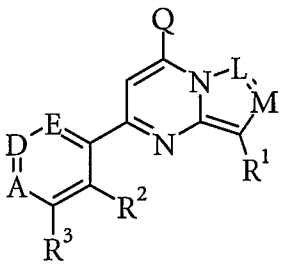
Case 22228

Pyrazolo and imidazo-pyrimidine derivatives

The present invention relates to novel pyrazolo- and imidazo-pyrimidine derivatives, processes for their preparation, pharmaceutical compositions containing said derivatives and their use in the prevention and treatment of diseases.

More particularly, the present invention relates to a compound of formula I



(I)

wherein

A is $=C(R^4)-$,

D is $=C(R^5)-$,

E is $=C(R^6)-$,

or one of A, D and E is =N-,

L is =N- or =C(H)-,

M is $=C(R^7)-$, when L is =N-, or M is =N-, when L is =C(H)-,

Q is CF_3 or CHF_2,

R^1 is –CN, unsubstituted pyridinyl, pyridinyl substituted by (C_1-C_4)-alkyl or by C_1-C_4 alkanol or is the corresponding pyridine-N-oxide,

R^2 is hydrogen, halogen, (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl,

R^3 is hydrogen, halogen, (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl,

R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

R^6 is hydrogen or halogen, and

R^7 is hydrogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by CN,

with the proviso that when A is =C(R^4)-, D is =C(H)-, E is =C(H)-, L is =N-, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and (a) M is =C(H)-, R^4 is not hydrogen, chloro or methoxy; or (b) M is =C(CH_3)-, R^4 is not hydrogen,

and their pharmaceutically acceptable addition salts.

Examples for alkyl include straight chain and branched saturated carbon chains containing from one to 4 carbon atoms, e.g. methyl, ethyl, and the isomers of propyl and butyl, e.g. isopropyl and tert.butyl. Examples for substituted alkyl include CF_3 and CH_2CN. An example for alkoxy is ethoxy, an example for substituted ethoxy is OCH_2CF_3. Examples for cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Examples for pyridinyl are pyridin-2-yl, pyridin-3-yl and pyridin-4-yl. Examples for substituted pyridinyl are methylpyridinyl, dimethylpyridinyl, hydroxymethylpyridinyl and methyloxypyridinyl, e.g. 2-methylpyridinyl, 2,6-dimethylpyridinyl, 2-hydroxymethylpyridinyl and 2-methyl-1-oxypyridinyl, e.g. 2-methylpyridin-4-yl, 2,6-dimethylpyridin-4-yl, 2-hydroxymethylpyridin-4-yl and 2-methyl-1-oxypyridin-4-yl.

Examples for halogen are chlorine and fluorine.

Unless otherwise specified, the term "alkanol" as defined therein denotes an alkyl radical having 1 to 10 carbon atoms, preferably 1 to 6 and still more preferably 1 to 4 carbon atoms as defined above, which is substituted by one, two or three, preferably one, hydroxyl group(s),. Examples of alkanols include methanol, ethanol, n-propan-2-ol, n-propan-3-ol, isopropanol, i-butanol and those specifically exemplified in the instant application among the examples.

The term "pharmaceutically acceptable addition salt" refers to any salt derived from an inorganic or organic acid or base. Examples include the hydrochloride, sulfate, fumarate, mesylate, phosphate, maleate and tartrate salts. Such salts may be prepared according to common and general methods known by the person skilled in the art.

Encompassed by formula I, are those compounds of formula wherein:

A is =C(R^4)-,

D is =C(R^5)-,

E is =C(R^6)-,

or one of A, D and E is =N-,

L is =N- or =C(H)-,

M is =C(R^7)-, when L is =N-, or M is =N-, when L is =C(H)-,

Q is CF_3,

R^1 is –CN, unsubstituted pyridinyl, pyridinyl substituted by (C_1-C_4)-alkyl or the corresponding pyridine-N-oxide,

R^2 is hydrogen, halogen, (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl,

R^3 is hydrogen, halogen, (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl,

R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

R^6 is hydrogen or halogen, and

R^7 is hydrogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by CN,

with the proviso that when A is =C(R^4)-, D is =C(H)-, E is =C(H)-, L is =N-, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and (a) M is =C(H)-, R^4 is not hydrogen, chloro or methoxy; or (b) M is =C(CH_3)-, R^4 is not hydrogen,

and their pharmaceutically acceptable addition salts.

In one embodiment the present invention provides a compound of formula I wherein A is =C(R^4)-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine. In another embodiment the invention provides a compound of formula I wherein A is =C(R^4)-, wherein R^4 is hydrogen, Cl, F, CH_3, CF_3, OCH_3, OCH_2CH_3 or OCH_2CF_3. In still another embodiment the invention provides a compound of formula I wherein A is =C(R^4)-, wherein R^4 is CF_3.

In one embodiment the present invention provides a compound of formula I wherein D is =C(R^5)-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine. In another embodiment the invention provides a compound of formula I wherein D is =C(R^5)-, wherein R^5 is hydrogen, Cl, F, CH_3 or CF_3. In still another embodiment the invention provides a compound of formula I wherein D is =C(R^5)-, wherein R^5 is hydrogen, F or CH_3.

In one embodiment the present invention provides a compound of formula I wherein E is =C(R^6)-, wherein R^6 is hydrogen or halogen. In another embodiment the invention provides a compound of formula I wherein E is =C(R^6)-, wherein R^6 is hydrogen.

In one embodiment the present invention provides a compound of formula I wherein L is =N-. In another embodiment the invention provides a compound of formula I wherein L is =C(H)-.

In one embodiment the present invention provides a compound of formula I wherein M is =C(R^7)-, wherein R^7 is hydrogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by CN. In another embodiment the invention provides a compound of formula I wherein M is =C(R^7)-, wherein R^7 is hydrogen. In still another embodiment the invention provides a compound of formula I wherein M is =C(R^7)-, wherein R^7 is unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN. In still another embodiment the present invention provides a compound of formula I wherein M is =C(R^7)-, wherein R^7 is CH_3 or CH_2CN. In another embodiment the present invention provides a compound of formula I wherein M is =N-.

In one embodiment the present invention provides a compound of formula I wherein R^1 is –CN. In another embodiment the invention provides a compound of formula I wherein R^1 is unsubstituted pyridinyl, pyridinyl substituted by (C_1-C_4)-alkyl or the corresponding pyridine-N-oxide. In still another embodiment the invention provides a compound of formula I wherein R^1 is pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, methylpyridin-4-yl, dimethylpyridin-4-yl, hydroxymethylpyridin-4-yl or methyloxypyridin-4-yl. In still another embodiment the invention provides a compound of formula I wherein R^1 is pyridin-3-yl, pyridin-4-yl, 2-methylpyridin-4-yl, 2,6-dimethylpyridin-4-yl, 2-hydroxymethylpyridin-4-yl or 2-methyl-1-oxy-pyridin-4-yl. In still another embodiment the invention provides a compound of formula I wherein R^1 is pyridin-4-yl, 2-methylpyridin-4-yl or 2,6-dimethylpyridin-4-yl.

In one embodiment the present invention provides a compound of formula I wherein R^2 is hydrogen.

In one embodiment the present invention provides a compound of formula I wherein R^3 is hydrogen.

In one embodiment the present invention provides a compound of formula I wherein

A is $=C(R^4)-$, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

D is $=C(R^5)-$, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

E is $=C(R^6)-$, wherein R^6 is hydrogen or halogen,

L is $=N-$ or $=C(H)-$,

M is $=C(R^7)-$, wherein R^7 is hydrogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by CN, when L is $=N-$; or M is $=N-$, when L is $=C(H)-$,

R^1 is –CN, unsubstituted pyridinyl, pyridinyl substituted by (C_1-C_4)-alkyl, or the corresponding pyridine-N-oxide,

R^2 is hydrogen, halogen, (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl,

R^3 is hydrogen, halogen, (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl,

with the proviso that when A is $=C(R^4)-$, D is $=C(H)-$, E is $=C(H)-$, L is $=N-$, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and (a) M is $=C(H)-$, R^4 is not hydrogen, chloro or methoxy; or (b) M is $=C(CH_3)-$, R^4 is not hydrogen.

In another embodiment the present invention provides a compound of formula I wherein

A is $=C(R^4)-$, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

D is $=C(R^5)-$, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

E is $=C(R^6)-$, wherein R^6 is hydrogen or halogen,

L is $=N-$,

M is $=C(R^7)-$, wherein R^7 is hydrogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by CN,

R^1 is –CN, unsubstituted pyridinyl, pyridinyl substituted (C_1-C_4)-alkyl, or the corresponding pyridine-N-oxide,

R^2 is hydrogen, halogen or (C_1-C_4)-alkyl

R^3 is hydrogen, halogen or (C_1-C_4)-alkyl

with the proviso that when A is =C(R^4)-, D is =C(H)-, E is =C(H)-, L is =N-, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and (a) M is =C(H)-, R^4 is not hydrogen, chloro or methoxy; or (b) M is =C(CH_3)-, R^4 is not hydrogen.

In still another embodiment the present invention provides a compound of formula I wherein

A is =C(R^4)-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

D is =C(R^5)-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

E is =C(R^6)-, wherein R^6 is hydrogen or halogen,

L is =N-,

M is =C(R^7)-, wherein R^7 is hydrogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

R^1 is –CN,

R^2 is hydrogen, halogen or (C_1-C_4)-alkyl,

R^3 is hydrogen, halogen or (C_1-C_4)-alkyl,

with the proviso that when A is =C(R^4)-, D is =C(H)-, E is =C(H)-, L is =N-, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and (a) M is =C(H)-, R^4 is not hydrogen, chloro or methoxy; or (b) M is =C(CH_3)-, R^4 is not hydrogen.

In still another embodiment the present invention provides a compound of formula I wherein

A is =C(R^4)-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine,

D is =C(R^5)-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine,

E is =C(R^6)-, wherein R^6 is hydrogen or halogen,

L is =N-,

M is =C(R^7)-, wherein R^7 is hydrogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN,

R^1 is –CN, and

R^2 and R^3 are hydrogen,

with the proviso that when A is =C(R^4)-, D is =C(H)-, E is =C(H)-, L is =N-, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and M is =C(H)-, R^4 is not hydrogen, chloro or methoxy.

In still another embodiment the present invention provides a compound of formula I wherein

A is =C(R^4)-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine,

D is =C(R^5)-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine,

E is =C(R^6)-, wherein R^6 is hydrogen or halogen,

L is =N-,

M is =C(R^7)-, wherein R^7 is hydrogen,

R^1 is –CN, and

R^2 and R^3 are hydrogen,

with the proviso that when A is =C(R^4)-, D is =C(H)-, E is =C(H)-, L is =N-, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and M is =C(H)-, R^4 is not hydrogen, chloro or methoxy.

In still another embodiment the present invention provides a compound of formula I wherein

A is =C(R^4)-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine,

D is =C(R^5)-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine,

E is =C(R^6)-, wherein R^6 is hydrogen,

L is =N-,

M is =C(R^7)-, wherein R^7 is hydrogen,

R^1 is –CN, and

R^2 and R^3 are hydrogen,

with the proviso that when A is =C(R^4)-, D is =C(H)-, E is =C(H)-, L is =N-, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and M is =C(H)-, R^4 is not hydrogen, chloro or methoxy.

In still another embodiment the present invention provides a compound of formula I wherein

A is $=C(R^4)-$, wherein R^4 is hydrogen, Cl, F, methyl or trifluoromethyl, or 2-trifluoroethoxy,

D is $=C(R^5)-$, wherein R^5 is hydrogen, Cl, F, methyl or trifluoromethyl,

E is $=C(R^6)-$, wherein R^6 is hydrogen,

L is $=N-$,

M is $=C(R^7)-$, wherein R^7 is hydrogen,

R^1 is –CN, and

R^2 and R^3 are hydrogen,

with the proviso that when A is $=C(R^4)-$, D is $=C(H)-$, E is $=C(H)-$, L is $=N-$, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and M is $=C(H)-$, R^4 is not hydrogen, chloro or methoxy.

In still another embodiment the present invention provides a compound of formula I wherein

A is $=C(R^4)-$, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine,

D is $=C(R^5)-$, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine

E is $=C(R^6)-$, wherein R^6 is hydrogen or halogen

L is $=N-$,

M is $=C(R^7)-$, wherein R^7 is unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN,

R^1 is –CN, and

R^2 and R^3 are hydrogen,

with the proviso that when A is $=C(R^4)-$, D is $=C(H)-$, E is $=C(H)-$, L is $=N-$, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and M is $=C(CH_3)-$, R^4 is not hydrogen.

In still another embodiment the present invention provides a compound of formula I wherein

A is $=C(R^4)-$, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine ,

D is $=C(R^5)-$, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine,

E is $=C(R^6)-$, wherein R^6 is hydrogen or halogen,

L is $=N-$,

M is $=C(R^7)-$, wherein R^7 is hydrogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN

R^1 is unsubstituted pyridinyl, pyridinyl substituted by (C_1-C_4)-alkyl, or the corresponding pyridine-N-oxide,

R^2 is hydrogen, halogen or (C_1-C_4)-alkyl, and

R^3 is hydrogen, halogen or (C_1-C_4)-alkyl.

In still another embodiment the present invention provides a compound of formula I wherein

A is $=C(R^4)-$, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine,

D is $=C(R^5)-$, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine,

E is $=C(R^6)-$, wherein R^6 is hydrogen or halogen,

L is $=N-$,

M is $=C(R^7)-$, wherein R^7 is hydrogen,

R^1 is unsubstituted pyridinyl, pyridinyl substituted by (C_1-C_4)-alkyl, or the corresponding pyridine-N-oxide,

R^2 and R^3 are hydrogen.

In still another embodiment the present invention provides a compound of formula I wherein

A is $=C(R^4)-$, wherein R^4 is hydrogen, halogen, (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy,

D is $=C(R^5)-$, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine,

E is $=C(R^6)-$, wherein R^6 is hydrogen or halogen,

L is $=N-$,

M is $=C(R^7)-$, wherein R^7 is hydrogen,

R^1 is unsubstituted pyridin-4-yl or pyridin-4-yl substituted by (C_1-C_4)-alkyl,

R^2 and R^3 are hydrogen.

In still another embodiment the present invention provides a compound of formula I wherein

A is $=C(R^4)-$, wherein R^4 is (C_1-C_4)-alkyl substituted by fluorine,

D is $=C(R^5)-$, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine,

E is $=C(R^6)$-, wherein R^6 is hydrogen,

L is =N-,

M is $=C(R^7)$-, wherein R^7 is hydrogen,

R^1 is unsubstituted pyridin-4-yl or pyridin-4-yl substituted by (C_1-C_4)-alkyl,

R^2 and R^3 are hydrogen.

