate as a white solid (5.00 g, 79%). MS (ES+) *m/z*: 274.1 $[M+H]^+$.

Step 2: A solution of 2-(2-bromoethoxy)tetrahydro-2H-pyran (5.74 g, 4.15 mL, 27.40 mmol), (Z)-phenyl N'-cyano-N-(3,4-difluorophenyl)carbamimidate (5.00 g, 18.30 mmol) and K_2CO_3 (5.06 g, 36.60 mmol) in DMF (180 mL) was heated at 85°C overnight. An extra amount of 2-(2-bromoethoxy)tetrahydro-2H-pyran (5.74 g, 4.15 mL, 27.40 mmol) and K_2CO_3 (5.06 g, 36.60 mmol) were added and the reaction stirred at 100°C for a further 8 hours and then at 75°C overnight. The reaction mixture was cooled down to RT, poured onto a saturated aqueous solution of NH_4Cl and the product extracted three times with EtOAc. The organic layers were

combined, washed with water and then with brine, dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was then purified by column chromatography using (Hept:EtOAc 100:0 to 70:30) to afford (Z)-phenyl N'-cyano-N-(3,4-difluorophenyl)-N-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)carbamimidate as a yellow oil (1.75 g, 24%). MS (ES+) *m/z*: 402.2 $[M+H]^+$.

Step 3: To a solution of (Z)-Phenyl N'-cyano-N-(3,4-difluorophenyl)-N-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl) carbamimidate (1.75 g, 4.36 mmol) in methanol (12 mL) was added hydrazine hydrate 25% in H_2O (873 mg, 864.00 µl, 4.36 mmol). The reaction mixture was stirred at 35°C for 1 hour and then evaporated *in vacuo* to give N3-(3,4-Difluorophenyl)-N3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-4H-1,2,4-triazole-3,5-diamine (1.79 g, 91%) which was used directly for the next step without further purification. (1.79 g, 91%). MS (ES+) *m/z*: 340.2 $[M+H]^+$.

Step 4: The crude of N3-(3,4-difluorophenyl)-N3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-4H-1,2,4-triazole-3,5-diamine (1.79 g, 5.27 mmol) was dissolved in a mixture of aqueous HCl 2M (9 mL) an methanol (43 mL). The reaction mixture was stirred at RT for 1 hour and concentrated *in vacuo*. The residue was diluted with EtOAc and washed with an aqueous $NaHCO_3$ solution. The organic layer was dried Na_2SO_4 and the product purified by combiflash chromatography (CH_2Cl_2:MeOH 100:0 to 90:10) to afford 2-((5-Amino-4H-1,2,4-triazol-3-yl)(3,4-difluorophenyl)amino)ethanol as a white solid (0.39 g, 29%). MS (ES+) *m/z*: 256.2 $[M+H]^+$.

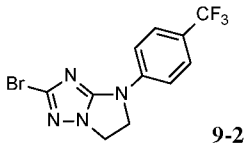
Step 5: To a THF (4 mL) solution of 2-((5-Amino-4H-1,2,4-triazol-3-yl)(3,4-difluorophenyl) amino)ethanol (50.00 mg, 196 µmol) and triphenylphosphine (154 mg, 588 µmol) was added DEAD (70 mg, 64 µl, 392 µmol) the reaction was stirred at RT for 24 hours. The reaction was stirred for further 7 hours at 50°C and then one extra amount of triphenylphosphine (154 mg, 588 µmol), DEAD (70 mg, 64 µl, 392 µmol) and THF (4 mL) were added. The reaction mixture was left to stir at RT overnight. The mixture was diluted with EtOAc and washed three times with water and brine; the organic phase was dried over sodium sulfate, filtered and evaporated *in vacuo*. The crude was purified using combiflash chromatography (CH_2Cl_2:MeOH 100:0 to

90:10) to afford 4-(3,4-difluorophenyl)-5,6-dihydro-4H-imidazo[1,2-b][1,2,4]triazol-2-amine as a white solid (7.2 mg, 15%). MS (ES+) *m/z*: 238.1 $[M+H]^+$.

Step 6: *tert*-Butyl nitrile (232 mg, 268 µl, 2.0 mmol) and cupric bromide (452 mg, 96 µl, 2.0 mmol) were combined in CH_3CN (40 mL) and stirred at 60°C before a solution of 4-(3,4-difluorophenyl)-5,6-dihydro-4H-imidazo[1,2-b][1,2,4]triazol-2-amine (140 mg, 590 µmol) in CH_3CN (40 mL) was added drop wise. The reaction mixture was stirred at 75°C for 2 hours, concentrated *in vacuo*, diluted with 1M HCl and extracted three times with EtOAc. The combined organic layer was dried over sodium sulfate, filtered and evaporated *in vacuo*. The crude was purified by combiflash chromatography (Hept:EtOAc 100:0 to 50:50) to afford 2-bromo-4-(3,4-difluorophenyl)-5,6-dihydro-4H-imidazo[1,2-b][1,2,4]triazole (0.12 g, 69%) as an off-white solid. MS (ES+) *m/z*: 301.0 and 303.0 $[M+H]^+$. (Br isotopes).

Intermediate **9-2**:

2-bromo-4-[4-(trifluoromethyl)phenyl]-5,6-dihydroimidazo[1,2-b][1,2,4]triazole

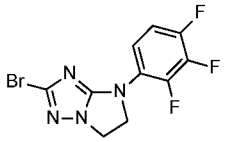


9-2

In analogy to the preparation of the intermediate **9-1**, starting from 4-(trifluoromethyl)aniline was prepared 0.12 g of the intermediate 2-bromo-4-[4-(trifluoromethyl)phenyl]-5,6-dihydro imidazo[1,2-b][1,2,4]triazole (**9-2**) as a white solid. MS (ES+) *m/z*: 333.0 and 335.0 $[M+H]^+$. (Br isotopes)

Intermediate **9-3**:

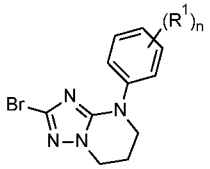
2-bromo-4-(2,3,4-trifluorophenyl)-5,6-dihydroimidazo[1,2-b][1,2,4]triazole



9-3

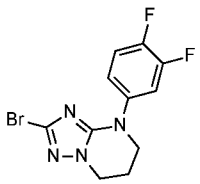
In analogy to the preparation of the intermediate **9-1**, starting from 2,3,4-trifluoroaniline was prepared 0.12 g of the intermediate 2-bromo-4-(2,3,4-trifluorophenyl)-5,6-dihydroimidazo[1,2-b][1,2,4]triazole (**9-3**) as a white solid. MS (ES+) *m/z*: 319.0 and 321.0 $[M+H]^+$. (Br isotopes)

Intermediates of type 15



Intermediate **15-1**:

2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine



15-1

Step 1: 3,4-Difluoroaniline (3.00 g, 23.20 mmol) and diphenyl cyanocarbonimidate (5.53 g, 23.20 mmol) were dissolved in 2-propanol (64.00 mL). The reaction mixture was stirred at RT overnight. The crude was evaporated *in vacuo* and purified by column chromatography (Hept:EtOAc 100:0 to 50:50) to afford (Z)-phenyl N'-cyano-N-(3,4-difluorophenyl) carbamimidate as a white solid (5.00 g, 79%). MS (ES+) *m/z*: 274.1 $[M+H]^+$.

Step 2: A solution of (Z)-phenyl N'-cyano-N-(3,4-difluorophenyl)carbamimidate (17.69 g, 64.70 mmol), 2-(3-bromopropoxy)tetrahydro-2H-pyran (22.80 g, 17.10 mL, 97.10 mmol) and K_2CO_3 (17.90 g, 129.00 mmol) in DMF (200 mL) was heated overnight at 85°C. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (Hept:EtOAc 90:10 to 50:50) to give 3-cyano-1-(3,4-difluorophenyl)-2-phenyl-1-(3-tetrahydropyran-2-yloxypropyl)isourea as a white solid (26.90 g, 49%). MS (ES+) *m/z*: 416.2 $[M+H]^+$.

Step 3: To a solution of of (Z)-phenyl N'-cyano-N-(3,4-difluorophenyl)-N-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)carbamimidate (10.20 g, 24.60 mmol) in MeOH (70 mL) was added hydrazine hydrate 25% in water (4.92 g, 4.87 mL, 24.60 mmol). The reaction mixture was stirred at RT overnight, evaporated and purified by column chromatography (CH_2Cl_2:MeOH 99:1 to

92.5:7.5) to afford N3-(3,4-difluorophenyl)-N3-(3-tetrahydropyran-2-yloxypropyl)-4H-1,2,4-triazole-3,5-diamine as a colourless foam (8.68 g, 78%). MS (ES+) *m/z*: 354.2 $[M+H]^+$.