In another embodiment the present invention provides a compound of formula I wherein

A is $=C(R^4)$-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine,

D is $=C(R^5)$-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine,

E is $=C(R^6)$-, wherein R^6 is hydrogen or halogen,

L is =C(H)-,

M is =N-,

R^1 is –CN, unsubstituted pyridinyl, pyridinyl substituted by (C_1-C_4)-alkyl, or the corresponding pyridine-N-oxide,

R^2 is hydrogen, halogen or (C_1-C_4)-alkyl, and

R^3 is hydrogen, halogen or (C_1-C_4)-alkyl.

In another embodiment the present invention provides a compound of formula I wherein

A is $=C(R^4)$-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine,

D is $=C(R^5)$-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine,

E is $=C(R^6)$-, wherein R^6 is hydrogen or halogen,

L is =C(H)-,

M is =N-,

R^1 is –CN,

R^2 is hydrogen, halogen or (C_1-C_4)-alkyl, and

R^3 is hydrogen, halogen or (C_1-C_4)-alkyl.

In another embodiment the present invention provides a compound of formula I wherein

A is $=C(R^4)$-, wherein R^4 is hydrogen or halogen,

D is $=C(R^5)-$, wherein R^5 is hydrogen,

E is $=C(R^6)-$, wherein R^6 is hydrogen or halogen,

L is $=C(H)-$,

M is $=N-$,

R^1 is $-CN$,

R^2 and R^3 are hydrogen.

In one embodiment the present invention provides a compound of formula I selected from

2-phenyl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile,

2-(3-chloro-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile,

2-(4-trifluoromethyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile,

5-(4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile,

5-(4-fluoro-3-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile,

5-(3-chloro-4-fluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile,

5-(4-chloro-3-methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile,

5-(3,4-dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile,

5-(4-chloro-3-methyl-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile,

5-(3,4-dichloro-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile,

5-(4-chloro-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(4-chloro-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(4-chloro-3-methyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-chloro-4-fluoro-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-chloro-4-fluoro-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3,4-dichloro-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3,4-dichloro-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-fluoro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile,

5-(4-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-fluoro-4-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(4-chloro-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(4-chloro-3-methyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-chloro-4-fluoro-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3,4-dichloro-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(4-trifluoromethyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-trifluoromethyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-fluoro-4-trifluoromethyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(4-methyl-3-trifluoromethyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(4-chloro-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(4-chloro-3-methyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-chloro-4-fluoro-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3,4-dichloro-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(4-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-fluoro-4-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

2-(4-methyl-3-trifluoromethyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile,

5-(3-methyl-4-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-methyl-4-trifluoromethyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-methyl-4-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

2-(3-methyl-4-trifluoromethyl-phenyl)-4-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-8-carbonitrile,

2-(3-methyl-4-trifluoromethyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile,

2-(4-trifluoroethoxy-3-trifluoromethyl-phenyl)-4-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-8-carbonitrile,

2-(4-trifluoroethoxy-3-trifluoromethyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile,

5-(4-ethoxy-3-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(4-trifluorothoxy-3-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(4-ethoxy-3-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(4-trifluoroethoxy-3-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-methyl-4-trifluoromethyl-phenyl)-3-(2-hydroxymethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(4-chloro-3-methyl-phenyl)-3-(2-methyl-1-oxy-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

2-(4-Chloro-3-methyl-phenyl)-8-pyridin-3-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,

2-(3-Chloro-4-fluoro-phenyl)-8-pyridin-3-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,

2-(4-Dichloro-phenyl)-8-pyridin-3-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,

8-Pyridin-3-yl-4-trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine,

2-(3-Methyl-4-trifluoromethyl-phenyl)-8-pyridin-3-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,

2-(4-Chloro-3-methyl-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,

2-(3-Chloro-4-fluoro-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,

2-(4-Dichloro-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,

8-Pyridin-4-yl-4-trifluoromethyl-2-(3-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine,

8-Pyridin-4-yl-4-trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine,

2-(4-Methyl-3-trifluoromethyl-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,

2-(4-Ethoxy-3-trifluoromethyl-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,

8-Pyridin-4-yl-2-[4-(2,2,2-trifluoro-ethoxy)-3-trifluoromethyl-phenyl]-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,

2-(3-Methyl-4-trifluoromethyl-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,

2-(4-Chloro-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,

2-(3-Chloro-4-fluoro-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,

2-(4-Dichloro-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,

8-(2-Methyl-pyridin-4-yl)-4-trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine,

2-(4-Ethoxy-3-trifluoromethyl-phenyl)-8-(2-methyl-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,

8-(2-Methyl-pyridin-4-yl-2-[4-(2,2,2-trifluoro-ethoxy)-3-trifluoromethyl-phenyl]-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,

2-(3-Methyl-4-trifluoromethyl-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,

{4-[5-(4-Chloro-3-methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-pyridin-2-yl}-methanol,

{4-[5-(3,4-Dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-pyridin-2-yl}-methanol,

5-(3-Ethoxy-4-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-Ethoxy-4-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,
2-(3-Ethoxy-4-trifluoromethyl-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,
3-Pyridin-4-yl-5-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,
3-(2,6-Dimethyl-pyridin-4-yl)-5-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,
3-(2-Methyl-pyridin-4-yl)-5-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,
8-Pyridin-4-yl-2-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,
8-(2-Methyl-pyridin-4-yl)-2-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,
5-(3,4-Bis-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,
5-(3,4-Bis-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,
2-(3,4-Bis-trifluoromethyl-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,
2-(4-Bromo-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine,
5-(4-Bromo-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,
5-(4-Bromo-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,
7-Difluoromethyl-3-pyridin-4-yl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine,
7-Difluoromethyl-3-(2-methyl-pyridin-4-yl)-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine, and
7-Difluoromethyl-3-(2-methyl-pyridin-4-yl)-5-(3-methyl-4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine.

In another embodiment the present invention provides a compound of formula I selected from

5-(4-chloro-3-methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile,
5-(4-chloro-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(4-chloro-3-methyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-chloro-4-fluoro-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(4-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-fluoro-4-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(4-chloro-3-methyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3,4-dichloro-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-fluoro-4-trifluoromethyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(4-chloro-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3,4-dichloro-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(4-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

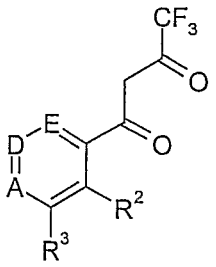
5-(3-methyl-4-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-methyl-4-trifluoromethyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine,

5-(3-methyl-4-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine, and

5-(4-ethoxy-3-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine.

The present invention also provides a process for the preparation of a compound of formula I comprising reacting a compound of formula II



(II)

wherein

A is =C(R^4)-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

D is =C(R^5)-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

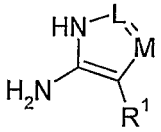
E is =C(R^6)-, wherein R^6 is hydrogen or halogen,

or one of A, D and E is =N-,

R^2 is hydrogen, halogen, (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl, and

R^3 is hydrogen, halogen, (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl,

with a compound of formula III



(III)

wherein

L is =N- or =C(H)-,

M is =C(R^7)-, when L is =N-, or M is =N-, when L is =C(H)-,

R^1 is –CN, unsubstituted pyridinyl, pyridinyl substituted by (C_1-C_4)-alkyl or the corresponding pyridine-N-oxide, and

R^7 is hydrogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by CN.

The starting compounds of formula II and III are known or may be prepared from corresponding known compounds.

The reaction may take place in the presence of a solvent, e.g. acetic acid, under, e.g., reflux conditions. The preparation of compounds of formula I is illustrated in the following examples.

Example S1: Preparation of 1-phenyl-4,4,4-trifluoro-butane-1,3-diones (General procedure A)

To a stirred solution of ethyl trifluoroacetate (1.1 eq.) in tert-butyl-methyl-ether was added dropwise a 5.4M solution of sodium methanolate in methanol followed by a solution of an acetophenone derivative (1.1 eq.) in tert-butyl-methyl-ether. The reaction mixture was stirred at room temperature for 20 h, poured into ice/water, acidified with 2N HCl and extracted with diethyl ether (two times). The combined organic layers were washed with brine (two times), dried ($MgSO_4$) and evaporated. The product was used without further purification.

acetophenone derivative	resulting 1-phenyl-4,4,4-trifluoro-butane-1,3-dione	No.
3-chloro-acetophenone	1-(3-chloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.1
4-methyl-acetophenone	1-(4-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.2
2-chloro-acetophenone	1-(2-chloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.3
2,4-dichloro-acetophenone	1-(2,4-dichloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.4
3-methyl-acetophenone	1-(3-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.5
3-trifluoromethyl-acetophenone	1-(3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.6
4-trifluoromethyl-acetophenone	1-(4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.7
3-fluoro-acetophenone	1-(3-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.8
4-fluoro-acetophenone	1-(4-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.9
2,4-difluoro-acetophenone	1-(2,4-difluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.10
2-fluoro-acetophenone	1-(2-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.11
3,4-difluoro-acetophenone	1-(3,4-difluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.12

acetophenone derivative	resulting 1-phenyl-4,4,4-trifluoro-butane-1,3-dione	No.
4-fluoro-3-trifluoromethyl-acetophenone	1-(4-fluoro-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.13
3-chloro-4-fluoro-acetophenone	1-(3-chloro-4-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.14
4-chloro-3-methyl-acetophenone	1-(4-chloro-3-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.15
3,4-dichloro-acetophenone	1-(3,4-dichloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.16
4-chloro-acetophenone	1-(4-chloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.17
3-fluoro-4-trifluoromethyl-acetophenone	1-(3-fluoro-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.18
3-methyl-4-trifluoromethyl-acetophenone	1-(3-methyl-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.19
4-trifluoroethoxy-3-trifluoromethyl-acetophenone	1-(4-trifluoroethoxy-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.20
4-methyl-3-trifluoromethyl-acetophenone	1-(4-methyl-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.21
4-ethoxy-3-trifluoromethyl-acetophenone	1-(4-ethoxy-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.22
acetophenone	1-phenyl-4,4,4-trifluoro-butane-1,3-dione	S1.23
4-methoxy-acetophenone	1-(4-methoxy-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.24
2-methyl-acetophenone	1-(2-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.25
3-ethoxy-4-trifluoromethyl-acetophenone	1-(3-ethoxy-4-trifluoromethyl-phenyl)- 4,4,4-trifluoro-butane-1,3-dione	S1.26
3-(2,2,2-	1-[3-(2,2,2-trifluoroethoxy)-4-trifluoromethyl-	S1.27

acetophenone derivative	resulting 1-phenyl-4,4,4-trifluoro-butane-1,3-dione	No.
trifluoroethoxy)-4-trifluoromethyl-acetophenone	phenyl]- 4,4,4-trifluoro-butane-1,3-dione	
3,4-bis-trifluoromethyl-acetophenone	1-(3,4-bis-trifluoromethyl-phenyl)- 4,4,4-trifluoro-butane-1,3-dione	S1.28
4-bromo-acetophenone	1-(4-bromo-phenyl)-4,4,4-trifluoro-butane-1,3-dione	S1.29
4-methoxy-acetophenone	4,4-difluoro-1-(4-methoxy-phenyl)- butane-1,3-dione	S1.30

No.: compound number of resulting 1-phenyl-4,4,4-trifluoro-butane-1,3-dione

Example S2: **Preparation of 1-pyridinyl-4,4,4-trifluoro-butane-1,3-diones (General procedure A)**

To a stirred solution of ethyl trifluoroacetate (1.1 eq.) in tert-butyl-methyl-ether was added dropwise a 5.4M solution of sodium methanolate in methanol followed by a solution of an acetylpyridine derivative (1.1 eq.) in tert-butyl-methyl-ether. The reaction mixture was stirred at room temperature for 20 h, poured into ice/water, acidified with 2N HCl and extracted with diethyl ether (two times). The combined organic layers were washed with water (20 ml), the combined water layers neutralised with sat. $NaHCO_3$ solution and evaporated to dryness. The obtained solid was stirred three times in warm dichloromethane/MeOH 9:1 and filtered. The combined organic layers were dried ($MgSO_4$) and evaporated. The crude product can be further purified by crystallisation.

acetylpyridine derivative	resulting 1-phenyl-4,4,4-trifluoro-butane-1,3-dione	No.
2-acetylpyridine	1-pyridin-2-yl-4,4,4-trifluoro-butane-1,3-dione	S2.1
3-acetylpyridine	1-pyridin-3-yl-4,4,4-trifluoro-butane-1,3-dione	S2.2
4-acetylpyridine	1-pyridin-4-yl-4,4,4-trifluoro-butane-1,3-dione	S2.3

Example S3: **Preparation of 3-amino-pyridinyl-pyrazoles**

Following a procedure as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] the following 3-amino-pyridinyl-pyrazoles were prepared starting from the appropriate pyridine:

pyridine	resulting 3-amino-pyridinyl-pyrazole [CAS No.]	No.
3-cyanomethyl-pyridine	3-amino-4-(3-pyridinyl)-pyrazole [40545-68-2]	S3.1
4-cyanomethyl-pyridine	3-amino-4-(4-pyridinyl)-pyrazole [216661-87-9]	S3.2
2-cyanomethyl-pyridine	3-amino-4-(2-pyridinyl)-pyrazole [493038-87-2]	S3.3
4-cyanomethyl-2,6-dimethyl-pyridine [130138-46-4]	3-amino-4-(2,6-dimethyl-4-pyridinyl)-pyrazole	S3.4
4-cyanomethyl-2-methyl-pyridine [130138-46-4]	3-amino-4-(2-methyl-4-pyridinyl)-pyrazole	S3.5

No.: compound number of resulting 3-amino-pyridinyl-pyrazole

Example S4: Preparation of 4-(2-Methyl-pyridin-4-yl)-2H-pyrazol-3-ylamine

a) To a stirred mixture of 4-hydroxymethyl-2-methyl-pyridine [CAS No. 105250-16-6] (3.37 g, 27.4 mmol), potassium cyanide (3.56 g, 54.7 mmol) and 18-crown-6 (0.72 g, 2.74 mmol) in acetonitrile (75 ml) was added dropwise at 15 – 20°C a solution of tributylphosphine (7.16 g, 30.1 mmol) in acetonitrile (25 ml). The reaction mixture was stirred at room temperature for 25 h, poured into water (100 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with water (3 x 100 ml), brine (100 ml) dried ($MgSO_4$) and evaporated. The crude product was further purified by column chromatography on silica gel (ethyl acetate) to yield 4-cyanomethyl-2-methyl-pyridine (2.26 g, 62%) as a brown oil.

b) A stirred mixture of 4-cyanomethyl-2-methyl-pyridine (2.51 g, 19.0 mmol) and N,N-dimethylformamide-dimethylacetal (7.63 ml, 57.0 mmol) was heated under reflux conditions for 15 min, evaporated and the crude product purified by column chromatography on silica gel (dichloromethane/methanol/NH4OH 80:10:1) to give 2.08 g of a solid, which was crystallized from diethyl ether/hexane to yield 3-dimethylamino-2-(2-methyl-pyridin-4-yl)-acrylonitrile (1.94 g, 55%) as a brown solid; mp 126°C.

c) To stirred solution of 3-dimethylamino-2-(2-methyl-pyridin-4-yl)-acrylonitrile (1.8 g, 9.61 mmol) in ethanol (18 ml) was added at room temperature hydrazine monohydrate (1.03 ml, 21.1 mmol), the reaction mixture was heated under reflux conditions for 16h and evaporated. Purification by column chromatography on silica gel (dichloromethane/methanol/NH4OH 80:10:1) and crystallization from diethyl ether yielded 4-(2-methyl-pyridin-4-yl)-2H-pyrazol-3-ylamine (0.6 g, 36%) as an orange solid. MS (ISP) 175.1 [$(M+H)^+$]; mp 230°C.