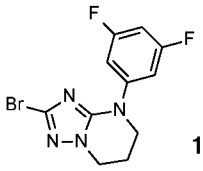
Step 4: To a solution of N3-(3,4-difluorophenyl)-N3-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)-4H-1,2,4-triazole-3,5-diamine (6.75 g, 19.10 mmol) in MeOH (150 mL) followed by addition of aqueous HCl 2M (30 mL). The reaction mixture was stirred at RT for 90 minutes and concentrated *in vacuo*. The residue was diluted with EtOAc and washed with an aqueous $NaHCO_3$ solution. The organic layer was dried on Na_2SO_4 and the product purified by combiflash chromatography to afford 3-(N-(5-Amino-4H-1,2,4-triazol-3-yl)-3,4-difluoro-anilino)propan-1-ol as a white solid (5.14 g, 95%). MS (ES+) *m/z*: 270.1 $[M+H]^+$.

Step 5: To a solution of 3-((5-amino-4H-1,2,4-triazol-3-yl)(3,4-difluorophenyl)amino) propan-1-ol (4.55 g, 16.90 mmol) in DMF (90 mL) at -15/-20°C, was added triphenylphosphine (6.65 g, 25.30 mmol). The mixture was stirred at -15/-20°C for 15 minutes, then at -30°C, DEAD (4.55 g, 4.10 ml, 25.30 mmol) was added drop wise over of 20 minutes. The mixture was stirred at -30°C for 90 minutes. Water was added to the reaction mixture and then concentrated under vacuo, and the product extracted with EtOAc. The combined organic layers were washed once with brine, dried over sodium sulfate, filtered and evaporated *in vacuo*. The crude was purified using silica chromatography (CH_2Cl_2:MeOH 99:1 to 96:4) to afford 4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine as a white solid (3.41 g, 80%). MS (ES+) *m/z*: 252.1 $[M+H]^+$.

Step 6: To a black solution of *tert*-butyl nitrite (1.01 g, 1.17 mL, 8.86 mmol) and cupric bromide (1.98 g, 420 µl, 8.86 mmol) in CH_3CN (150 mL) at 60°C, 4-(3,4-difluorophenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (1.63 g, 5.90 mmol,) in 50 mL CH_3CN was added drop wise. After addition, the reaction mixture was heated to 75°C and stirred for 30 minutes. The reaction mixture was concentrated *in vacuo*, diluted with 2 mL of 1M HCl and extracted 3 times with EtOAc. The organic layers were dried over sodium sulfate and concentrated. The crude was purified by chromatography (CH_2Cl_2:MeOH 99.5:0.5) to afford 2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine as a light yellow solid (1.86 g, 82%). MS (ES+) *m/z*: 315.0 and 317.0 $[M+H]^+$. (Br isotopes).

Intermediate **15-2**:

2-bromo-4-(3,5-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine

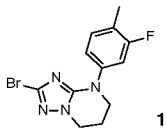


15-3

In analogy to the preparation of the intermediate **15-1**, starting from 3,5-difluoroaniline was prepared 234 mg of the intermediate 2-bromo-4-(3,5-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazlo[1,5-a]pyrimidine (**15-2**) as a white solid. MS (ES+) *m/z*: 315.0 and 317.0 $[M+H]^+$. (Br isotopes).

Intermediate **15-3**:

2-bromo-4-(3-fluoro-4-methyl-phenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine

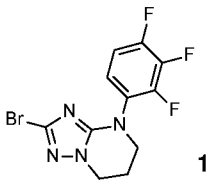


15-3

In analogy to the preparation of the intermediate **15-1**, starting from 3-fluoro-4-methyl-aniline was prepared 662 mg of the intermediate 2-bromo-4-(3-fluoro-4-methyl-phenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-3**) as a light yellow oil. MS (ES+) *m/z*: 311.0 and 313.0 $[M+H]^+$. (Br isotopes).

Intermediate **15-4**:

2-bromo-4-(2,3,4-trifluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine



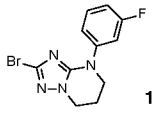
15-4

In analogy to the preparation of the intermediate **15-1**, starting from 2,3,4-trifluoroaniline was prepared 134 mg of the intermediate 2-bromo-4-(2,3,4-trifluorophenyl)-6,7-dihydro-5H-

[1,2,4]triazolo[1,5-a]pyrimidine (**15-4**) as a light brown solid. MS (ES+) *m/z*: 333.0 and 335.0 $[M+H]^+$. (Br isotopes).

Intermediate **15-5**:

2-bromo-4-(3-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine

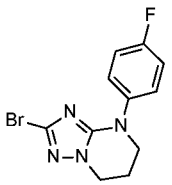


15-5

In analogy to the preparation of the intermediate **15-1**, starting from 3-fluoroaniline was prepared 210 mg of the intermediate 2-bromo-4-(3-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-5**) as a light yellow solid. MS (ES+) *m/z*: 297.0 and 299.0 $[M+H]^+$. (Br isotopes).

Intermediate **15-6**:

2-bromo-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine

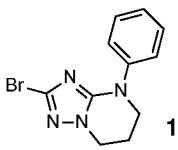


15-6

In analogy to the preparation of the intermediate **15-1**, starting from 4-fluoroaniline was prepared 1.11 g of the intermediate 2-bromo-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-6**) as a light yellow solid. MS (ES+) *m/z*: 297.0 and 299.0 $[M+H]^+$. (Br isotopes).

Intermediate **15-7**:

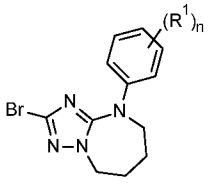
2-bromo-4-phenyl-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine



15-7

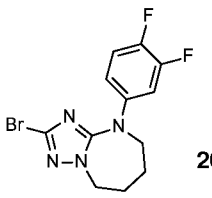
In analogy to the preparation of the intermediate **15-1**, starting from aniline was prepared 240 mg of the intermediate 2-bromo-4-phenyl-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-7**) as a white solid. MS (ES+) *m/z*: 279.0 and 281.0 $[M+H]^+$. (Br isotopes).

Intermediates of type 20



Intermediate **20-1**:

2-bromo-4-(3,4-difluorophenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepine



20-1

Step 1: 3,4-Difluoroaniline (3.00 g, 23.20 mmol) and diphenyl cyanocarbonimidate (5.53 g, 23.20 mmol) were dissolved in 2-propanol (64.00 mL). The reaction mixture was stirred at RT overnight. The crude was evaporated *in vacuo* and purified by column chromatography (Hept:EtOAc 100:0 to 50:50) to afford (Z)-phenyl N'-cyano-N-(3,4-difluorophenyl) carbamimidate as a white solid (5.00 g, 79%). MS (ES+) *m/z*: 274.1 $[M+H]^+$.

Step 2: A solution of (Z)-phenyl N'-cyano-N-(3,4-difluorophenyl)carbamimidate (10.0 g, 36.6 mmol), 2-(3-bromobutoxy)tetrahydro-2H-pyran (13.30 g, 54.90 mmol) and K_2CO_3 (10.10 g, 73.20 mmol) in DMF (350 mL) was heated overnight at 85°C. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (Hept:EtOAc 90:10 to 50:50) to give 3-cyano-1-(3,4-difluorophenyl)-2-phenyl-1-(4-tetrahydropyran-2-yloxybutyl)isourea as a colorless oil (5.31 g, 34%). MS (ES+) *m/z*: 430.2 $[M+H]^+$.

Step 3: To a solution of 3-cyano-1-(3,4-difluorophenyl)-2-phenyl-1-(4-tetrahydropyran-2-yloxybutyl)isourea (5.29 g, 12.30 mmol) in MeOH (40 mL) was added hydrazine hydrate 25% in water (2.47 g, 2.44 mL, 12.30 mmol). The reaction mixture was stirred at RT for 7 hours,

evaporated and purified by column chromatography (CH_2Cl_2:MeOH 99:1 to 92.5:7.5) to afford N3-(3,4-difluorophenyl)-N3-(3-tetrahydropyran-2-yloxybutyl)-4H-1,2,4-triazole-3,5-diamine as a colourless oil (3.54 g, 78%). MS (ES+) *m/z*: 368.2 $[M+H]^+$.

Step 4: To a solution of N3-(3,4-difluorophenyl)-N3-(3-tetrahydropyran-2-yloxybutyl)-4H-1,2,4-triazole-3,5-diamine (3.50 g, 9.53 mmol) in MeOH (85 mL) was added an aqueous HCl 2M solution (17 mL). The reaction mixture was stirred at RT for 90 minutes and concentrated *in vacuo*. The residue was diluted with EtOAc and washed with an aqueous $NaHCO_3$ solution. The organic layer was dried on Na_2SO_4 and the product purified by combiflash chromatography to afford 4-(N-(5-amino-4H-1,2,4-triazol-3-yl)-3,4-difluoro-anilino)butan-1-ol as a white solid (2.51 g, 93%). MS (ES+) *m/z*: 284.1 $[M+H]^+$.