Example S5: Preparation of 4-(2,6-Dimethyl-pyridin-4-yl)-2H-pyrazol-3-ylamine

a) A stirred mixture of 4-cyanomethyl-2,6-dimethyl-pyridine [CAS No. 130138-46-4] (2.20 g, 15.1 mmol) and N,N-dimethylformamide-dimethylacetal (6.04 ml, 45.2 mmol) was heated under reflux conditions for 15 min, evaporated and the crude product purified by column chromatography on silica gel (dichloromethane/methanol/NH_4OH 80:10:1) to give 2.6 g of a solid, which was crystallized from diethyl ether/hexane to yield 3-dimethylamino-2-(2,6-dimethyl-pyridin-4-yl)-acrylonitrile (2.44 g, 81%) as a brown solid; mp 149°C.

b) To stirred solution of 3-dimethylamino-2-(2,6-dimethyl-pyridin-4-yl)-acrylonitrile (2.2 g, 10.9 mmol) in ethanol (22 ml) was added at room temperature hydrazine monohydrate (1.17 ml, 24.1 mmol), the reaction mixture was heated under reflux conditions for 23h and evaporated. Purification by column chromatography on silica gel (dichloromethane/methanol/NH_4OH 80:10:1) and crystallization from diethyl ether yielded 4-(2,6-dimethyl-pyridin-4-yl)-2H-pyrazol-3-ylamine (0.8 g, 39%) as a light brown solid. MS (ISP) 189.3 $[(M+H)^+]$; mp 222°C.

S6: 2-Amino-3-(3-pyridinyl)-1H-imidazole dihydrochloride

a) To a stirred solution of sulphuric acid (14 ml, 95 – 97%) and HNO_3 (10 ml, fum.) was added at 0°C 3-(3-pyridinyl)-1H-imidazole [CAS No. 51746-85-1, commercially available] (4.25 g, 29.3 mmol). The reaction mixture was stirred at room temperature for 45 min and at 50°C for 6h and poured into ice-water (100 ml). Solid $NaHCO_3$ was added to the stirred mixture until the pH reached 5-6, the precipitated product was collected by filtration and washed with water and hexane to yield 2-nitro-3-(3-pyridinyl)-1H-imidazole (5.53 g, 99%) as an off-white solid; mp 261°C.

b) A stirred solution of 2-nitro-3-(3-pyridinyl)-1H-imidazole (5.14 g, 27.0 mmol) in methanol (800 ml) was hydrogenated at room temperature on Raney Nickel (2.5 g) for 4h. The catalyst was removed by filtration, 3N hydrochloric acid (30 ml) was added and the solution evaporated to 50 ml. While stirring diethyl ether was added and the precipitated product was collected by filtration to yield 2-amino-3-(3-pyridinyl)-1H-imidazole dihydrochloride (5.39 g, 86%) as a brown solid. MS (ISP) 161.2 $[(M+H)^+]$; mp 253°C.

S7: 2-Amino-3-(4-pyridinyl)-1H-imidazole

a) To a stirred solution of sulphuric acid (21 ml, 95 – 97%) and HNO_3 (15 ml, fum.) was added at 0°C 3-(4-pyridinyl)-1H-imidazole [CAS No. 51746-87-3] (6.36 g, 43.8 mmol). The reaction mixture was stirred at room temperature for 45 min, at 55°C for 23h and at 100°C for 2h and poured into ice-water (200 ml). Sodium hydroxide solution (32%) was added to the stirred mixture until the pH reached 5-6, the precipitated product was collected by filtration and washed with water and hexane to yield 2-nitro-3-(4-pyridinyl)-1H-imidazole (7.95 g, 95%) as a light yellow solid; mp 234°C.

b) A stirred solution of 2-nitro-3-(4-pyridinyl)-1H-imidazole (1.19 g, 6.26 mmol) in 7N methanol/NH_3 (25 ml) and methanol (25 ml) was hydrogenated at room temperature on Raney Nickel (1 g) for 4h. The catalyst was removed by filtration and the solution evaporated. The crude product was purified by column chromatography on silica gel (dichloromethane/ methanol/NH_4OH 40:10:1) to yield 2-amino-3-(4-pyridinyl)-1H-imidazole (0.85 g, 85%) as a green solid. MS (ISP) 161.2 [$(M+H)^+$]; mp 190°C.

<u>S8: 2-Amino-3-(2-methyl-4-pyridinyl)-1H-imidazole</u>

a) To a stirred suspension of 4-acetyl-2-methyl-pyridine [CAS No. 2732-28-7] (9.7 g, 71.8 mmol) in water (115 ml) was added at room temperature hydroxylamine hydrochloride (8.48 g, 122 mmol) and the mixture was heated to 70°C. At this temperature methanol (145 ml) was added dropwise over a period of 15 min and afterwards a solution of sodium acetate trihydrate (25.4 g, 187 mmol) in water (115 ml) was added dropwise over a period of 15 min. The reaction mixture was stirred at 80°C for 3.5 h, brine (150 ml) was added and the solution was extracted with ethyl acetate (2 x 250 ml). The combined organic layers were washed with brine (150 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by crystallization from ethyl acetate/hexane to give 1-(2-methyl-pyridin-4-yl)-ethanone oxime (7.25 g, 67%) as an off-white solid; mp 154°C.

b) To a stirred solution of 1-(2-methyl-pyridin-4-yl)-ethanone oxime (7.14 g, 47.5 mmol) in pyridine (20 ml) was added at room temperature toluene-4-sulfonyl chloride (9.88 g, 51.8 mmol), the reaction mixture was stirred for 3h, poured into ice-water (300 ml) and the precipitated solid collected by filtration. Hexane (100 ml) was added, the mixture was stirred at room temperature for 1h and the product collected by filtration to give 1-(2-methyl-pyridin-4-yl)-(O-toluene-4-sufonyl)-ethanone oxime (11.1 g, 77%) as a white solid; mp 91°C.

c) To a stirred suspension of 1-(2-methyl-pyridin-4-yl)-(O-toluene-4-sufonyl)-ethanone oxime (11.0 g, 36.1 mmol) in ethanol (35 ml) was added a solution of potassium ethanolate (5.03 g, 56.7 mmol) in ethanol (35 ml) and the reaction mixture was stirred at room temperature for 17 h. The precipitated solid was collected by filtration and washed with diethyl ether (200 ml). The combined filtrates were washed with 2N HCl (2 x 80 ml, 1 x 40 ml) and the combined water layers evaporated to give crude 1-(2-methyl-pyridin-4-yl)-2-amino-ethanone dihydrochloride (8.51 g, 99%) as a light brown solid, which was used without further purification.

d) To a stirred solution of crude 1-(2-methyl-pyridin-4-yl)-2-amino-ethanone dihydrochloride (8.50 g, 35.8 mmol) in water (60 ml) was added at room temperature potassium thiocyanate (16.4 g, 168 mmol) and the reaction mixture was heated under reflux conditions for 3h and at 0°C for 2 h. The precipitated solid was collected by filtration, saturated sodium bicarbonate solution (100 ml) was added and the mixture was stirred at room temperature for 2 h. The product was collected by filtration to give 4-(2-methyl-pyridin-4-yl)-1,3-dihydro-imidazole-2-thione (5.44 g, 79%) as a light brown solid; MS (ISP) 192.2 $[(M+H)^+]$.

e) To a stirred solution of HNO_3 (43.3.ml, 65%) and water (130 ml) was added at 80°C in small portions 4-(2-methyl-pyridin-4-yl)-1,3-dihydro-imidazole-2-thione (5.20 g, 27.2 mmol) and the mixture was heated under reflux conditions for 2 h. The reaction mixture was cooled (ice) and solid $NaHCO_3$ was added to get a basic solution. Solid NaCl was added and the solution was extracted with THF (3 x 200 ml). The combined organic layers were dried ($MgSO_4$) and evaporated to give 3-(2-methyl-4-pyridinyl)-1H-imidazole (4.16 g, 96%) as a yellow solid; MS (ISP) 160.2 $[(M+H)^+]$.

f) To a stirred solution of sulphuric acid (14 ml, 95 – 97%) and HNO_3 (10 ml, fum.) was added at 0°C 3-(2-methyl-4-pyridinyl)-1H-imidazole (4.0 g, 25.1 mmol). The reaction mixture was stirred at room temperature for 50 min, at 100°C for 2.5 h and at 110°C for 10h and poured into ice-water (70 ml). Solid $NaHCO_3$ was added to the stirred mixture until the pH reached 5. The solution was extracted with THF (4 x 200 ml), the combined organic layers were dried (MgSO4) and evaporated to give 2-nitro-3-(2-methyl-4-pyridinyl)-1H-imidazole (3.4 g, 66%) as a light yellow solid; MS (ISP) 205.2 $[(M+H)^+]$.

g) A stirred solution of 2-nitro-3-(2-methyl-4-pyridinyl)-1H-imidazole (3.40 g, 16.6 mmol) in 7N methanol/NH_3 (70 ml) and methanol (70 ml) was hydrogenated at room

temperature on Raney Nickel (2.9 g) for 2h. The catalyst was removed by filtration and the solution evaporated. The crude product was purified by column chromatography on silica gel (dichloromethane/ methanol/NH_4OH 40:10:1) to yield 2-amino-3-(2-methyl-4-pyridinyl)-1H-imidazole (1.71 g, 59%) as a green solid. MS (ISP) 175.1 $[(M+H)^+]$; mp 167°C.

Example 1: **Preparation of phenyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitriles and pyridinyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitriles (General Procedure B)**

A stirred mixture of commercially available 3-amino-4-cyano-pyrazole (1 eq.) and a 1-phenyl-4,4,4-trifluoro-butane-1,3-dione or 1-pyridin-2-yl-4,4,4-trifluoro-butane-1,3-dione (1 eq.), prepared according to general procedure A, in acetic acid was heated under reflux conditions for 3.5 h. The reaction mixture was evaporated and the product was isolated by column chromatography (heptane/ethyl acetate) and further purified by crystallization. If the product precipitates during the reaction it can be isolated by filtration and further purified by crystallization.

Ex.	dione	compound name	MS (ISP) / mp
1.1	S1.1	5-(3-chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	323.1 $[(M+H)^+]$ mp 204°C
1.2	S1.2	5-(4-methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	303.1 $[(M+H)^+]$ mp 121°C
1.3	S1.3	5-(2-chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	323.1 $[(M+H)^+]$ mp 169°C
1.4	S1.4	5-(2,4-dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	357.1 $[(M+H)^+]$ mp 180°C
1.5	S1.5	5-(3-methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	303.2 $[(M+H)^+]$ mp 202°C
1.6	S1.6	5-(3-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	357.0 $[(M+H)^+]$ mp 192°C
1.7	S1.7	5-(4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	357.0 $[(M+H)^+]$ mp 176°C
1.8	S1.8	5-(3-fluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	306.9 $[(M+H)^+]$ mp 199°C
1.9	S1.9	5-(4-fluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-	306.9 $[(M+H)^+]$

Ex.	dione	compound name	MS (ISP) / mp
		a]pyrimidine-3-carbonitrile	mp 198°C
1.10	S1.10	5-(2,4-difluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	325.0 [(M+H)$^+$] mp 149°C
1.11	S1.11	5-(2-fluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	307.1 [(M+H)$^+$] mp 165°C
1.12	S1.12	5-(3,4-difluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	325.0 [(M+H)$^+$] mp 192°C
1.13	S1.13	5-(4-fluoro-3-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	375.0 [(M+H)$^+$] mp 204°C
1.14	S1.14	5-(3-chloro-4-fluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	341.0 [(M+H)$^+$] mp 190°C
1.15	S1.15	5-(4-chloro-3-methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	337.1 [(M+H)$^+$] mp 216°C
1.16	S1.16	5-(3,4-dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	356.9 [(M+H)$^+$] mp 206°C
1.17	S1.18	5-(3-fluoro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	375.0 [(M+H)$^+$] mp 184°C
1.18	S1.19	2-(3-methyl-4-trifluoromethyl-phenyl)-4-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-8-carbonitrile	371.1 [(M+H)$^+$] mp 209°C
1.19	S1.20	2-(4-trifluoroethoxy-3-trifluoromethyl-phenyl)-4-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-8-carbonitrile	453.0 [M$^+$] mp 215°C
1.20	S2.1	5-pyridin-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	289.9 [(M+H)$^+$] mp 208°C
1.21	S2.2	5-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	290.2 [(M+H)$^+$] mp 193°C
1.22	S2.3	5-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	289.8 [(M+H)$^+$] mp 233°C

Example 1.1

5-(3-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(3-chloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (251 mg, 1.0 mmol), prepared from commercially available 3-chloro-acetophenone according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (150 mg, 46%). MS (ISP) 323.1 [$(M+H)^+$]; mp 204°C.

Example 1.2

5-(4-Methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(4-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (230 mg, 1.0 mmol), prepared from commercially available 4-methyl-acetophenone according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a light yellow solid (151 mg, 50%). MS (ISP) 303.1 [$(M+H)^+$]; mp 121°C.

Example 1.3

5-(2-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(2-chloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (251 mg, 1.0 mmol), prepared from commercially available 2-chloro-acetophenone according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as an off-white solid (73 mg, 23%). MS (ISP) 323.1 [$(M+H)^+$]; mp 169°C.

Example 1.4

5-(2,4-Dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(2,4-dichloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (285 mg, 1.0 mmol), prepared from commercially available 2,4-dichloro-acetophenone according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a light brown solid (63 mg, 18%). MS (ISP) 357.1 [$(M+H)^+$]; mp 180°C.

Example 1.5

5-(3-Methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(3-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (230 mg, 1.0 mmol), prepared from commercially available 3-methyl-acetophenone according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (164 mg, 54%). MS (ISP) 303.2 $[(M+H)^+]$; mp 202°C.