Step 5: At 0°C, cyanomethylenetrimethylphosphorane 0.5 M in THF (8.47 mL, 4.24 mmol) was added drop wise within 15 minutes to a solution of 4-((5-amino-4H-1,2,4-triazol-3-yl)(3,4-difluorophenyl)amino)butan-1-ol (1.00 g, 3.53 mmol) in THF (120 mL) at 0°C and stirred at RT overnight. The mixture was concentrated under vacuo, and the crude diluted with EtOAc and washed with water. The organic layer was dried over sodium sulfate, filtered and evaporated *in vacuo*. The crude was purified using silica chromatography (CH_2Cl_2:MeOH 99:1 to 96:4) to afford 4-(3,4-difluorophenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepin-2-amine as a white solid (0.2 g, 21%). MS (ES+) *m/z*: 266.1 $[M+H]^+$.

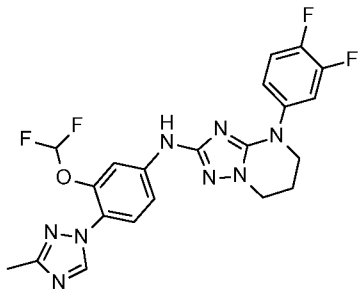
Step 6: To a black solution of *tert*-butyl nitrite (115 mg, 0.13 mL, 1.01 mmol) and cupric bromide (225 mg, 47.7 µl, 1.01 mmol) in CH_3CN (15 mL) at 60°C, 4-(3,4-difluorophenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepin-2-amine (178 mg, 0.671 mmol,) in 25 mL CH_3CN was added drop wise. After addition, the reaction mixture was heated to 75°C and stirred for 30 minutes. The reaction mixture was concentrated *in vacuo*, diluted with 2 mL of 1M HCl and extracted 3 times with EtOAc. The organic layers were dried over sodium sulfate and concentrated. The crude was purified by chromatography (CH_2Cl_2:MeOH 99.5:0.5) to afford 2-bromo-4-(3,4-difluorophenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepine as a light yellow oil (0.13 g, 58%). MS (ES+) *m/z*: 329.0 and 331.0 $[M+H]^+$. (Br isotopes).

General procedure 1: Buchwald coupling reaction

To a solution of an intermediate **8**, **9**, **14**, **15**, **19** or **20** in 1,4-dioxane was added 1.5 equivalent of an intermediate **10**. The reaction mixture was degased and a $Pd(OAc)_2$ (0.2 eq.), Xantphos (0.25 eq.) and cesium carbonate (2.0 eq.) were added. The reaction mixture was heated at 100°C until completion of the reaction (usually between 0.5 and 8 hours) and concentrated under vacuo. A purification was done either by column chromatography or reverse phase preparative HPLC to afford the desired product.

Example 1

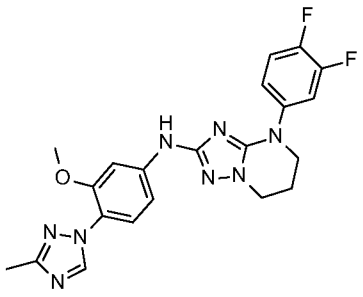
N-[3-(difluoromethoxy)-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-1**) and 3-(difluoromethoxy)-4-(3-methyl-1,2,4-triazol-1-yl)aniline was prepared 80 mg of the title compound as a light yellow solid. MS (ES+) *m/z*: 475.2 $[(M+H)^+]$.

Example 2

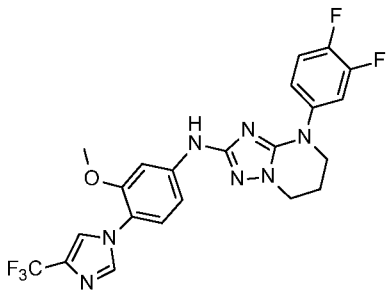
4-(3,4-difluorophenyl)-N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-1**) and 3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)aniline was prepared 61 mg of the title compound as a light yellow solid. MS (ES+) *m/z*: 439.2 [$(M+H)^+$].

Example 3

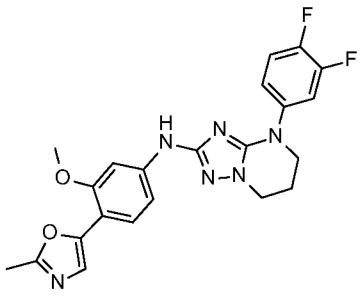
4-(3,4-difluorophenyl)-N-[3-methoxy-4-[4-(trifluoromethyl)imidazol-1-yl]phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-1**) and 3-methoxy-4-[4-(trifluoromethyl)imidazol-1-yl] aniline was prepared 62 mg of the title compound as a white solid. MS (ES+) *m/z*: 492.2 [$(M+H)^+$].

Example 4

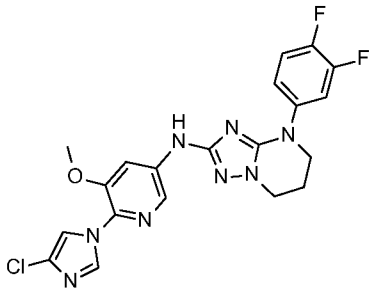
4-(3,4-difluorophenyl)-N-[3-methoxy-4-(2-methyloxazol-5-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-1**) and 3-methoxy-4-(2-methyloxazol-5-yl)aniline was prepared 35 mg of the title compound as a light yellow solid. MS (ES+) *m/z*: 438.4 [$(M+H)^+$].

Example 5

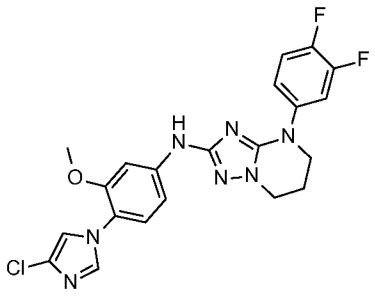
N-[6-(4-chloroimidazol-1-yl)-5-methoxy-3-pyridyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (described as precursor of **15-1**) and 5-bromo-2-(4-chloroimidazol-1-yl)-3-methoxy-pyridine was prepared 16 mg of the title compound as a white solid. MS (ES+) *m/z*: 459.1 [$(M+H)^+$].

Example 6

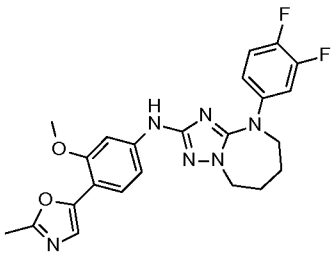
N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-1**) and 4-(4-chloroimidazol-1-yl)-3-methoxy-aniline was prepared 10 mg of the title compound as a white solid. MS (ES+) *m/z*: 458.1 [$(M+H)^+$].

Example 7

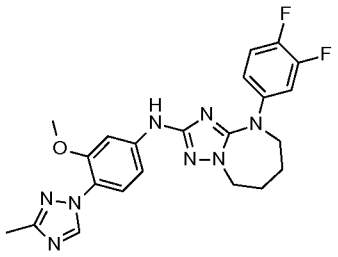
4-(3,4-difluorophenyl)-N-[3-methoxy-4-(2-methyloxazol-5-yl)phenyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepine (**20-1**) and 3-methoxy-4-(2-methyloxazol-5-yl)aniline was prepared 7.5 mg of the title compound as a white solid. MS (ES+) *m/z*: 453.2 [$(M+H)^+$].

Example 8

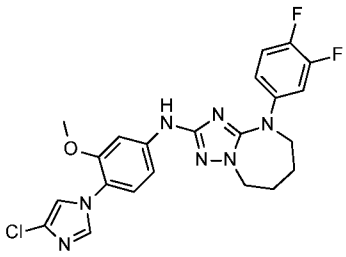
4-(3,4-difluorophenyl)-N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepine (**20-1**) and 3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)aniline was prepared 11 mg of the title compound as a white solid. MS (ES+) *m/z*: 453.3 [$(M+H)^+$].

Example 9

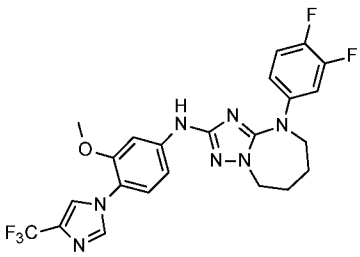
N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(3,4-difluorophenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepine (**20-1**) and 4-(4-chloroimidazol-1-yl)-3-methoxy-aniline was prepared 7 mg of the title compound as a white solid. MS (ES+) *m/z*: 472.1 [$(M+H)^+$].