Example 1.6

5-(3-Trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (284 mg, 1.0 mmol), prepared from commercially available 3-trifluoromethyl-acetophenone according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a white solid (151 mg, 42%). MS (ISP) 357.0 $[(M+H)^+]$; mp 192°C.

Example 1.7

5-(4-Trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (284 mg, 1.0 mmol), prepared from commercially available 4-trifluoromethyl-acetophenone according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as an off-white solid (137 mg, 38%). MS (ISP) 357.0 $[(M+H)^+]$; mp 176°C.

Example 1.8

5-(3-Fluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(3-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (234 mg, 1.0 mmol), prepared from commercially available 3-fluoro-acetophenone according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a light yellow solid (141 mg, 46%). MS (ISP) 306.9 $[(M+H)^+]$; mp 199°C.

Example 1.9

5-(4-Fluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(4-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (234 mg, 1.0 mmol), prepared from commercially available 4-fluoro-acetophenone according to general

procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (118 mg, 39%). MS (ISP) 306.9 [$(M+H)^+$]; mp 198°C.

Example 1.10

5-(2,4-Difluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(2,4-difluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (252 mg, 1.0 mmol), prepared from commercially available 2,4-difluoro-acetophenone according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a light yellow solid (72 mg, 22%). MS (ISP) 325.0 [$(M+H)^+$]; mp 149°C.

Example 1.11

5-(2-Fluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(2-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (234 mg, 1.0 mmol), prepared from commercially available 2-fluoro-acetophenone according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a light yellow solid (83 mg, 27%). MS (ISP) 307.1 [$(M+H)^+$]; mp 165°C.

Example 1.12

5-(3,4-Difluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(3,4-difluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (252 mg, 1.0 mmol), prepared from commercially available 3,4-difluoro-acetophenone according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a light yellow solid (137 mg, 42%).

Example 1.13

5-(4-Fluoro-3-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(4-fluoro-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (302 mg, 1.0 mmol), prepared from commercially available 4-fluoro3-trifluoromethyl-acetophenone according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as an off-white solid (144 mg, 38%). MS (ISP) 375.0 [$(M+H)^+$]; mp 204°C.

Example 1.14

5-(3-Chloro-4-fluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(3-chloro-4-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (269 mg, 1.0 mmol), prepared from commercially available 3-chloro-4-fluoro-acetophenone according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as an off-white solid (109 mg, 32%). MS (ISP) 341.0 [$(M+H)^+$]; mp 190°C.

Example 1.15

5-(4-Chloro-3-methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(4-chloro-3-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (264 mg, 1.0 mmol), prepared from commercially available 4-chloro-3-methyl-acetophenone according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as an off-white solid (128 mg, 38%). MS (ISP) 337.1 [$(M+H)^+$]; mp 216°C.

Example 1.16

5-(3,4-Dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(3,4-dichloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (285 mg, 1.0 mmol), prepared from commercially available 3,4-dichloro-acetophenone according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (140 mg, 39%). MS (ISP) 356.9 [$(M+H)^+$]; mp 206°C.

Example 1.17

5-(3-Fluoro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(3-fluoro-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (302 mg, 1.0 mmol), prepared from commercially available 3-fluoro-4-trifluoromethyl-acetophenone according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as an off-white solid (139 mg, 37%). MS (ISP) 375.0 [$(M+H)^+$]; mp 184°C.

Example 1.18

2-(3-Methyl-4-trifluoromethyl-phenyl)-4-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(3-methyl-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (224 mg, 0.75 mmol), prepared from 3-methyl-4-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-cyano-pyrazole (81 mg, 0.75 mmol) according to general procedure B yielded the title compound as an off-white solid (142 mg, 51%). MS (ISP) 371.1 $[(M+H)^+]$; mp 209°C.

Example 1.19

2-(4-Trifluoroethoxy-3-trifluoromethyl-phenyl)-4-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(4-trifluoroethoxy-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (382 mg, 1.0 mmol), prepared from 4-trifluoroethoxy-3-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as an off-white solid (226 mg, 50%). MS (ISP) 453.0 $[M^+]$; mp 215°C.

Example 1.20

5-Pyridin-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-pyridin-2-yl-4,4,4-trifluoro-butane-1,3-dione (217 mg, 1.0 mmol), prepared from commercially available 2-acetylpyridine according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a light brown solid (135 mg, 47%). MS (ISP) 289.9 $[(M+H)^+]$; mp 208°C.

Example 1.21

5-Pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-pyridin-3-yl-4,4,4-trifluoro-butane-1,3-dione (217 mg, 1.0 mmol), prepared from commercially available 3-acetylpyridine according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as an off-white solid (45 mg, 16%). MS (ISP) 290.2 $[(M+H)^+]$; mp 193°C.

Example 1.22

5-Pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-pyridin-4-yl-4,4,4-trifluoro-butane-1,3-dione (217 mg, 1.0 mmol), prepared from commercially available 4-acetylpyridine according to general procedure A, and 3-amino-4-cyano-pyrazole (108 mg, 1.0 mmol) according to general procedure B

yielded the title compound as a light yellow solid (110 mg, 38%). MS (ISP) 289.8 [(M+H)$^+$]; mp 233°C.

Example 2: Preparation of phenyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitriles (General Procedure B)

A stirred mixture of commercially available 3-amino-4-cyano-5-methyl-pyrazole (1 eq.) and a 1-phenyl-4,4,4-trifluoro-butane-1,3-dione (1 eq.), prepared according to general procedure A, in acetic acid was heated under reflux conditions for about 3.5 h. The reaction mixture was evaporated and the product was isolated by column chromatography (heptane/ethyl acetate) and further purified by crystallization. If the product precipitates during the reaction it can be isolated by filtration and further purified by crystallization.

Ex.	dione	compound name	MS (ISP) / mp
2.1	S1.7	2-methyl-5-(4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	371.1 [(M+H)$^+$] mp 184°C
2.2	S1.6	2-methyl-5-(3-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	371.1 [(M+H)$^+$] mp 215°C
2.3	S1.17	5-(4-chloro-phenyl)-2-methyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	337.1 [(M+H)$^+$] mp 238°C
2.4	S1.14	5-(3-chloro-4-fluoro-phenyl)-2-methyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	355.0 [(M+H)$^+$] mp 196°C

Example 2.1

2-Methyl-5-(4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (284 mg, 1.0 mmol), prepared from commercially available 4-trifluoromethyl-acetophenone according to general procedure A, and commercially available 3-amino-4-cyano-5-methyl-pyrazole (122 mg, 1.0 mmol) according to general procedure B yielded the title compound as a light yellow solid (234 mg, 63%). MS (ISP) 371.1 [(M+H)$^+$]; mp 184°C.

Example 2.2

2-Methyl-5-(3-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (284 mg, 1.0 mmol), prepared from commercially available 3-trifluoromethyl-acetophenone according to general procedure A, and commercially available 3-amino-4-cyano-5-methyl-pyrazole (122 mg, 1.0 mmol) according to general procedure B yielded the title compound as a light yellow solid (272 mg, 73%). MS (ISP) 371.1 [$(M+H)^+$]; mp 215°C.

Example 2.3

5-(4-Chloro-phenyl)-2-methyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(4-chloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (251 mg, 1.0 mmol), prepared from commercially available 4-chloro-acetophenone according to general procedure A, and commercially available 3-amino-4-cyano-5-methyl-pyrazole (122 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (222 mg, 66%). MS (ISP) 337.1 [$(M+H)^+$]; mp 238°C.

Example 2.4

5-(3-Chloro-4-fluoro-phenyl)-2-methyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(3-chloro-4-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (269 mg, 1.0 mmol), prepared from commercially available 3-chloro-4-fluoro-acetophenone according to general procedure A, and commercially available 3-amino-4-cyano-5-methyl-pyrazole (122 mg, 1.0 mmol) according to general procedure B yielded the title compound as a light yellow solid (243 mg, 69%). MS (ISP) 355.0 [$(M+H)^+$]; mp 196°C.

Example 3: Preparation of phenyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitriles (General Procedure B)

A stirred mixture of commercially available 3-amino-4-cyano-5-cyanomethyl-pyrazole (1 eq.) and a 1-phenyl-4,4,4-trifluoro-butane-1,3-dione (1 eq.), prepared according to general procedure A, in acetic acid was heated under reflux conditions for 3.5 h. The reaction mixture was evaporated and the product was isolated by column chromatography (heptane/ethyl acetate) and further purified by crystallization. If the product precipitates during the reaction it can be isolated by filtration and further purified by crystallization.

Ex.	dione	compound name	MS (ISP) / mp
3.1	S1.14	5-(3-chloro-4-fluoro-phenyl)-2-cyanomethyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	380.1 [(M+H)$^+$] mp 185°C
3.2	S1.15	5-(4-chloro-3-methyl-phenyl)-2-cyanomethyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile	376.1 [(M+H)$^+$] mp 238°C

Example 3.1

5-(3-Chloro-4-fluoro-phenyl)-2-cyanomethyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(3-chloro-4-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (269 mg, 1.0 mmol), prepared from commercially available 3-chloro-4-fluoro-acetophenone according to general procedure A, and commercially available 3-amino-4-cyano-5-cyanomethyl-pyrazole (147 mg, 1.0 mmol) according to general procedure B yielded the title compound as a light yellow solid (223 mg, 59%). MS (ISP) 380.1 [(M+H)$^+$]; mp 185°C.

Example 3.2

5-(4-Chloro-3-methyl-phenyl)-2-cyanomethyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Reaction of 1-(4-chloro-3-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (132 mg, 0.5 mmol), prepared from commercially available 4-chloro-3-methyl-acetophenone according to general procedure A, and commercially available 3-amino-4-cyano-5-cyanomethyl-pyrazole (74 mg, 0.5 mmol) according to general procedure B yielded the title compound as a light yellow solid (99 mg, 53%). MS (ISP) 376.1 [(M+H)$^+$]; mp 238°C.

Example 4: Preparation of 5-phenyl-3-pyridinyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidines (General Procedure B)

A stirred mixture of a 3-amino-4-pyridinyl-pyrazole (1 eq.) and a 1-phenyl-4,4,4-trifluoro-butane-1,3-dione (1 eq.), prepared according to general procedure A, in acetic acid was heated under reflux conditions for 3.5 h. The reaction mixture was evaporated and the product was isolated by column chromatography (heptane/ethyl acetate) and further purified by crystallization. If the product precipitates during the reaction it can be isolated by filtration and further purified by crystallization.

Ex.	dione	pyrazole	compound name	MS (ISP) / mp
4.1	S1.17	S3.1	5-(4-chloro-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	375.3 [(M+H)$^+$] mp 188°C
4.2	S1.17	S3.2	5-(4-chloro-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	375.3 [(M+H)$^+$] mp 274°C
4.3	S1.15	S3.1	5-(4-chloro-3-methyl-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	375.3 [(M+H)$^+$] mp 193°C
4.4	S1.15	S3.2	5-(4-chloro-3-methyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	389.2 [(M+H)$^+$] mp 247°C
4.5	S1.15	S3.3	5-(4-chloro-3-methyl-phenyl)-3-pyridin-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	389.2 [(M+H)$^+$] mp 183°C
4.6	S1.14	S3.1	5-(3-chloro-4-fluoro-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	393.1 [(M+H)$^+$] mp 190°C
4.7	S1.14	S3.2	5-(3-chloro-4-fluoro-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	393.1 [(M+H)$^+$] mp 265°C
4.8	S1.14	S3.3	5-(3-chloro-4-fluoro-phenyl)-3-pyridin-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	393.1 [(M+H)$^+$] mp 197°C
4.9	S1.16	S3.1	5-(3,4-dichloro-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	409.1 [(M+H)$^+$] mp 224°C
4.10	S1.16	S3.2	5-(3,4-dichloro-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	409.2 [(M+H)$^+$] mp 260°C
4.11	S1.16	S3.3	5-(3,4-dichloro-phenyl)-3-pyridin-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	409.2 [(M+H)$^+$] mp 188°C
4.12	S1.7	S3.3	5-(4-trifluoromethyl-phenyl)-3-pyridin-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	409.2 [(M+H)$^+$] mp 202°C
4.13	S1.6	S3.1	5-(3-trifluoromethyl-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	409.2 [(M+H)$^+$] mp 171°C
4.14	S1.7	S3.1	5-(4-trifluoromethyl-phenyl)-3-pyridin-3-	409.2 [(M+H)$^+$]

Ex.	dione	pyrazole	compound name	MS (ISP) / mp
			yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	mp 163°C
4.15	S1.7	S3.2	5-(4-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	409.2 [(M+H)$^+$] mp 261°C
4.16	S1.6	S3.2	5-(3-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	409.2 [(M+H)$^+$] mp 241°C
4.17	S1.18	S3.2	5-(3-fluoro-4-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	427.0 [(M+H)$^+$] mp 262°C
4.18	S1.18	S3.1	5-(3-fluoro-4-trifluoromethyl-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	427.0 [(M+H)$^+$] mp 162°C
4.19	S1.17	S3.4	5-(4-chloro-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	403.2 [(M+H)$^+$] mp 256°C
4.20	S1.15	S3.4	5-(4-chloro-3-methyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	417.2 [(M+H)$^+$] mp 254°C
4.21	S1.14	S3.4	5-(3-chloro-4-fluoro-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	421.1 [(M+H)$^+$] mp 271°C
4.22	S1.16	S3.4	5-(3,4-dichloro-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	437.1 [(M+H)$^+$] mp 281°C
4.23	S1.7	S3.4	5-(4-trifluoromethyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	437.2 [(M+H)$^+$] mp 257°C
4.24	S1.6	S3.4	5-(3-trifluoromethyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	437.2 [(M+H)$^+$] mp 236°C
4.25	S1.18	S3.4	5-(3-fluoro-4-trifluoromethyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	455.0 [(M+H)$^+$] mp 245°C

Ex.	dione	pyrazole	compound name	MS (ISP) / mp
4.26	S1.21	S3.1	5-(4-methyl-3-trifluoromethyl-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	423.2 [(M+H)$^+$] mp 182°C
4.27	S1.21	S3.2	5-(4-methyl-3-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	423.1 [(M+H)$^+$] mp 218°C
4.28	S1.21	S3.4	5-(4-methyl-3-trifluoromethyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	451.2 [(M+H)$^+$] mp 258°C
4.29	S1.17	S3.5	5-(4-chloro-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	389.1 [(M+H)$^+$] mp 220°C
4.30	S1.15	S3.5	5-(4-chloro-3-methyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	403.5 [(M+H)$^+$] mp 240°C
4.31	S1.14	S3.5	5-(3-chloro-4-fluoro-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	407.3 [(M+H)$^+$] mp 292°C
4.32	S1.16	S3.5	5-(3,4-dichloro-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	423.0 [(M+H)$^+$] mp 275°C
4.33	S1.7	S3.5	5-(4-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	423.0 [(M+H)$^+$] mp 243°C
4.34	S1.6	S3.5	5-(3-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	423.3 [(M+H)$^+$] mp 232°C
4.35	S1.18	S3.5	5-(3-fluoro-4-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	441.5 [(M+H)$^+$] mp 250°C
4.36	S1.19	S3.1	5-(3-methyl-4-trifluoromethyl-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	423.3 [(M+H)$^+$] mp 177°C
4.37	S1.19	S3.2	5-(3-methyl-4-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-	423.3 [(M+H)$^+$] mp 227°C

Ex.	dione	pyrazole	compound name	MS (ISP) / mp
			pyrazolo[1,5-a]pyrimidine	
4.38	S1.19	S3.4	5-(3-methyl-4-trifluoromethyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	451.5 [(M+H)$^+$] mp 253°C
4.39	S1.19	S3.5	5-(3-methyl-4-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	437.5 [(M+H)$^+$] mp 237°C
4.40	S1.22	S3.1	5-(4-ethoxy-3-trifluoromethyl-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	453.5 [(M+H)$^+$] mp 178°C
4.41	S1.22	S3.2	5-(4-ethoxy-3-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	453.5 [(M+H)$^+$] mp 233°
4.42	S1.20	S3.1	5-(4-trifluoroethoxy-3-trifluoromethyl-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	507.5 [(M+H)$^+$] mp 181°C
4.43	S1.20	S3.2	5-(4-trifluorothoxy-3-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	507.5 [(M+H)$^+$] mp 247°C
4.44	S1.22	S3.5	5-(4-ethoxy-3-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	467.2 [(M+H)$^+$] mp 250°C
4.45	S1.20	S3.4	5-(4-trifluoroethoxy-3-trifluoromethyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	535.5 [(M+H)$^+$] mp 229°C
4.46	S1.20	S3.5	5-(4-trifluoroethoxy-3-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	521.5 [(M+H)$^+$] mp 210°C
4.47	S1.26	S3.2	5-(3-Ethoxy-4-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	MS (ISP) 453.1 [(M+H)$^+$] mp 251°C
4.48	S1.26	S3.4	3-(2,6-Dimethyl-pyridin-4-yl)-5-(3-ethoxy-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	MS (ISP) 481.4 [(M+H)$^+$] mp 257°C
4.49	S1.26	S3.5	5-(3-Ethoxy-4-trifluoromethyl-phenyl)-3-	MS (ISP) 467.4

Ex.	dione	pyrazole	compound name	MS (ISP) / mp
			(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	$[(M+H)^+]$ mp 226°C
4.50	S1.27	S3.2	3-Pyridin-4-yl-5-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	MS (ISP) 507.4 $[(M+H)^+]$ mp 251°C
4.51	S1.27	S3.4	3-(2,6-Dimethyl-pyridin-4-yl)-5-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	MS (ISP) 535.4 $[(M+H)^+]$ mp 245°C
4.52	S1.27	S3.5	3-(2-Methyl-pyridin-4-yl)-5-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	MS (ISP) 521.4 $[(M+H)^+]$ mp 201°C.
4.53	S1.28	S3.2	5-(3,4-Bis-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine.Yellow solid.	MS (ISP) 477.2 $[(M+H)^+]$ mp 209°C
4.54	S1.28	S3.5	5-(3,4-Bis-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	MS (ISP) 491.3 $[(M+H)^+]$ mp 223°C
4.55	S1.29	S3.2	5-(4-Bromo-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	MS (ISP) 421.2 $[(M+H)^+]$ mp 289°C
4.56	S1.29	S3.5	5-(4-Bromo-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	MS (ISP) 433.3 $[(M+H)^+]$ mp 226°C
4.57	S1.29	S3.4	5-(4-Bromo-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	MS (ISP) 447.2 $[(M+H)^+]$ mp 258°C
4.58	S1.30	S3.2	5-(4-Methoxy-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	MS (ISP) 371.2 $[(M+H)^+]$ mp 244°C.

Example 4.1

5-(4-Chloro-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-chloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (251 mg, 1.0 mmol), prepared from commercially available 4-chloro-acetophenone according to general procedure A, and 3-amino-4-(3-pyridinyl)-pyrazole [CAS No. 40545-68-2; prepared from 3-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (160 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (306 mg, 82%). MS (ISP) 375.3 [$(M+H)^+$]; mp 188°C.

Example 4.2

5-(4-Chloro-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-chloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (125 mg, 0.5 mmol), prepared from commercially available 4-chloro-acetophenone according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (135 mg, 72%). MS (ISP) 375.3 [$(M+H)^+$]; mp 274°C.

Example 4.3

5-(4-Chloro-3-methyl-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-chloro-3-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (265 mg, 1.0 mmol), prepared from commercially available 4-chloro-3-methyl-acetophenone according to general procedure A, and 3-amino-4-(3-pyridinyl)-pyrazole [CAS No. 40545-68-2; prepared from 3-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 — 3541] (160 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (274 mg, 70%). MS (ISP) 375.3 [$(M+H)^+$]; mp 193°C.

Example 4.4

5-(4-Chloro-3-methyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-chloro-3-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (132 mg, 0.5 mmol), prepared from commercially available 4-chloro-3-methyl-acetophenone according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (145 mg, 75%). MS (ISP) 389.2 [$(M+H)^+$]; mp 247°C.

Example 4.5

5-(4-Chloro-3-methyl-phenyl)-3-pyridin-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-chloro-3-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (265 mg, 1.0 mmol), prepared from commercially available 4-chloro-3-methyl-acetophenone according to general procedure A, and 3-amino-4-(2-pyridinyl)-pyrazole [CAS No. 493038-87-2; prepared from 2-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (160 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (270 mg, 69%). MS (ISP) 389.2 [$(M+H)^+$]; mp 183°C.

Example 4.6

5-(3-Chloro-4-fluoro-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-chloro-4-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (269 mg, 1.0 mmol), prepared from commercially available 3-chloro-4-fluoro-acetophenone according to general procedure A, and 3-amino-4-(3-pyridinyl)-pyrazole [CAS No. 40545-68-2; prepared from 3-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (160 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (270 mg, 69%). MS (ISP) 393.1 [$(M+H)^+$]; mp 190°C.

Example 4.7

5-(3-Chloro-4-fluoro-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-chloro-4-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (134 mg, 0.5 mmol), prepared from commercially available 3-chloro-4-fluoro-acetophenone according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (82 mg, 42%). MS (ISP) 393.1 [$(M+H)^+$]; mp 265°C.

Example 4.8

5-(3-Chloro-4-fluoro-phenyl)-3-pyridin-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-chloro-4-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (269 mg, 1.0 mmol), prepared from commercially available 3-chloro-4-fluoro-acetophenone

according to general procedure A, and 3-amino-4-(2-pyridinyl)-pyrazole [CAS No. 493038-87-2; prepared from 2-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (160 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (279 mg, 71%). MS (ISP) 393.1 [$(M+H)^+$]; mp 197°C.

Example 4.9

5-(3,4-Dichloro-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3,4-dichloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (285 mg, 1.0 mmol), prepared from commercially available 3,4-dichloro-acetophenone according to general procedure A, and 3-amino-4-(3-pyridinyl)-pyrazole [CAS No. 40545-68-2; prepared from 3-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (160 mg, 1.0 mmol) according to general procedure B yielded the title compound as a light yellow solid (274 mg, 67%). MS (ISP) 409.1 [$(M+H)^+$]; mp 224°C.

Example 4.10

5-(3,4-Dichloro-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3,4-dichloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (285 mg, 1.0 mmol), prepared from commercially available 3,4-dichloro-acetophenone according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (160 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (94 mg, 46%). MS (ISP) 409.2 [$(M+H)^+$]; mp 260°C.

Example 4.11

5-(3,4-Dichloro-phenyl)-3-pyridin-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3,4-dichloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (285 mg, 1.0 mmol), prepared from commercially available 3,4-dichloro-acetophenone according to general procedure A, and 3-amino-4-(2-pyridinyl)-pyrazole [CAS No. 493038-87-2; prepared from 2-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (160 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (223 mg, 55%). MS (ISP) 409.2 [$(M+H)^+$]; mp 188°C.

Example 4.12

5-(4-Trifluoromethyl-phenyl)-3-pyridin-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (142 mg, 0.5 mmol), prepared from commercially available 3,4-dichloro-acetophenone according to general procedure A, and 3-amino-4-(2-pyridinyl)-pyrazole [CAS No. 493038-87-2; prepared from 2-cyanomethyl–pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (145 mg, 71%). MS (ISP) 409.2 [$(M+H)^+$]; mp 202°C.

Example 4.13

5-(3-Trifluoromethyl-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (142 mg, 0.5 mmol), prepared from commercially available 3-trifluoromethyl-acetophenone according to general procedure A, and 3-amino-4-(3-pyridinyl)-pyrazole [CAS No. 40545-68-2; prepared from 3-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (126 mg, 62%). MS (ISP) 409.2 [$(M+H)^+$]; mp 171°C.

Example 4.14

5-(4-Trifluoromethyl-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (142 mg, 0.5 mmol), prepared from commercially available 4-trifluoromethyl-acetophenone according to general procedure A, and 3-amino-4-(3-pyridinyl)-pyrazole [CAS No. 40545-68-2; prepared from 3-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (142 mg, 70%). MS (ISP) 409.2 [$(M+H)^+$]; mp 163°C.

Example 4.15

5-(4-Trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (142 mg, 0.5 mmol), prepared from commercially available 4-trifluoromethyl-acetophenone according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (93 mg, 46%). MS (ISP) 409.2 [$(M+H)^+$]; mp 261°C.

Example 4.16

5-(3-Trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (142 mg, 0.5 mmol), prepared from commercially available 3-trifluoromethyl-acetophenone according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (95 mg, 47%). MS (ISP) 409.2 [$(M+H)^+$]; mp 241°C.

Example 4.17

5-(3-Fluoro-4-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-fluoro-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (151 mg, 0.5 mmol), prepared from commercially available 3-fluoro-4-trifluoromethyl-acetophenone according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (92 mg, 43%). MS (ISP) 427.0 [$(M+H)^+$]; mp 262°C.

Example 4.18

5-(3-Fluoro-4-trifluoromethyl-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-fluoro-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (151 mg, 0.5 mmol), prepared from commercially available 3-fluoro-4-trifluoromethyl-acetophenone according to general procedure A, and 3-amino-4-(3-pyridinyl)-pyrazole [CAS No. 40545-68-2; prepared from 3-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (135 mg, 63%). MS (ISP) 427.0 [$(M+H)^+$]; mp 162°C.

Example 4.19

5-(4-Chloro-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-chloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (125 mg, 0.5 mmol), prepared from commercially available 4-chloro-acetophenone according to general

procedure A, and 3-amino-4-(2,6-dimethyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2,6-dimethyl-pyridine, CAS No. 130138-46-4, see part synthesis of amino-pyrazole derivatives] (94 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (95 mg, 47%). MS (ISP) 403.2 [$(M+H)^+$]; mp 256°C.

Example 4.20

5-(4-Chloro-3-methyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-chloro-3-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (132 mg, 0.5 mmol), prepared from commercially available 4-chloro-3-methyl-acetophenone according to general procedure A, and 3-amino-4-(2,6-dimethyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2,6-dimethyl-pyridine, see part synthesis of amino-pyrazole derivatives] (94 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (95 mg, 46%). MS (ISP) 417.2 [$(M+H)^+$]; mp 254°C.

Example 4.21

5-(3-Chloro-4-fluoro-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-chloro-4-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (134 mg, 0.5 mmol), prepared from commercially available 3-chloro-4-fluoro-acetophenone according to general procedure A, and 3-amino-4-(2,6-dimethyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2,6-dimethyl-pyridine, CAS No. 130138-46-4, see part synthesis of amino-pyrazole derivatives] (94 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (97 mg, 46%). MS (ISP) 421.1 [$(M+H)^+$]; mp 271°C.

Example 4.22

5-(3,4-Dichloro-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3,4-dichloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (143 mg, 0.5 mmol), prepared from commercially available 3,4-dichloro-acetophenone according to general procedure A, and 3-amino-4-(2,6-dimethyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2,6-dimethyl-pyridine, CAS No. 130138-46-4, see part synthesis of amino-pyrazole derivatives] (94 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (106 mg, 48%). MS (ISP) 437.1 [$(M+H)^+$]; mp 281°C.

Example 4.23

5-(4-Trifluoromethyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (142 mg, 0.5 mmol), prepared from commercially available 4-trifluoromethyl-acetophenone according to general procedure A, and 3-amino-4-(2,6-dimethyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2,6-dimethyl-pyridine, CAS No. 130138-46-4, see part synthesis of amino-pyrazole derivatives] (94 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (102 mg, 47%). MS (ISP) 437.2 $[(M+H)^+]$; mp 257°C.

Example 4.24

5-(3-Trifluoromethyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (142 mg, 0.5 mmol), prepared from commercially available 3-trifluoromethyl-acetophenone according to general procedure A, and 3-amino-4-(2,6-dimethyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2,6-dimethyl-pyridine, CAS No. 130138-46-4, see part synthesis of amino-pyrazole derivatives] (94 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (99 mg, 45%). MS (ISP) 437.2 $[(M+H)^+]$; mp 236°C.

Example 4.25

5-(3-Fluoro-4-trifluoromethyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-fluoro-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (151 mg, 0.5 mmol), prepared from commercially available 3-fluoro-4-trifluoromethyl-acetophenone according to general procedure A, and 3-amino-4-(2,6-dimethyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2,6-dimethyl-pyridine, CAS No. 130138-46-4, see part synthesis of amino-pyrazole derivatives] (94 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (46 mg, 20%). MS (ISP) 455.0 $[(M+H)^+]$; mp 245°C.

Example 4.26

5-(4-Methyl-3-trifluoromethyl-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-methyl-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (149 mg, 0.5 mmol), prepared from 4-methyl-3-trifluoromethyl-acetophenone according

to general procedure A, and 3-amino-4-(3-pyridinyl)-pyrazole [CAS No. 40545-68-2; prepared from 3-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (160 mg, 76%). MS (ISP) 423.2 [$(M+H)^+$]; mp 182°C.

Example 4.27

5-(4-Methyl-3-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-methyl-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (149 mg, 0.5 mmol), prepared from 4-methyl-3-trifluoromethyl-acetophenone according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (122 mg, 58%). MS (ISP) 423.1 [$(M+H)^+$]; mp 218°C.