Example 10

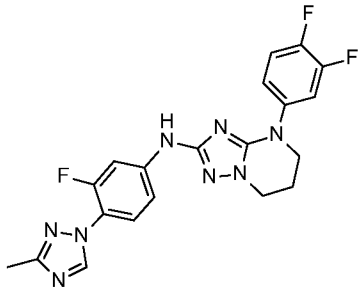
4-(3,4-difluorophenyl)-N-[3-methoxy-4-[4-(trifluoromethyl)imidazol-1-yl]phenyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepine (**20-1**) and 3-methoxy-4-[4-(trifluoromethyl)imidazol-1-yl] aniline was prepared 10 mg of the title compound as a white solid. MS (ES+) *m/z*: 505.4 $[(M+H)^+]$.

Example 11

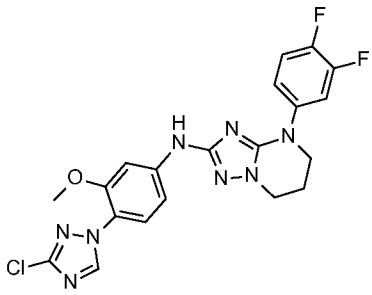
4-(3,4-difluorophenyl)-N-[3-fluoro-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-1**) and 3-fluoro-4-(3-methyl-1,2,4-triazol-1-yl)aniline was prepared 16 mg of the title compound as a white solid. MS (ES+) *m/z*: 427.3 $[(M+H)^+]$.

Example 12

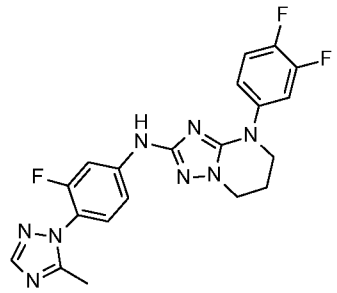
N-[4-(3-chloro-1,2,4-triazol-1-yl)-3-methoxy-phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-1**) and 4-(3-chloro-1,2,4-triazol-1-yl)-3-methoxy-aniline was prepared 9 mg of the title compound as a white solid. MS (ES+) *m/z*: 459.1 $[(M+H)^+]$.

Example 13

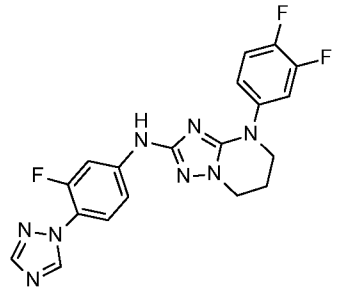
4-(3,4-difluorophenyl)-N-[3-fluoro-4-(5-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-1**) and 3-fluoro-4-(5-methyl-1,2,4-triazol-1-yl)aniline was prepared 6 mg of the title compound as a white solid. MS (ES+) *m/z*: 427.2 [$(M+H)^+$].

Example 14

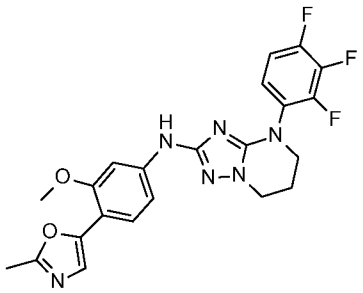
4-(3,4-difluorophenyl)-N-[3-fluoro-4-(1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-1**) and 3-fluoro-4-(1,2,4-triazol-1-yl)aniline was prepared 4 mg of the title compound as a white solid. MS (ES+) *m/z*: 413.1 [$(M+H)^+$].

Example 15

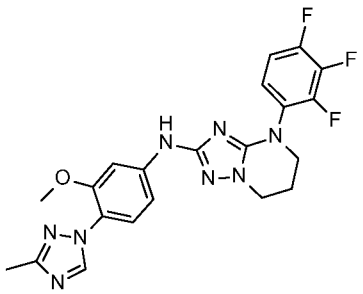
N-[3-methoxy-4-(2-methyloxazol-5-yl)phenyl]-4-(2,3,4-trifluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(2,3,4-trifluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-4**) and 3-methoxy-4-(2-methyloxazol-5-yl)aniline was prepared 10 mg of the title compound as a white solid. MS (ES+) *m/z*: 457.3 [$(M+H)^+$].

Example 16

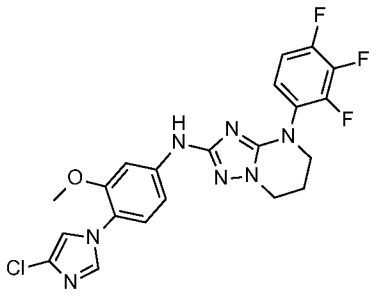
N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-4-(2,3,4-trifluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(2,3,4-trifluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-4**) and 3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)aniline was prepared 10 mg of the title compound as a white solid. MS (ES+) *m/z*: 457.2 [$(M+H)^+$].

Example 17

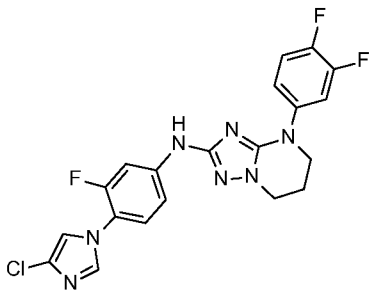
N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(2,3,4-trifluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(2,3,4-trifluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-4**) and 4-(4-chloroimidazol-1-yl)-3-methoxy-aniline was prepared 7 mg of the title compound as a white solid. MS (ES+) *m/z*: 476.1 [$(M+H)^+$].

Example 18

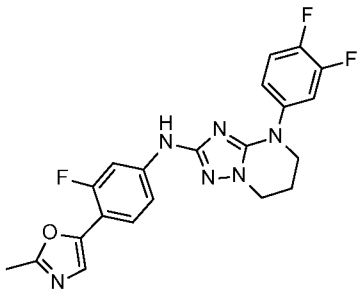
N-[4-(4-chloroimidazol-1-yl)-3-fluoro-phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-1**) and 4-(4-chloroimidazol-1-yl)-3-fluoro-aniline was prepared 11 mg of the title compound as a white solid. MS (ES+) *m/z*: 446.1 [$(M+H)^+$].

Example 19

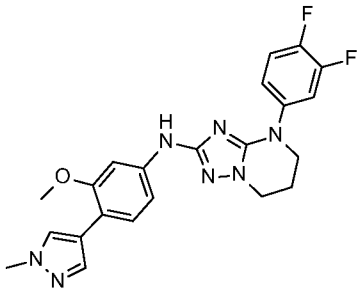
4-(3,4-difluorophenyl)-N-[3-fluoro-4-(2-methyloxazol-5-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (precursor of **15-1**) and 5-(4-bromo-2-fluoro-phenyl)-2-methyl-oxazole was prepared 16 mg of the title compound as a white solid. MS (ES+) *m/z*: 427.2 [$(M+H)^+$].

Example 20

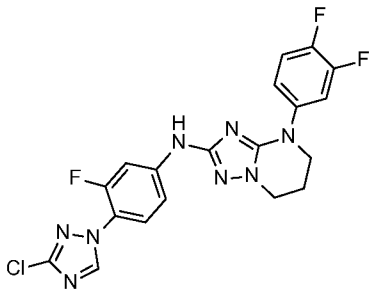
4-(3,4-difluorophenyl)-N-[3-methoxy-4-(1-methylpyrazol-4-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-1**) and 3-methoxy-4-(1-methylpyrazol-4-yl)aniline was prepared 11 mg of the title compound as a white solid. MS (ES+) *m/z*: 438.2 [$(M+H)^+$].

Example 21

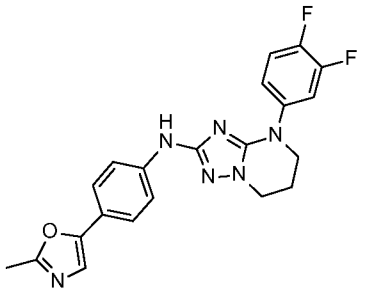
N-[4-(3-chloro-1,2,4-triazol-1-yl)-3-fluoro-phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-1**) and 4-(3-chloro-1,2,4-triazol-1-yl)-3-fluoro-aniline was prepared 6 mg of the title compound as a white solid. MS (ES+) *m/z*: 447.2 [$(M+H)^+$].

Example 22

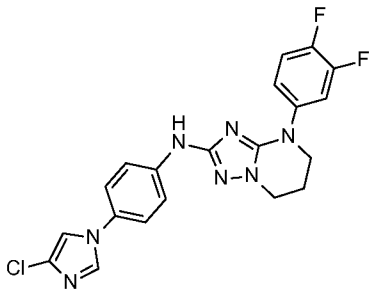
4-(3,4-difluorophenyl)-N-[4-(2-methyloxazol-5-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-1**) and 4-(2-methyloxazol-5-yl)aniline was prepared 6 mg of the title compound as a white solid. MS (ES+) *m/z*: 409.2 [$(M+H)^+$].