Example 4.28

5-(4-Methyl-3-trifluoromethyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-methyl-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (149 mg, 0.5 mmol), prepared from 4-methyl-3-trifluoromethyl-acetophenone (synthesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(2,6-dimethyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2,6-dimethyl-pyridine, see part synthesis of amino-pyrazole derivatives] (94 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (114 mg, 51%). MS (ISP) 451.2 [$(M+H)^+$]; mp 258°C.

Example 4.29

5-(4-Chloro-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-chloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (125 mg, 0.5 mmol), prepared from commercially available 4-chloro–acetophenone according to general procedure A, and 3-amino-4-(2-methyl-4-pyridinyl)-pyrazole [see part synthesis of amino-pyrazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (84 mg, 43%). MS (ISP) 389.1 [$(M+H)^+$]; mp 220°C.

Example 4.30

5-(4-Chloro-3-methyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-chloro-3-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (132 mg, 0.5 mmol), prepared from commercially available 4-chloro-3-methyl-acetophenone according to general procedure A, and 3-amino-4-(2-methyl-4-pyridinyl)-pyrazole [see part synthesis of amino-pyrazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (97 mg, 48%). MS (ISP) 403.5 [$(M+H)^+$]; mp 240°C.

Example 4.31

5-(3-Chloro-4-fluoro-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-chloro-4-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (134 mg, 0.5 mmol), prepared from commercially available 3-chloro-4-fluoro-acetophenone according to general procedure A, and 3-amino-4-(2-methyl-4-pyridinyl)-pyrazole [see part synthesis of amino-pyrazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (86 mg, 42%). MS (ISP) 407.3 [$(M+H)^+$]; mp 292°C.

Example 4.32

5-(3,4-Dichloro-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3,4-dichloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (143 mg, 0.5 mmol), prepared from commercially available 3,4-dichloro-acetophenone according to general procedure A, and 3-amino-4-(2-methyl-4-pyridinyl)-pyrazole [see part synthesis of amino-pyrazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (100 mg, 47%). MS (ISP) 423.0 [$(M+H)^+$]; mp 275°C.

Example 4.33

5-(4-Trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (142 mg, 0.5 mmol), prepared from commercially available 4-trifluoromethyl-acetophenone according to general procedure A, and 3-amino-4-(2-methyl-4-pyridinyl)-pyrazole [see part synthesis of amino-pyrazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (111 mg, 53%). MS (ISP) 423.0 [$(M+H)^+$]; mp 243°C.

Example 4.34

5-(3-Trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (142 mg, 0.5 mmol), prepared from commercially available 3-trifluoromethyl-acetophenone according to general procedure A, and 3-amino-4-(2-methyl-4-pyridinyl)-pyrazole [see part synthesis of amino-pyrazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (108 mg, 51%). MS (ISP) 423.3 [$(M+H)^+$]; mp 232°C.

Example 4.35

5-(3-Fluoro-4-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-fluoro-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (151 mg, 0.5 mmol), prepared from commercially available 3-fluoro-4-trifluoromethyl-acetophenone according to general procedure A, and 3-amino-4-(2-methyl-4-pyridinyl)-pyrazole [see part synthesis of amino-pyrazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (85 mg, 39%). MS (ISP) 441.5 [$(M+H)^+$]; mp 250°C.

Example 4.36

5-(3-Methyl-4-trifluoromethyl-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-methyl-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (149 mg, 0.5 mmol), prepared from 3-methyl-4-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(3-pyridinyl)-pyrazole [CAS No. 40545-68-2; prepared from 3-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (116 mg, 55%). MS (ISP) 423.3 [$(M+H)^+$]; mp 177°C.

Example 4.37

5-(3-Methyl-4-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-methyl-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (149 mg, 0.5 mmol), prepared from 3-methyl-4-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-

pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (104 mg, 49%). MS (ISP) 423.3 [$(M+H)^+$]; mp 227°C.

Example 4.38

5-(3-Methyl-4-trifluoromethyl-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-methyl-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (149 mg, 0.5 mmol), prepared from 3-methyl-4-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(2,6-dimethyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2,6-dimethyl-pyridine, CAS No. 130138-46-4, see part synthesis of amino-pyrazole derivatives] (94 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (107 mg, 48%). MS (ISP) 451.5 [$(M+H)^+$]; mp 253°C.

Example 4.39

5-(3-Methyl-4-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-methyl-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (149 mg, 0.5 mmol), prepared from 3-methyl-4-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(2-methyl-4-pyridinyl)-pyrazole [see part synthesis of amino-pyrazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (113 mg, 52%). MS (ISP) 437.5 [$(M+H)^+$]; mp 237°C.

Example 4.40

5-(4-Ethoxy-3-trifluoromethyl-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-ethoxy-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (164 mg, 0.5 mmol), prepared from 4-ethoxy-3-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(3-pyridinyl)-pyrazole [CAS No. 40545-68-2; prepared from 3-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (155 mg, 68%). MS (ISP) 453.5 [$(M+H)^+$]; mp 178°C.

Example 4.41

5-(4-Ethoxy-3-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-ethoxy-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (1164 mg, 0.5 mmol), prepared from 4-ethoxy-3-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (128 mg, 57%). MS (ISP) 453.5 [$(M+H)^+$]; mp 233°C.

Example 4.42

5-(4-Trifluoroethoxy-3-trifluoromethyl-phenyl)-3-pyridin-3-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-trifluoroethoxy-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (191 mg, 0.5 mmol), prepared from 4-trifluoroethoxy-3-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(3-pyridinyl)-pyrazole [CAS No. 40545-68-2; prepared from 3-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (174 mg, 69%). MS (ISP) 507.5 [$(M+H)^+$]; mp 181°C.

Example 4.43

5-[4-(2,2,2-Trifluorothoxy)-3-trifluoromethyl-phenyl]-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-[4-(2,2,2-trifluoroethoxy)-3-trifluoromethyl-phenyl]-4,4,4-trifluoro-butane-1,3-dione (191 mg, 0.5 mmol), prepared from 4-(2,2,2-trifluoroethoxy)-3-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (139 mg, 55%). MS (ISP) 507.5 [$(M+H)^+$]; mp 247°C.

Example 4.44

5-(4-Ethoxy-3-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-ethoxy-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (164 mg, 0.5 mmol), prepared from 4-ethoxy-3-trifluoromethyl-acetophenone(synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(2-methyl-4-pyridinyl)-pyrazole [see part synthesis of amino-pyrazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded

the title compound as a yellow solid (145 mg, 62%). MS (ISP) 467.2 [$(M+H)^+$]; mp 250°C.

Example 4.45

5-[4-(2,2,2-Trifluoroethoxy)-3-trifluoromethyl-phenyl]-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-[4-(2,2,2-trifluoroethoxy)-3-trifluoromethyl-phenyl]-4,4,4-trifluoro-butane-1,3-dione (191 mg, 0.5 mmol), prepared from 4-(2,2,2-trifluoroethoxy)-3-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(2,6-dimethyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2,6-dimethyl-pyridine, CAS No. 130138-46-4, see part synthesis of amino-pyrazole derivatives] (94 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (165 mg, 62%). MS (ISP) 535.5 [$(M+H)^+$]; mp 229°C.

Example 4.46

5-[4-(2,2,2-Trifluoroethoxy)-3-trifluoromethyl-phenyl]-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-[4-(2,2,2-trifluoroethoxy)-3-trifluoromethyl-phenyl]-4,4,4-trifluoro-butane-1,3-dione (191 mg, 0.5 mmol), prepared from 4-(2,2,2-trifluoroethoxy)-3-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(2-methyl-4-pyridinyl)-pyrazole [see part synthesis of amino-pyrazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (176 mg, 68%). MS (ISP) 521.5 [$(M+H)^+$]; mp 210°C.

Example 4.47

5-(3-Ethoxy-4-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-ethoxy-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (164 mg, 0.5 mmol), prepared from 3-ethoxy-4-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (108 mg, 48%). MS (ISP) 453.1 [$(M+H)^+$]; mp 251°C.

Example 4.48

3-(2,6-Dimethyl-pyridin-4-yl)-5-(3-ethoxy-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-ethoxy-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (164 mg, 0.5 mmol), prepared from 3-ethoxy-4-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(2,6-dimethyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2,6-dimethyl-pyridine, CAS No. 130138-46-4, as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (94 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (120 mg, 50%). MS (ISP) 481.4 $[(M+H)^+]$; mp 257°C.

Example 4.49

5-(3-Ethoxy-4-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3-ethoxy-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (164 mg, 0.5 mmol), prepared from 3-ethoxy-4-trifluoromethyl-acetophenone(synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(2-methyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2-methyl-pyridine, as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (113 mg, 49%). MS (ISP) 467.4 $[(M+H)^+]$; mp 226°C.

Example 4.50

3-Pyridin-4-yl-5-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-[3-(2,2,2-trifluoroethoxy)-4-trifluoromethyl-phenyl]-4,4,4-trifluoro-butane-1,3-dione (191 mg, 0.5 mmol), prepared from 4-(2,2,2-trifluoroethoxy)-3-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (127 mg, 50%). MS (ISP) 507.4 $[(M+H)^+]$; mp 251°C.

Example 4.51

3-(2,6-Dimethyl-pyridin-4-yl)-5-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-[3-(2,2,2-trifluoroethoxy)-4-trifluoromethyl-phenyl]-4,4,4-trifluoro-butane-1,3-dione (191 mg, 0.5 mmol), prepared from 4-(2,2,2-trifluoroethoxy)-3-

trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(2,6-dimethyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2,6-dimethyl-pyridine, CAS No. 130138-46-4, as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (94 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (139 mg, 52%). MS (ISP) 535.4 [$(M+H)^+$]; mp 245°C.

Example 4.52

3-(2-Methyl-pyridin-4-yl)-5-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-[3-(2,2,2-trifluoroethoxy)-4-trifluoromethyl-phenyl]-4,4,4-trifluoro-butane-1,3-dione (191 mg, 0.5 mmol), prepared from 4-(2,2,2-trifluoroethoxy)-3-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(2-methyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2-methyl-pyridine, as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (140 mg, 54%). MS (ISP) 521.4 [$(M+H)^+$]; mp 201°C.

Example 4.53

5-(3,4-Bis-trifluoromethyl-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3,4-bis-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (176 mg, 0.5 mmol), prepared from commercially available 3,4-bis-trifluoromethyl-acetophenone [CAS No. 129604-25-7] according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (83 mg, 35%). Yellow solid. MS (ISP) 477.2 [$(M+H)^+$]; mp 209°C.

Example 4.54

5-(3,4-Bis-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(3,4-bis-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (176 mg, 0.5 mmol), prepared from commercially available 3,4-bis-trifluoromethyl-acetophenone [CAS No. 129604-25-7] according to general procedure A, and 3-amino-4-(2-methyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2-methyl-pyridine, as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (93 mg, 38%). MS (ISP) 491.3 [$(M+H)^+$]; mp 223°C.

Example 4.55

5-(4-Bromo-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-bromo-phenyl)-4,4,4-trifluoro-butane-1,3-dione (148 mg, 0.5 mmol), prepared from commercially available 4-bromo-acetophenone according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (79 mg, 38%). MS (ISP) 421.2 [$(M+H)^+$]; mp 289°C.

Example 4.56

5-(4-Bromo-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-bromo-phenyl)-4,4,4-trifluoro-butane-1,3-dione (148 mg, 0.5 mmol), prepared from commercially available 4-bromo-acetophenone according to general procedure A, and 3-amino-4-(2-methyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2-methyl-pyridine, as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (94 mg, 43%). MS (ISP) 433.3 [$(M+H)^+$]; mp 226°C.

Example 4.57

5-(4-Bromo-phenyl)-3-(2,6-dimethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-bromo-phenyl)-4,4,4-trifluoro-butane-1,3-dione (148 mg, 0.5 mmol), prepared from commercially available 4-bromo-acetophenone according to general procedure A, and 3-amino-4-(2,6-dimethyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2,6-dimethyl-pyridine, CAS No. 130138-46-4, as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (94 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (93 mg, 42%). MS (ISP) 447.2 [$(M+H)^+$]; mp 258°C.

Example 4.58

5-(4-Methoxy-phenyl)-3-pyridin-4-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Reaction of 1-(4-methoxy-phenyl)-4,4,4-trifluoro-butane-1,3-dione (123 mg, 0.5 mmol), prepared from commercially available 4-methoxy-acetophenone according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (110 mg, 59%). MS (ISP) 371.2 [$(M+H)^+$]; mp 244°C.

Example 5: Preparation of phenyl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitriles and pyridinyl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitriles

A stirred mixture of commercially available 4-amino-5-cyano-1H-imidazole (1 eq.) and a 1-phenyl-4,4,4-trifluoro-butane-1,3-dione or 1-pyridin-2-yl-4,4,4-trifluoro-butane-1,3-dione (1 eq.), prepared according to general procedure A, in acetic acid was heated under reflux conditions for 3.5 h. The reaction mixture was evaporated and the product was isolated by column chromatography (heptane/ethyl acetate) and further purified by crystallization. If the product precipitates during the reaction it can be isolated by filtration and further purified by crystallization.

Ex.	dione	compound name	MS (ISP) / mp
5.1	S1.23	2-phenyl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	289.0 [(M+H)$^+$] mp 202°C
5.2	S1.17	2-(4-chloro-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	323.1 [(M+H)$^+$] mp 205°C
5.3	S1.1	2-(3-chloro-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	323.1 [(M+H)$^+$] mp 221°C
5.4	S1.2	2-(4-methyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	303.1 [(M+H)$^+$] mp 197°C
5.5	S1.24	2-(4-methoxy-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	319.1 [(M+H)$^+$] mp 192°C
5.6	S1.3	2-(2-chloro-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	323.1 [(M+H)$^+$] mp 180°C
5.7	S1.4	2-(2,4-dichloro-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	357.0 [(M+H)$^+$] mp 139°C
5.8	S1.25	2-(2-methyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	303.0 [(M+H)$^+$] mp 151°C
5.9	S1.5	2-(3-methyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	302.9 [(M+H)$^+$] mp 202°C
5.10	S1.2	2-(4-trifluoromethyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	357.0 [(M+H)$^+$] mp 236°C
5.11	S1.6	2-(3-trifluoromethyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	357.0 [(M+H)$^+$] mp 202°C

Ex.	dione	compound name	MS (ISP) / mp
5.12	S1.8	5-(3-fluoro-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	307.0 [(M+H)$^+$] mp 210°C
5.13	S1.9	5-(4-fluoro-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	307.0 [(M+H)$^+$] mp 206°C
5.14	S1.10	5-(2,4-difluoro-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	325.2 [(M+H)$^+$] mp 169°C
5.15	S1.11	5-(2-fluoro-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	307.1 [(M+H)$^+$] mp 147°C
5.16	S1.12	5-(3,4-difluoro-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	325.2 [(M+H)$^+$] mp 187°C
5.17	S1.13	5-(4-fluoro-3-trifluoromethyl-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	375.3 [(M+H)$^+$] mp 207°C
5.18	S1.14	5-(3-chloro-4-fluoro-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	341.1 [(M+H)$^+$] mp 195°C
5.19	S1.15	5-(4-chloro-3-methyl-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	337.1 [(M+H)$^+$] mp 238°C
5.20	S1.16	5-(3,4-dichloro-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	357.2 [(M+H)$^+$] mp 219°C
5.21	S1.18	5-(3-fluoro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	375.0 [(M+H)$^+$] mp 210°C
5.22	S1.21	2-(4-methyl-3-trifluoromethyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	371.1 [(M+H)$^+$] mp 220°C
5.23	S1.19	2-(3-methyl-4-trifluoromethyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	371.1 [(M+H)$^+$] mp 217°C
5.24	S1.20	2-(4-trifluoroethoxy-3-trifluoromethyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	453.0 [M$^+$] mp 189°C
5.25	S2.1	2-pyridin-2-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	289.9 [(M+H)$^+$] mp 205°C

Ex.	dione	compound name	MS (ISP) / mp
5.26	S2.2	2-pyridin-3-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	290.1 [(M+H)$^+$] mp 222°C
5.27	S2.3	2-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile	289.8 [(M+H)$^+$] mp 254°C

Example 5.1

2-Phenyl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-phenyl-4,4,4-trifluoro-butane-1,3-dione (216 mg, 1.0 mmol), prepared from commercially available acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (107 mg, 37%). MS (ISP) 289.0 [(M+H)$^+$]; mp 202°C.

Example 5.2

2-(4-Chloro-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(4-chloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (251 mg, 1.0 mmol), prepared from commercially available 4-chloro-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (124 mg, 38%). MS (ISP) 323.1 [(M+H)$^+$]; mp 205°C.

Example 5.3

2-(3-Chloro-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(3-chloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (251 mg, 1.0 mmol), prepared from commercially available 3-chloro-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (133 mg, 41%). MS (ISP) 323.1 [(M+H)$^+$]; mp 221°C.

Example 5.4

2-(4-Methyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(4-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (230 mg, 1.0 mmol), prepared from commercially available 4-methyl-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (133 mg, 44%). MS (ISP) 303.1 [(M+H)$^+$]; mp 197°C.

Example 5.5

2-(4-Methoxy-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(4-methoxy-phenyl)-4,4,4-trifluoro-butane-1,3-dione (246 mg, 1.0 mmol), prepared from commercially available 4-methoxy-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (125 mg, 39%). MS (ISP) 319.1 [$(M+H)^+$]; mp 192°C.

Example 5.6

2-(2-Chloro-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(2-chloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (251 mg, 1.0 mmol), prepared from commercially available 2-chloro-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (55 mg, 17%). MS (ISP) 323.1 [$(M+H)^+$]; mp 180°C.

Example 5.7

2-(2,4-Dichloro-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(2,4-dichloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (285 mg, 1.0 mmol), prepared from commercially available 2,4-dichloro-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (43 mg, 12%). MS (ISP) 357.0 [$(M+H)^+$]; mp 139°C.

Example 5.8

2-(2-Methyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(2-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (230 mg, 1.0 mmol), prepared from commercially available 2-methyl-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (19 mg, 6%). MS (ISP) 303.0 [$(M+H)^+$]; mp 151°C.

Example 5.9

2-(3-Methyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(3-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (230 mg, 1.0 mmol), prepared from commercially available 3-methyl-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to

general procedure B yielded the title compound as a yellow solid (161 mg, 53%). MS (ISP) 302.9 [$(M+H)^+$]; mp 202°C.

Example 5.10

2-(4-Trifluoromethyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (284 mg, 1.0 mmol), prepared from commercially available 4-trifluoromethyl-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (151 mg, 42%). MS (ISP) 357.0 [$(M+H)^+$]; mp 236°C.

Example 5.11

2-(3-Trifluoromethyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (284 mg, 1.0 mmol), prepared from commercially available 3-trifluoromethyl-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (125 mg, 35%). MS (ISP) 357.0 [$(M+H)^+$]; mp 202°C.

Example 5.12

5-(3-Fluoro-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(3-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (234 mg, 1.0 mmol), prepared from commercially available 3-fluoro-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (128 mg, 42%). MS (ISP) 307.0 [$(M+H)^+$]; mp 210°C.

Example 5.13

5-(4-Fluoro-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(4-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (234 mg, 1.0 mmol), prepared from commercially available 4-fluoro-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (119 mg, 39%). MS (ISP) 307.0 [$(M+H)^+$]; mp 206°C.

Example 5.14

5-(2,4-Difluoro-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(2,4-difluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (252 mg, 1.0 mmol), prepared from commercially available 2,4-difluoro-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (75 mg, 23%). MS (ISP) 325.2 [$(M+H)^+$]; mp 169°C.

Example 5.15

5-(2-Fluoro-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(2-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (234 mg, 1.0 mmol), prepared from commercially available 2-fluoro-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (99 mg, 32%). MS (ISP) 307.1 [$(M+H)^+$]; mp 147°C.

Example 5.16

5-(3,4-Difluoro-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(3,4-difluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (252 mg, 1.0 mmol), prepared from commercially available 3,4-difluoro-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (107 mg, 33%). MS (ISP) 325.2 [$(M+H)^+$]; mp 187°C.

Example 5.17

5-(4-Fluoro-3-trifluoromethyl-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(4-fluoro-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (302 mg, 1.0 mmol), prepared from commercially available 4-fluoro-3-trifluoromethyl-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (141 mg, 38%). MS (ISP) 375.3 [$(M+H)^+$]; mp 207°C.

Example 5.18

5-(3-Chloro-4-fluoro-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(3-chloro-4-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (269 mg, 1.0 mmol), prepared from commercially available 3-chloro-4-fluoro-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0

mmol) according to general procedure B yielded the title compound as a yellow solid (120 mg, 35%). MS (ISP) 341.1 [$(M+H)^+$]; mp 195°C.

Example 5.19

5-(4-Chloro-3-methyl-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(4-chloro-3-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (265 mg, 1.0 mmol), prepared from commercially available 4-chloro-3-methyl-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (171 mg, 51%). MS (ISP) 337.1 [$(M+H)^+$]; mp 238°C.

Example 5.20

5-(3,4-Dichloro-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(3,4-dichloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (285 mg, 1.0 mmol), prepared from commercially available 3,4-dichloro-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (161 mg, 45%). MS (ISP) 357.2 [$(M+H)^+$]; mp 219°C.

Example 5.21

5-(3-Fluoro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(3-fluoro-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (302 mg, 1.0 mmol), prepared from commercially available 3-fluoro-4-trifluoromethyl-acetophenone according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (110 mg, 29%). MS (ISP) 375.0 [$(M+H)^+$]; mp 210°C.

Example 5.22

2-(4-Methyl-3-trifluoromethyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(4-methyl-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (298 mg, 1.0 mmol), prepared from 4-methyl-3-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (143 mg, 39%). MS (ISP) 371.1 [$(M+H)^+$]; mp 220°C.

Example 5.23

2-(3-Methyl-4-trifluoromethyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(3-methyl-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (224 mg, 0.75 mmol), prepared from 3-methyl-4-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 4-amino-5-cyano-1H-imidazole (81 mg, 0.75 mmol) according to general procedure B yielded the title compound as a yellow solid (131 mg, 47%). MS (ISP) 371.1 [$(M+H)^+$]; mp 217°C.

Example 5.24

2-(4-Trifluoroethoxy-3-trifluoromethyl-phenyl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-(4-trifluoroethoxy-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (382 mg, 1.0 mmol), prepared from 4-trifluoroethoxy-3-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (182 mg, 40%). MS (ISP) 453.0 [M^+]; mp 189°C.

Example 5.25

2-Pyridin-2-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-pyridin-2-yl-4,4,4-trifluoro-butane-1,3-dione (217 mg, 1.0 mmol), prepared from commercially available 2-acetylpyridine according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (135 mg, 47%). MS (ISP) 289.9 [$(M+H)^+$]; mp 205°C.

Example 5.26

2-Pyridin-3-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-pyridin-3-yl-4,4,4-trifluoro-butane-1,3-dione (217 mg, 1.0 mmol), prepared from commercially available 3-acetylpyridine according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (37 mg, 13%). MS (ISP) 290.1 [$(M+H)^+$]; mp 222°C.

Example 5.27

2-Pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine-8-carbonitrile

Reaction of 1-pyridin-4-yl-4,4,4-trifluoro-butane-1,3-dione (217 mg, 1.0 mmol), prepared from commercially available 4-acetylpyridine according to general procedure A, and 4-amino-5-cyano-1H-imidazole (108 mg, 1.0 mmol) according to general procedure B yielded the title compound as a yellow solid (77 mg, 27%). MS (ISP) 289.8 $[(M+H)^+]$; mp 254°C.

Example 6: 5-phenyl)-3-(2-hydroxymethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidines (General procedure C)

General procedure C:

a) To a stirred solution of a 5-phenyl-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine prepared according to general procedure B (example 4) in dichloromethane MeOH and 3-chloro-perbenzoic acid are added at RT. The solution is stirred at RT for about 17h, sat. $NaHCO_3$ solution and dichloromethane is added and the mixture was stirred for about 30 min. The organic layer is separated, washed with a $Na_2S_2O_3$ solution, sat. $NaHCO_3$ solution, brine and dried (Mg_2SO_4). Evaporation of the solvent yields a crude 5-phenyl-3-(2-methyl-1-oxo-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine compound as a solid, which can be used without further purification.

b) A stirred mixture of a 5-phenyl-3-(2-methyl-1-oxo-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine compound and acetic acid anhydride is refluxed for about 30 min, poured into sat. $NaHCO_3$ solution and extracted with dichloromethane (e.g. 3 times 20 ml). The combined organic layers is washed with brine and dried ($MgSO_4$). Purification of the crude product by column chromatography on silica gel (ethyl acetate/ hexane 1:1) yields a 4-[5-phenyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-pyridin-2-ylmethyl acetate compound as a solid.

c) To a stirred solution of said 4-[5-phenyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-pyridin-2-ylmethyl acetate compound in MeOH is added at RT NaOMe.The reaction mixture is stirred for about 17h, poured into water and extracted with dichloromethane (e.g. 3 times 40 ml). The combined organic layers is washed with brine, dried ($MgSO_4$) and evaporated. The crude product can be further purified by column chromatography on silica gel (e.g. ethyl acetate) to yield the title compounds as a solid.

Ex.	Pyrimidine compound	compound name	MS (ISP) / mp

Ex.	Pyrimidine compound	compound name	MS (ISP) / mp
6.1	4.33	5-(4-Trifluoromethyl-phenyl)-3-(2-hydroxymethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	MS (ISP) 439.3 $[(M+H)^+]$ mp 102°C
6.2	4.39	5-(3-Methyl-4-trifluoromethyl-phenyl)-3-(2-hydroxymethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine	MS (ISP) 453.4 $[(M+H)^+]$ mp 231°C
6.3	4.30	{4-[5-(4-Chloro-3-methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-pyridin-2-yl}-methanol	MS (ISP) 419.3 $[(M+H)^+]$ mp 220°C
6.4	4.32	{4-[5-(3,4-Dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-pyridin-2-yl}-methanol	MS (ISP) 439.2 $[(M+H)^+]$ mp 233°C

Example 6.1

5-(4-Trifluoromethyl-phenyl)-3-(2-hydroxymethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

a) To a stirred solution of 5-(4-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine (0.15 g, 0.36 mmol, synthesis: see example 89) in dichloromethane (3.5 ml) was added at room temperature MeOH (1 ml) and 3-chloro-perbenzoic acid (70%, 0.10 mg, 0.41 mmol). The yellow solution was stirred at RT for 17h, sat. $NaHCO_3$ solution (10 ml) and dichloromethane (10 ml) was added and the mixture was stirred for 30 min. The organic layer was separated, washed with 10% $Na_2S_2O_3$ solution (10 ml), sat. $NaHCO_3$ solution (20 ml), brine (30 ml) and dried (Mg_2SO_4). Evaporation of the solvent yielded crude 5-(4-trifluoromethyl-phenyl)-3-(2-methyl-1-oxo-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine as an orange solid (0.16 g), which was used without further purification.

b) A stirred mixture of 5-(4-trifluoromethyl-phenyl)-3-(2-methyl-1-oxo-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine (0.15 g, 0.33 mmol) and acetic acid anhydride (1 ml) was refluxed for 30 min, poured into sat. $NaHCO_3$ solution (20 ml) and extracted with dichloromethane (3 times 20 ml). The combined organic layers were washed with brine (50 ml) and dried ($MgSO_4$). Purification of the crude product by column chromatography on silica gel (ethyl acetate/ hexane 1:1) yielded 4-[5-(4-

trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-pyridin-2-ylmethyl acetate (0.16 g, 99%) as a brown solid.

c) To a stirred solution of 4-[5-(4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-pyridin-2-ylmethyl acetate (0.16 g, 0.33 mmol) in MeOH (1 ml) was added at room temperature NaOMe (5.4M in MeOH, 0.2 ml).The reaction mixture was stirred for 17h, poured into water (40 ml) and extracted with dichloromethane (3 times 40 ml). The combined organic layers were washed with brine (100 ml), dried ($MgSO_4$) and evaporated. The crude product was further purified by column chromatography on silica gel (ethyl acetate) to yield the title compound (112 mg, 78%) as an orange solid. MS (ISP) 439.3 [$(M+H)^+$]; mp 2102°C.

Example 6.2

5-(3-Methyl-4-trifluoromethyl-phenyl)-3-(2-hydroxymethyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine

Transformation of 5-(3-methyl-4-trifluoromethyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine (0.34 g, 0.78 mmol, synthesis: see example 96) according to the general method of example 108 yielded the title compound (80 mg, 23%) as an orange solid. MS (ISP) 453.4 [$(M+H)^+$]; mp 231°C.

Example 6.3

{4-[5-(4-Chloro-3-methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-pyridin-2-yl}-methanol

Transformation of 5-(4-chlor-3-methyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine (0.40 g, 1.0 mmol, synthesis: see example 86) according to the general method of example 108 yielded the title compound (140 mg, 33%) as an orange solid. MS (ISP) 419.3 [$(M+H)^+$]; mp 220°C.

Example 6.4

{4-[5-(3,4-Dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-pyridin-2-yl}-methanol

Transformation of 5-(3,4-dichloro-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine (0.43 g, 1.0 mmol, synthesis: see example 88) according to the general method of example 108 yielded the title compound (73 mg, 17%) as an orange solid. MS (ISP) 439.2 [$(M+H)^+$]; mp 233°C.