Example 23

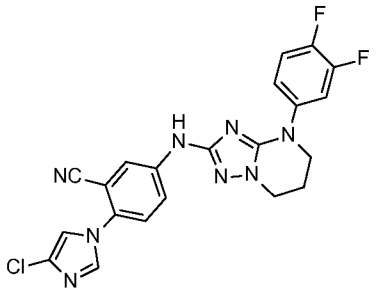
N-[4-(4-chloroimidazol-1-yl)phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (precursor of **15-1**) and 1-(4-bromophenyl)-4-chloro-imidazole was prepared 12 mg of the title compound as a white solid. MS (ES+) *m/z*: 428.2 [$(M+H)^+$].

Example 24

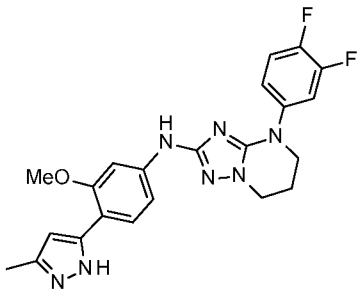
2-(4-chloroimidazol-1-yl)-5-[[4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]amino]benzonitrile



Using the general procedure 1, from 4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (precursor of **15-1**) and 5-bromo-2-(4-chloroimidazol-1-yl)benzonitrile was prepared 20 mg of the title compound as a white solid. MS (ES+) *m/z*: 453.2 [$(M+H)^+$].

Example 25

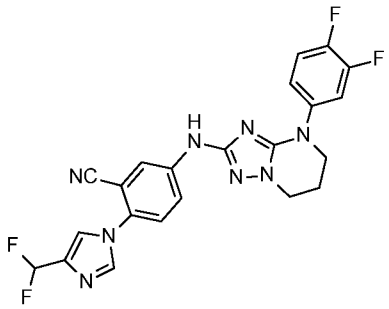
4-(3,4-difluorophenyl)-N-[3-methoxy-4-(3-methyl-1H-pyrazol-5-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (precursor of **15-1**) and 5-(4-bromo-2-methoxy-phenyl)-3-methyl-1H-pyrazole was prepared 11 mg of the title compound as a white solid. MS (ES+) *m/z*: 438.3 $[(M+H)^+]$.

Example 26

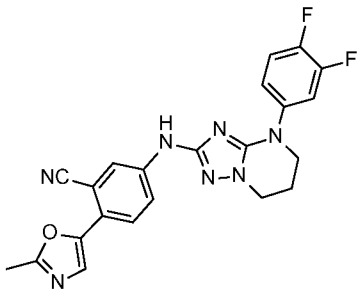
2-[4-(difluoromethyl)imidazol-1-yl]-5-[[4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]amino]benzonitrile



Using the general procedure 1, from 4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (precursor of **15-1**) and 5-bromo-2-[4-(difluoromethyl)imidazol-1-yl]benzonitrile was prepared 25 mg of the title compound as a white solid. MS (ES+) *m/z*: 469.2 $[(M+H)^+]$.

Example 27

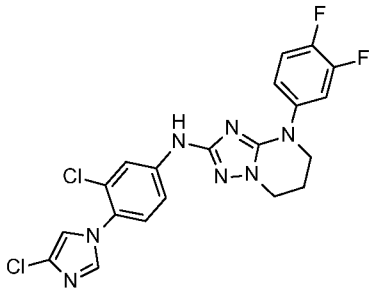
5-[[4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]amino]-2-(2-methyloxazol-5-yl)benzonitrile



Using the general procedure 1, from 4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (precursor of **15-1**) and 5-bromo-2-(2-methyloxazol-5-yl)benzonitrile was prepared 4 mg of the title compound as a white solid. MS (ES+) *m/z*: 434.2 [$(M+H)^+$].

Example 28

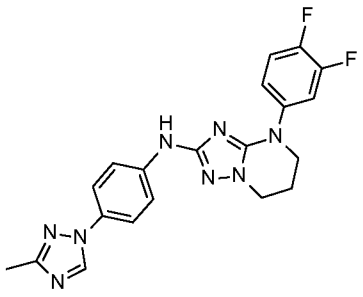
N-[3-chloro-4-(4-chloroimidazol-1-yl)phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (precursor of **15-1**) and 1-(4-bromo-2-chloro-phenyl)-4-chloro-imidazole was prepared 23 mg of the title compound as a white solid. MS (ES+) *m/z*: 462.3 [$(M+H)^+$].

Example 29

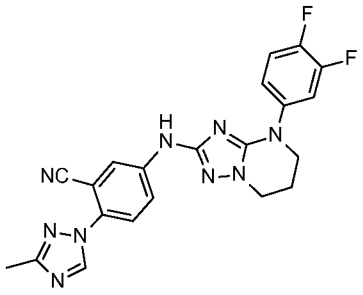
4-(3,4-difluorophenyl)-N-[4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-1**) and 4-(3-methyl-1,2,4-triazol-1-yl)aniline was prepared 8 mg of the title compound as a white solid. MS (ES+) *m/z*: 409.2 [$(M+H)^+$].

Example 30

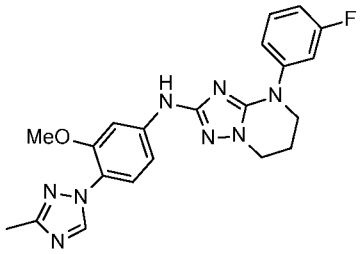
5-[[4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]amino]-2-(3-methyl-1,2,4-triazol-1-yl)benzonitrile



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-1**) and 5-amino-2-(3-methyl-1,2,4-triazol-1-yl)benzonitrile was prepared 10 mg of the title compound as a white solid. MS (ES+) *m/z*: 434.3 [$(M+H)^+$].

Example 31

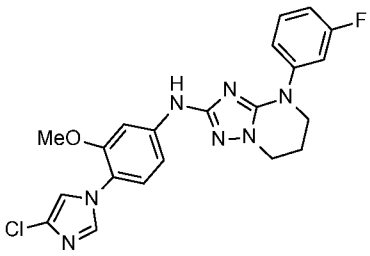
4-(3-fluorophenyl)-N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-5**) and 3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)aniline was prepared 23 mg of the title compound as a white solid. MS (ES+) *m/z*: 421.2 [$(M+H)^+$].

Example 32

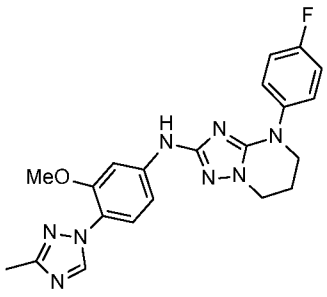
N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(3-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-5**) and 4-(4-chloroimidazol-1-yl)-3-methoxy-aniline was prepared 29 mg of the title compound as a white solid. MS (ES+) *m/z*: 440.2 [$(M+H)^+$].

Example 33

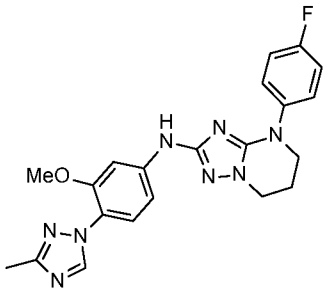
4-(4-fluorophenyl)-N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-6**) and 3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)aniline was prepared 21 mg of the title compound as a white solid. MS (ES+) *m/z*: 421.2 [$(M+H)^+$].

Example 33

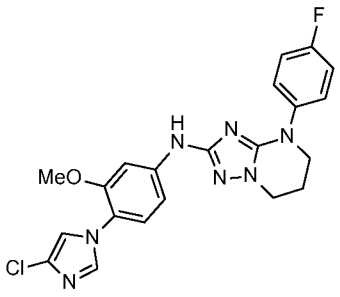
4-(4-fluorophenyl)-N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-6**) and 3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)aniline was prepared 21 mg of the title compound as a white solid. MS (ES+) *m/z*: 421.2 [$(M+H)^+$].

Example 34

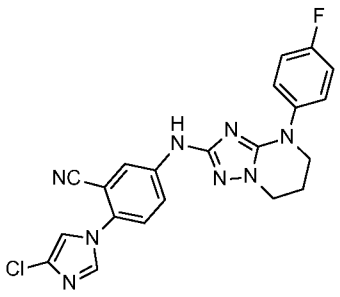
N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-6**) and 4-(4-chloroimidazol-1-yl)-3-methoxy-aniline was prepared 34 mg of the title compound as a white solid. MS (ES+) *m/z*: 440.1 [$(M+H)^+$].

Example 35

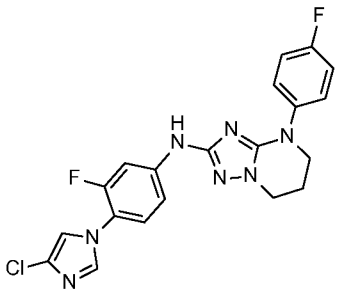
2-(4-chloroimidazol-1-yl)-5-[[4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]amino]benzonitrile



Using the general procedure 1, from 2-bromo-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (precursor of **15-6**) and 5-bromo-2-(4-chloroimidazol-1-yl)benzonitrile was prepared 36 mg of the title compound as a white solid. MS (ES+) *m/z*: 435.2 [$(M+H)^+$].

Example 36

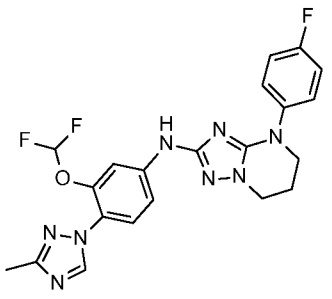
N-[4-(4-chloroimidazol-1-yl)-3-fluoro-phenyl]-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-6**) and 4-(4-chloroimidazol-1-yl)-3-fluoro-aniline was prepared 36 mg of the title compound as a white solid. MS (ES+) *m/z*: 428.2 [$(M+H)^+$].

Example 37

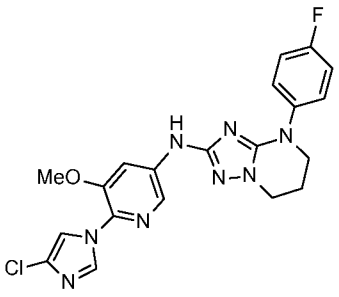
N-[3-(difluoromethoxy)-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-6**) and 3-(difluoromethoxy)-4-(3-methyl-1,2,4-triazol-1-yl)aniline was prepared 30 mg of the title compound as a white solid. MS (ES+) *m/z*: 457.2 [$(M+H)^+$].

Example 38

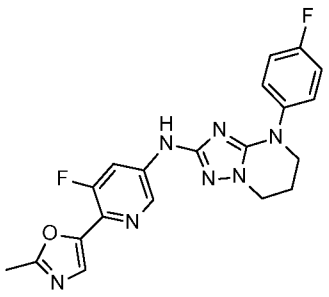
N-[6-(4-chloroimidazol-1-yl)-5-methoxy-3-pyridyl]-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-6**) and 6-(4-chloroimidazol-1-yl)-5-methoxy-pyridin-3-amine was prepared 23 mg of the title compound as a white solid. MS (ES+) *m/z*: 441.2 $[(M+H)^+]$.

Example 39

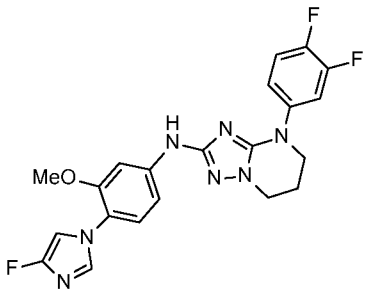
N-[5-fluoro-6-(2-methyloxazol-5-yl)-3-pyridyl]-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (precursor of **15-6**) and 5-(5-bromo-3-fluoro-2-pyridyl)-2-methyl-oxazole was prepared 15 mg of the title compound as a white solid. MS (ES+) *m/z*: 409.2 $[(M+H)^+]$.

Example 40

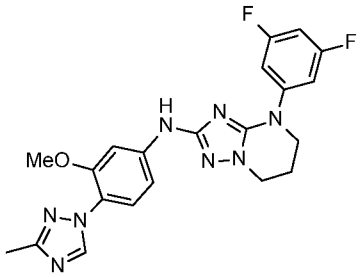
4-(3,4-difluorophenyl)-N-[4-(4-fluoroimidazol-1-yl)-3-methoxy-phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-1**) and 4-(4-fluoroimidazol-1-yl)-3-methoxy-aniline was prepared 24 mg of the title compound as a white solid. MS (ES+) *m/z*: 442.2 [$(M+H)^+$].

Example 41

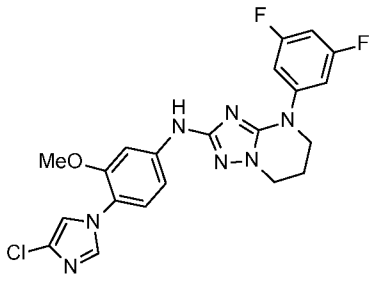
4-(3,5-difluorophenyl)-N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,5-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-2**) and 3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)aniline was prepared 16 mg of the title compound as a white solid. MS (ES+) *m/z*: 439.2 [$(M+H)^+$].

Example 42

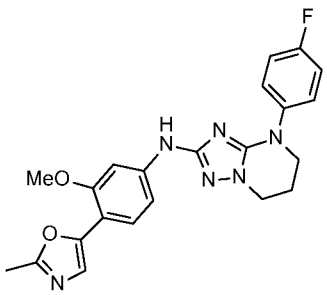
N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(3,5-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,5-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-2**) and 4-(4-chloroimidazol-1-yl)-3-methoxy-aniline was prepared 15 mg of the title compound as a white solid. MS (ES+) *m/z*: 458.2 [$(M+H)^+$].

Example 43

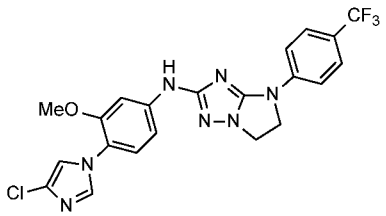
4-(4-fluorophenyl)-N-[3-methoxy-4-(2-methyloxazol-5-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-6**) and 3-methoxy-4-(2-methyloxazol-5-yl)aniline was prepared 13 mg of the title compound as a white solid. MS (ES+) *m/z*: 421.2 [$(M+H)^+$].

Example 44

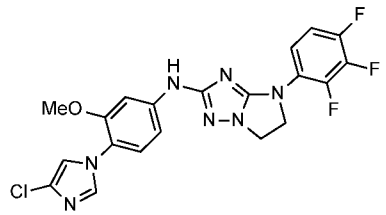
N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-[4-(trifluoromethyl)phenyl]-5,6-dihydroimidazo[1,2-b][1,2,4]triazol-2-amine



Using the general procedure 1, from 2-bromo-4-[4-(trifluoromethyl)phenyl]-5,6-dihydroimidazo[1,2-b][1,2,4]triazole (**9-2**) and 4-(4-chloroimidazol-1-yl)-3-methoxy-aniline was prepared 17 mg of the title compound as a white solid. MS (ES+) *m/z*: 476.2 [$(M+H)^+$].

Example 45

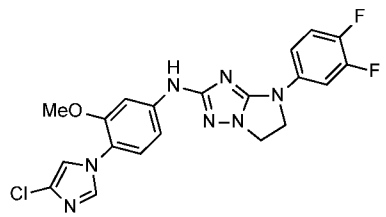
N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(2,3,4-trifluorophenyl)-5,6-dihydroimidazo[1,2-b][1,2,4]triazol-2-amine



Using the general procedure 1, from 2-bromo-4-(2,3,4-trifluorophenyl)-5,6-dihydroimidazo[1,2-b][1,2,4]triazole (**9-3**) and 4-(4-chloroimidazol-1-yl)-3-methoxy-aniline was prepared 32 mg of the title compound as a white solid. MS (ES+) *m/z*: 462.2 [$(M+H)^+$].

Example 46

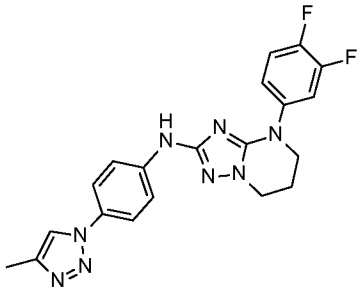
N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(3,4-difluorophenyl)-5,6-dihydroimidazo[1,2-b][1,2,4]triazol-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-5,6-dihydroimidazo[1,2-b][1,2,4]triazole (**9-1**) and 4-(4-chloroimidazol-1-yl)-3-methoxy-aniline was prepared 11 mg of the title compound as a white solid. MS (ES+) *m/z*: 444.2 [$(M+H)^+$].

Example 47

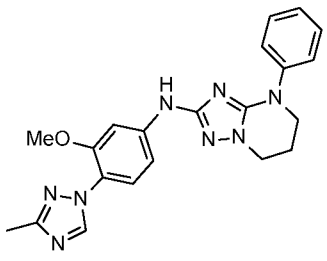
4-(3,4-difluorophenyl)-N-[4-(4-methyltriazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-1**) and 4-(4-methyltriazol-1-yl)aniline was prepared 20 mg of the title compound as a white solid. MS (ES+) *m/z*: 409.2 [$(M+H)^+$].

Example 48

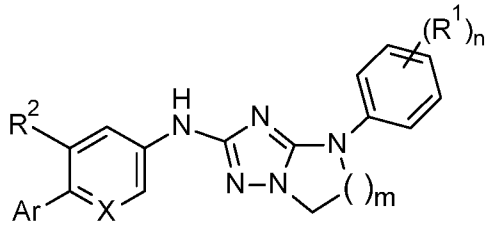
N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-4-phenyl-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine



Using the general procedure 1, from 2-bromo-4-phenyl-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (**15-7**) and 3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)aniline was prepared 11 mg of the title compound as a white solid. MS (ES+) *m/z*: 403.1 [$(M+H)^+$].

Claims

1. A compound of formula I



I

wherein

R^1 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy or lower alkoxy substituted by halogen;
and R^1 may be different if n is 2 or 3;

R^2 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, CN, lower alkoxy or lower alkoxy substituted by halogen;

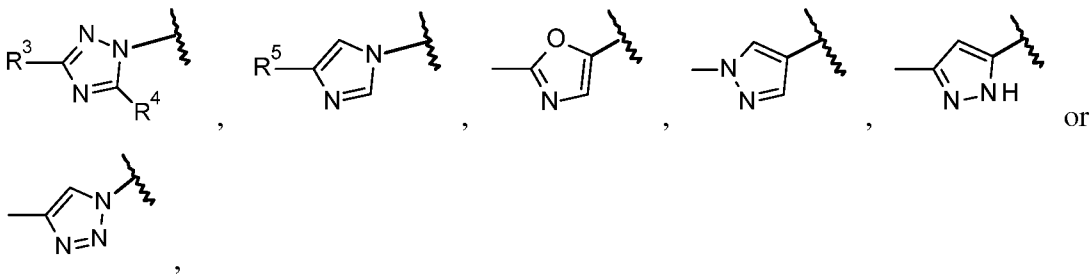
X is CH or N;

m is 1, 2 or 3;

$-(\ )_m$ is $-(CH_2)_m-$;

n is 1, 2 or 3;

Ar is a five membered heteroaryl group, selected from



wherein

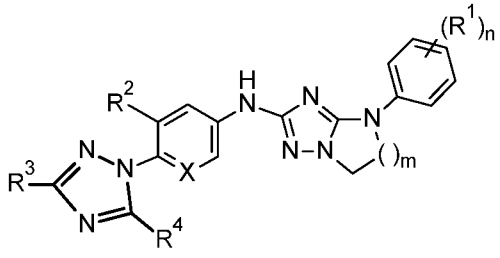
R^3 is hydrogen, methyl or chloro;

R^4 is hydrogen or methyl;

R^5 is F, Cl, CHF_2 or CF_3;

or a pharmaceutically active acid addition salt thereof.

2. A compound of formula I-1 according to claim 1,



I-1,

wherein

R^1 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy or lower alkoxy substituted by halogen;
and R^1 may be different if n is 2 or 3;

R^2 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, CN, lower alkoxy or lower alkoxy substituted by halogen;

X is CH or N;

m is 1, 2 or 3;

n is 1, 2 or 3;

R^3 is hydrogen, methyl or chloro;

R^4 is hydrogen or methyl;

$-(\ )_m$ is $-(CH_2)_m-$;

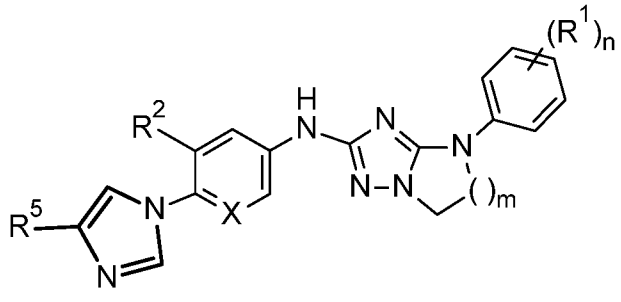
or a pharmaceutically active acid addition salt thereof.

3. A compound of formula I-1 according to claim 2, which compounds are

N-[3-(difluoromethoxy)-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
4-(3,4-difluorophenyl)-N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
4-(3,4-difluorophenyl)-N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepin-2-amine
4-(3,4-difluorophenyl)-N-[3-fluoro-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
N-[4-(3-chloro-1,2,4-triazol-1-yl)-3-methoxy-phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-

[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
4-(3,4-difluorophenyl)-N-[3-fluoro-4-(5-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
4-(3,4-difluorophenyl)-N-[3-fluoro-4-(1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-4-(2,3,4-trifluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
N-[4-(3-chloro-1,2,4-triazol-1-yl)-3-fluoro-phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
4-(3,4-difluorophenyl)-N-[4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
5-[[4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]amino]-2-(3-methyl-1,2,4-triazol-1-yl)benzonitrile
4-(3-fluorophenyl)-N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
4-(4-fluorophenyl)-N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
N-[3-(difluoromethoxy)-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
4-(3,5-difluorophenyl)-N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine or
N-[3-methoxy-4-(3-methyl-1,2,4-triazol-1-yl)phenyl]-4-phenyl-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine.

4. A compound of formula I-2 according to claim 1,



I-2,

wherein

R^1 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy or lower alkoxy substituted by halogen;
and R^1 may be different if n is 2 or 3;

R^2 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, CN, lower alkoxy or lower alkoxy substituted by halogen;

X is CH or N;

m is 1, 2 or 3;

n is 1, 2 or 3;

R^5 is F, Cl, CHF_2 or CF_3;

$-(\ )_m$ is $-(CH_2)_m-$;

or a pharmaceutically active acid addition salt thereof.

5. A compound of formula I-2 according to claim 4, which compounds are

4-(3,4-difluorophenyl)-N-[3-methoxy-4-[4-(trifluoromethyl)imidazol-1-yl]phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

N-[6-(4-chloroimidazol-1-yl)-5-methoxy-3-pyridyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(3,4-difluorophenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepin-2-amine

4-(3,4-difluorophenyl)-N-[3-methoxy-4-[4-(trifluoromethyl)imidazol-1-yl]phenyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepin-2-amine

N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(2,3,4-trifluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

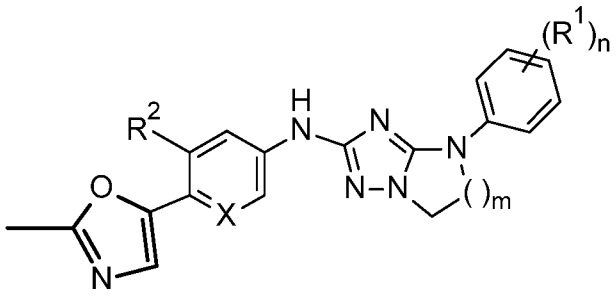
N-[4-(4-chloroimidazol-1-yl)-3-fluoro-phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

N-[4-(4-chloroimidazol-1-yl)phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

2-(4-chloroimidazol-1-yl)-5-[[4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]amino]benzonitrile

2-[4-(difluoromethyl)imidazol-1-yl]-5-[[4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]amino]benzonitrile
N-[3-chloro-4-(4-chloroimidazol-1-yl)phenyl]-4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(3-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
2-(4-chloroimidazol-1-yl)-5-[[4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]amino]benzonitrile
N-[4-(4-chloroimidazol-1-yl)-3-fluoro-phenyl]-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
N-[6-(4-chloroimidazol-1-yl)-5-methoxy-3-pyridyl]-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
4-(3,4-difluorophenyl)-N-[4-(4-fluoroimidazol-1-yl)-3-methoxy-phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(3,5-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine
N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-[4-(trifluoromethyl)phenyl]-5,6-dihydroimidazo[1,2-b][1,2,4]triazol-2-amine
N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(2,3,4-trifluorophenyl)-5,6-dihydroimidazo[1,2-b][1,2,4]triazol-2-amine or
N-[4-(4-chloroimidazol-1-yl)-3-methoxy-phenyl]-4-(3,4-difluorophenyl)-5,6-dihydroimidazo[1,2-b][1,2,4]triazol-2-amine.

6. A compound of formula I-3 according to claim 1,



I-3,

wherein

R^1 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy or lower alkoxy substituted by halogen;
and R^1 may be different if n is 2 or 3;

R^2 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, CN, lower alkoxy or lower alkoxy substituted by halogen;

X is CH or N;

m is 1, 2 or 3;

n is 1, 2 or 3;

$-(\ )_m$ is $-(CH_2)_m-$;

or a pharmaceutically active acid addition salt thereof.

7. A compound of formula I-3 according to claim 6, which compounds are

4-(3,4-difluorophenyl)-N-[3-methoxy-4-(2-methyloxazol-5-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

4-(3,4-difluorophenyl)-N-[3-methoxy-4-(2-methyloxazol-5-yl)phenyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a][1,3]diazepin-2-amine

N-[3-methoxy-4-(2-methyloxazol-5-yl)phenyl]-4-(2,3,4-trifluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

4-(3,4-difluorophenyl)-N-[3-fluoro-4-(2-methyloxazol-5-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

4-(3,4-difluorophenyl)-N-[4-(2-methyloxazol-5-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

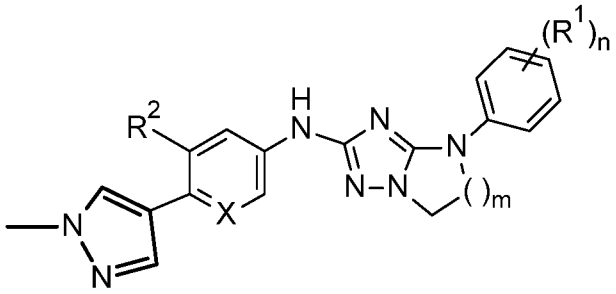
5-[[4-(3,4-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]amino]-2-(2-

methyloxazol-5-yl)benzonitrile

N-[5-fluoro-6-(2-methyloxazol-5-yl)-3-pyridyl]-4-(4-fluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine or

4-(4-fluorophenyl)-N-[3-methoxy-4-(2-methyloxazol-5-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine.

8. A compound of formula I-4 according to claim 1,



I-4,

wherein

R^1 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy or lower alkoxy substituted by halogen;
and R^1 may be different if n is 2 or 3;

R^2 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, CN, lower alkoxy or lower alkoxy substituted by halogen;

X is CH or N;

m is 1, 2 or 3;

n is 1, 2 or 3;

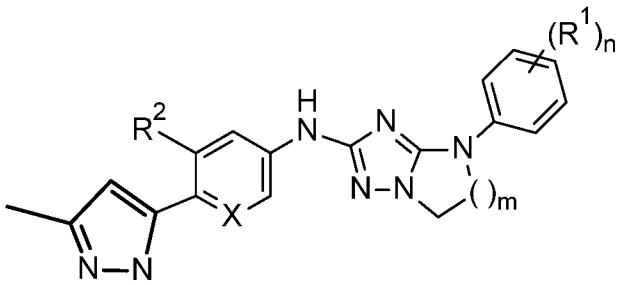
$-(\ )_m$ is $-(CH_2)_m-$;

or a pharmaceutically active acid addition salt thereof.

9. A compound of formula I-4 according to claim 8, which compound is

4-(3,4-difluorophenyl)-N-[3-methoxy-4-(1-methylpyrazol-4-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine.

10. A compound of formula I-5 according to claim 1,



I-5,

wherein

R^1 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy or lower alkoxy substituted by halogen;
and R^1 may be different if n is 2 or 3;

R^2 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, CN, lower alkoxy or lower alkoxy substituted by halogen;

X is CH or N;

m is 1, 2 or 3;

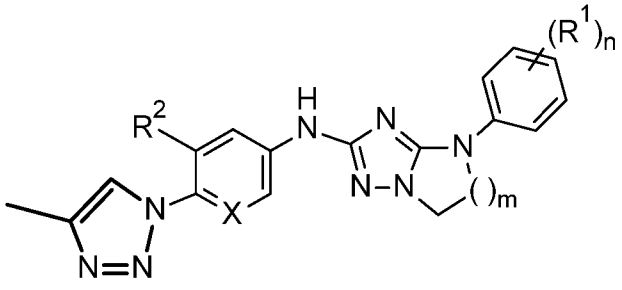
n is 1, 2 or 3;

$-(\,)_m$ is $-(CH_2)_m-$;

or a pharmaceutically active acid addition salt thereof.

11. A compound of formula I-5 according to claim 10, which compound is 4-(3,4-difluorophenyl)-N-[3-methoxy-4-(3-methyl-1H-pyrazol-5-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine.

12. A compound of formula I-6 according to claim 1,



I-6,

wherein

R^1 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy or lower alkoxy substituted by halogen;
and R^1 may be different if n is 2 or 3;

R^2 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, CN, lower alkoxy or lower alkoxy substituted by halogen;

X is CH or N;

m is 1, 2 or 3;

n is 1, 2 or 3;

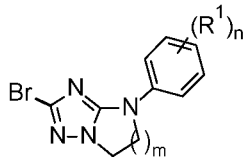
$-(\ )_m$ is $-(CH_2)_m-$;

or a pharmaceutically active acid addition salt thereof.

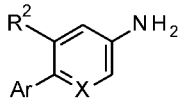
13. A compound of formula I-6 according to claim 12, 4-(3,4-difluorophenyl)-N-[4-(4-methyltriazol-1-yl)phenyl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine.

14. A process for preparing a compound of formula I as defined in any one of claims 1 - 13, which process comprises

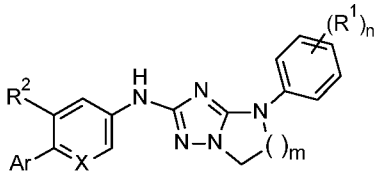
a) reacting a compound of formula 9



with a compound of formula 10-b



to a compound of formula I



wherein the substituents have the meaning as described above, and,

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts;

15. A compound according to any one of claims 1 - 13, whenever prepared by a process as claimed in claim 14.

16. A medicament containing one or more compounds as claimed in any one of claims 1 – 13 and pharmaceutically acceptable excipients.

17. A medicament according to claim 16 for the treatment of Alzheimer's disease, cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis, Dutch-type (HCHWA-D), multi-infarct dementia, dementia pugilistica or Down syndrome.

18. The use of a compound in any one of claims 1 - 13 for the manufacture of medicaments for the treatment of Alzheimer's disease, cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis, Dutch-type (HCHWA-D), multi-infarct dementia, dementia pugilistica or Down syndrome.

19. A compound according to any one of claims 1 – 13 for use as therapeutically active substance.

20. The use of a compound in any one of claims 1 – 13 for the treatment of Alzheimer's disease, cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis, Dutch-type (HCHWA-D), multi-infarct dementia, dementia pugilistica or Down syndrome.

21. A compound according to any one of claims 1 – 13 for the treatment of Alzheimer's disease, cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis, Dutch-type (HCHWA-D), multi-infarct dementia, dementia pugilistica or Down syndrome.

22. A method for the treatment of Alzheimer's disease, cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis, Dutch-type (HCHWA-D), multi-infarct

dementia, dementia pugilistica or Down syndrome, which method comprises administering an effective amount of a compound as defined in any one of claims 1 – 13.

23. The invention as hereinbefore described.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/074927

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/4196 A61K31/437 A61K31/551
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

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 practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/092272 A1 (HOFFMANN LA ROCHE [CH]; BAUMANN KARLHEINZ [DE]; GOETSCHI ERWIN [CH]; G) 4 August 2011 (2011-08-04) whole document specially claim 1 and compound 143; p. 26-p. 30	1-23
Y	WO 2011/101304 A2 (HOFFMANN LA ROCHE [CH]; BAUMANN KARLHEINZ [DE]; FLOHR ALEXANDER [DE];) 25 August 2011 (2011-08-25) whole document specially claim 1 and examples	1-23

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[X] Further documents are listed in the continuation of Box C.

[X] 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 application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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 documents, 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
4 December 2017	12/12/2017

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	Sahagún Krause, H

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/074927

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ULRIKA YNGVE ET AL: "Triazolopyrimidinones as [gamma]-secretase modulators: structure-activity relationship, modulator profile, and in vivo profiling", MEDCHEMCOMM, vol. 4, no. 2, 1 January 2013 (2013-01-01) , page 422, XP055431124, United Kingdom ISSN: 2040-2503, DOI: 10.1039/c2md20312j whole document specially Tables 2-4	1-23
Y	WO 2012/116965 A1 (HOFFMANN LA ROCHE [CH]; BAUMANN KARLHEINZ [DE]; GREEN LUKE [CH]; LIMBE) 7 September 2012 (2012-09-07) whole document specially claim 1 and examples	1-23

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2017/074927

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2017/074927

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011092272 A1	04-08-2011	AR 080083 A1	14-03-2012
		CA 2780421 A1	04-08-2011
		CN 102762561 A	31-10-2012
		EP 2531503 A1	12-12-2012
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		TW 201130837 A	16-09-2011
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		WO 2011092272 A1	04-08-2011
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		CY 1117976 T1	17-05-2017
		DK 2536710 T3	22-08-2016
		EP 2536710 A2	26-12-2012
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		JP 5559362 B2	23-07-2014
		JP 2013519701 A	30-05-2013
		KR 20120124489 A	13-11-2012
		LT 2536710 T	26-09-2016
		PL 2536710 T3	31-01-2017
		PT 2536710 T	27-09-2016
		RU 2012137956 A	27-03-2014
		TW 201130818 A	16-09-2011
		US 2011201605 A1	18-08-2011
		WO 2011101304 A2	25-08-2011
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