Example 7: 5-(4-Chloro-3-methyl-phenyl)-3-(2-methyl-1-oxy-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine (compound no. 7.1)

To a stirred solution of 5-(4-chloro-3-methyl-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine (0.50 g, 1.24 mmol) in dichloromethane (12 ml) was added at RT MeOH (3 ml) and 3-chloro-perbenzoic acid (70%, 0.36 mg, 1.44 mmol). The orange solution was stirred at RT for 17h, sat. $NaHCO_3$ solution (75 ml) and dichloromethane (50 ml) was added and the mixture was stirred for 30 min. The organic layer was separated, washed with 10% $Na_2S_2O_3$ solution (60 ml), sat. $NaHCO_3$ solution (60 ml), brine (100 ml) and dried (Mg_2SO_4). Evaporation of the solvent and crystallization yielded the title compound (0.51 g, 99%) as an orange solid. MS (ISP) 418.1 [M^+]; mp 279°C.

Oxidation of 5-(3,4-dichloro-phenyl)-3-(2-methyl-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine (0.63 g, 1.49 mmol) according to the above procedure yielded 5-(3,4-dichloro-phenyl)-3-(2-methyl-1-oxy-pyridin-4-yl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine compound no. 7.2 (0.63 g, 96%) as an orange solid. MS (ISP) 438.0 [M^+]; mp 287°C.

Example 8: Preparation of 5-phenyl-3-pyridinyl-7-trifluoromethyl-imidazol[1,5-a]pyrimidines (General Procedure B)

Ex.	dione	compound name	MS (ISP) / mp
8.1	S1.15	2-(4-Chloro-3-methyl-phenyl)-8-pyridin-3-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 289.3 [(M+H)$^+$] mp 210°C
8.2	S1.17	2-(4-Chloro-phenyl)-8-pyridin-3-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 375.5 [(M+H)$^+$] mp 206°C
8.3	S1.14	2-(3-Chloro-4-fluoro-phenyl)-8-pyridin-3-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 393.1 [(M+H)$^+$] mp 188°C
8.4	S1.16	2-(4-Dichloro-phenyl)-8-pyridin-3-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 409.4 [(M+H)$^+$] mp 226°C
8.5	S1.6	8-Pyridin-3-yl-4-trifluoromethyl-2-(3-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine	MS (ISP) 409.4 [(M+H)$^+$]

Ex.	dione	compound name	MS (ISP) / mp
			mp 194°C
8.6	S1.7	8-Pyridin-3-yl-4-trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine	MS (ISP) 409.4 [(M+H)$^+$] mp 231°C
8.7	S1.21	2-(4-Methyl-3-trifluoromethyl-phenyl)-8-pyridin-3-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 423.1 [(M+H)$^+$] mp 236°C
8.8	S1.19	2-(3-Methyl-4-trifluoromethyl-phenyl)-8-pyridin-3-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 423.3 [(M+H)$^+$] mp 173°C
8.9	S1.17	2-(4-Chloro-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 375.5 [(M+H)$^+$] mp 290°C.
8.10	S1.15	2-(4-Chloro-3-methyl-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 389.3 [(M+H)$^+$] mp 254°C.
8.11	S1.14	2-(3-Chloro-4-fluoro-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 393.1 [(M+H)$^+$] mp 266°C
8.12	S1.16	2-(4-Dichloro-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 409.3 [(M+H)$^+$] mp 262°C
8.13	S1.6	8-Pyridin-4-yl-4-trifluoromethyl-2-(3-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine	MS (ISP) 409.4 [(M+H)$^+$] mp 258°C
8.14	S1.7	8-Pyridin-4-yl-4-trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine	MS (ISP) 409.4 [(M+H)$^+$] mp 240°C
8.15	S1.19	2-(3-Fluoro-4-trifluoromethyl-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 427.4.0 [(M+H)$^+$] mp 267°C
8.16	S1.21	2-(4-Methyl-3-trifluoromethyl-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 423.3 [(M+H)$^+$] mp 222°C
8.17	S1.22	2-(4-Ethoxy-3-trifluoromethyl-phenyl)-8-pyridin-4-	MS (ISP) 453.5.0

Ex.	dione	compound name	MS (ISP) / mp
		yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	$[(M+H)^+]$ mp 244°C
8.18	S1.20	8-Pyridin-4-yl-2-[4-(2,2,2-trifluoro-ethoxy)-3-trifluoromethyl-phenyl]-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 507.5 $[(M+H)^+]$ mp 269°C
8.19	S1.19	2-(3-Methyl-4-trifluoromethyl-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 422.1 $[(M+H)^+]$ mp 225°C
8.20	S1.17	2-(4-Chloro-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 389.2 $[(M+H)^+]$ mp 232°C
8.21	S1.15	2-(4-Chloro-3-methyl-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 403.4 $[(M+H)^+]$ mp 246°C
8.22	S1.14	2-(3-Chloro-4-fluoro-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 407.3 $[(M+H)^+]$ mp 255°C
8.23	S1.16	2-(4-Dichloro-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 423.2 $[(M+H)^+]$ mp 271°C
8.24	S1.7	8-(2-Methyl-pyridin-4-yl)-4-trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine	MS (ISP) 423.2 $[(M+H)^+]$ mp 257°C
8.25	S1.6	8-(2-Methyl-pyridin-4-yl)-4-trifluoromethyl-2-(3-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine	MS (ISP) 423.2 $[(M+H)^+]$ mp 234°C
8.26	S1.18	2-(3-Fluoro-4-trifluoromethyl-phenyl)-8-(2-methyl-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 441.2 $[(M+H)^+]$ mp 252°C
8.27	S1.22	2-(4-Ethoxy-3-trifluoromethyl-phenyl)-8-(2-methyl-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 467.4 $[(M+H)^+]$ mp 249°C
8.28	S1.20	8-(2-Methyl-pyridin-4-yl-2-[4-(2,2,2-trifluoro-ethoxy)-3-trifluoromethyl-phenyl]-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 521.4 $[(M+H)^+]$ mp 219°C

Ex.	dione	compound name	MS (ISP) / mp
8.29	S1.19	2-(3-Methyl-4-trifluoromethyl-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 437.4 [(M+H)$^+$] mp 243°C
8.30	S1.26	2-(3-Ethoxy-4-trifluoromethyl-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 453.4 [(M+H)$^+$] mp 212°C
8.31	S1.26	2-(3-Ethoxy-4-trifluoromethyl-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 467.2 [(M+H)$^+$] mp 177°C
8.32	S1.27	8-Pyridin-4-yl-2-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 507.4 [(M+H)$^+$] mp 233°C
8.33	S1.27	8-(2-Methyl-pyridin-4-yl)-2-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 521.3 [(M+H)$^+$] mp 189°C
8.34	S1.28	2-(3,4-Bis-trifluoromethyl-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 477.2 [(M+H)$^+$] mp 211°C
8.35	S1.28	2-(3,4-Bis-trifluoromethyl-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 491.3 [(M+H)$^+$] mp 218°C
8.36	S1.29	2-(4-Bromo-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine	MS (ISP) 435.3 [(M+H)$^+$] mp 249°C

Example 8.1

2-(4-Chloro-3-methyl-phenyl)-8-pyridin-3-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(4-chloro-3-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (132 mg, 0.5 mmol), prepared from commercially available 4-chloro-3-methyl-acetophenone according to general procedure A, and 2-amino-3-(3-pyridinyl)-1H-imidazole dihydrochloride [synthesis: see part amino-imidazole derivatives] (117 mg, 0.5 mmol) according to general procedure B yielded the title compound as a red solid (43 mg, 22%). MS (ISP) 289.3 [(M+H)$^+$]; mp 210°C.

Example 8.2

2-(4-Chloro-phenyl)-8-pyridin-3-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(4-chloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (125 mg, 0.5 mmol), prepared from commercially available 4-chloro-acetophenone according to general procedure A, and 2-amino-3-(3-pyridinyl)-1H-imidazole dihydrochloride [synthesis: see part amino-imidazole derivatives] (117 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (43 mg, 23%). MS (ISP) 375.5 [$(M+H)^+$]; mp 206°C.

Example 8.3

2-(3-Chloro-4-fluoro-phenyl)-8-pyridin-3-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(3-chloro-4-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (134 mg, 0.5 mmol), prepared from commercially available 3-chloro-4-fluoro-acetophenone according to general procedure A, and 2-amino-3-(3-pyridinyl)-1H-imidazole dihydrochloride [synthesis: see part amino-imidazole derivatives] (117 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (62 mg, 32%). Orange solid. MS (ISP) 393.1 [$(M+H)^+$]; mp 188°C.

Example 8.4

2-(4-Dichloro-phenyl)-8-pyridin-3-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(3,4-dichloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (143 mg, 0.5 mmol), prepared from commercially available 3,4-dichloro-acetophenone according to general procedure A, and 2-amino-3-(3-pyridinyl)-1H-imidazole dihydrochloride [synthesis: see part amino-imidazole derivatives] (117 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (66 mg, 32%).

Red solid. MS (ISP) 409.4 [$(M+H)^+$]; mp 226°C.

Example 8.5

8-Pyridin-3-yl-4-trifluoromethyl-2-(3-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine

Reaction of 1-(3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (284 mg, 1.0 mmol), prepared from commercially available 3-trifluoromethyl-acetophenone according to general procedure A, and 2-amino-3-(3-pyridinyl)-1H-imidazole dihydrochloride [synthesis: see part amino-imidazole derivatives] (233 mg, 1.0 mmol) according to general procedure B yielded the title compound as a red solid (54 mg, 13%). MS (ISP) 409.4 [$(M+H)^+$]; mp 194°C.

Example 8.6

8-Pyridin-3-yl-4-trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine

Reaction of 1-(4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (284 mg, 1.0 mmol), prepared from commercially available 4-trifluoromethyl-acetophenone according to general procedure A, and 2-amino-3-(3-pyridinyl)-1H-imidazole dihydrochloride [synthesis: see part amino-imidazole derivatives] (233 mg, 1.0 mmol) according to general procedure B yielded the title compound as an orange solid (73 mg, 18%). MS (ISP) 409.4 $[(M+H)^+]$; mp 231°C.

Example 8.7

2-(4-Methyl-3-trifluoromethyl-phenyl)-8-pyridin-3-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(4-methyl-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (149 mg, 0.5 mmol), prepared from 4-methyl-3-trifluoromethyl-acetophenone (synthesis: see part acetophenone derivatives) according to general procedure A, and 2-amino-3-(3-pyridinyl)-1H-imidazole dihydrochloride [synthesis: see part amino-imidazole derivatives] (117 mg, 0.5 mmol) according to general procedure B yielded the title compound as a red solid (84 mg, 40%). MS (ISP) 423.1 $[(M+H)^+]$; mp 236°C.

Example 8.8

2-(3-Methyl-4-trifluoromethyl-phenyl)-8-pyridin-3-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(3-methyl-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (149 mg, 0.5 mmol), prepared from 3-methyl-4-trifluoromethyl-acetophenone (synthesis: see part acetophenone derivatives) according to general procedure A, and 2-amino-3-(3-pyridinyl)-1H-imidazole dihydrochloride [synthesis: see part amino-imidazole derivatives] (117 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (103 mg, 49%). MS (ISP) 423.3 $[(M+H)^+]$; mp 173°C.

Example 8.9

2-(4-Chloro-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(4-chloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (125 mg, 0.5 mmol), prepared from commercially available 4-chloro-acetophenone according to general procedure A, and 2-amino-3-(4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (44 mg, 23%). MS (ISP) 375.5 $[(M+H)^+]$; mp 290°C.

Example 8.10

2-(4-Chloro-3-methyl-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(4-chloro-3-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (132 mg, 0.5 mmol), prepared from commercially available 4-chloro-3-methyl-acetophenone according to general procedure A, and 2-amino-3-(4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (98 mg, 50%). MS (ISP) 389.3 $[(M+H)^+]$; mp 254°C.

Example 8.11

2-(3-Chloro-4-fluoro-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(3-chloro-4-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (134 mg, 0.5 mmol), prepared from commercially available 3-chloro-4-fluoro-acetophenone according to general procedure A, and 2-amino-3-(4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (84 mg, 43%). MS (ISP) 393.1 $[(M+H)^+]$; mp 266°C.

Example 8.12

2-(4-Dichloro-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(3,4-dichloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (143 mg, 0.5 mmol), prepared from commercially available 3,4-dichloro-acetophenone according to general procedure A, and 2-amino-3-(4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (95 mg, 46%). MS (ISP) 409.3 $[(M+H)^+]$; mp 262°C.

Example 8.13

8-Pyridin-4-yl-4-trifluoromethyl-2-(3-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine

Reaction of 1-(3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (142 mg, 0.5 mmol), prepared from commercially available 3-trifluoromethyl-acetophenone according to general procedure A, and 2-amino-3-(4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (100 mg, 49%). MS (ISP) 409.4 $[(M+H)^+]$; mp 258°C.

Example 8.14

8-Pyridin-4-yl-4-trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine

Reaction of 1-(4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (142 mg, 0.5 mmol), prepared from commercially available 4-trifluoromethyl-acetophenone according to general procedure A, and 2-amino-3-(4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (88 mg, 43%). MS (ISP) 409.4 [$(M+H)^+$]; mp 240°C.

Example 8.15

2-(3-Fluoro-4-trifluoromethyl-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(3-fluoro-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (151 mg, 0.5 mmol), prepared from commercially available 3-fluoro-4-trifluoromethyl-acetophenone according to general procedure A, and 2-amino-3-(4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (116 mg, 54%). MS (ISP) 427.4.0 [$(M+H)^+$]; mp 267°C.

Example 8.16

2-(4-Methyl-3-trifluoromethyl-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(4-methyl-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (149 mg, 0.5 mmol), prepared from 4-methyl-3-trifluoromethyl-acetophenone (synthesis: see part acetophenone derivatives) according to general procedure A, and 2-amino-3-(4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (101 mg, 48%). MS (ISP) 423.3 [$(M+H)^+$]; mp 222°C.

Example 8.17

2-(4-Ethoxy-3-trifluoromethyl-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(4-ethoxy-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (164 mg, 0.5 mmol), prepared from 4-ethoxy-3-trifluoromethyl-acetophenone (synthesis: see part acetophenone derivatives) according to general procedure A, and 2-amino-3-(4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (98 mg, 43%). MS (ISP) 453.5.0 [$(M+H)^+$]; mp 244°C.

Example 8.18

8-Pyridin-4-yl-2-[4-(2,2,2-trifluoro-ethoxy)-3-trifluoromethyl-phenyl]-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-[4-(2,2,2,-trifluoro-ethoxy)-3-trifluoromethyl-phenyl]-4,4,4-trifluoro-butane-1,3-dione (191 mg, 0.5 mmol), prepared from 4-(2,2,2-trifluoro-ethoxy)-3-trifluoromethyl-acetophenone (synthesis: see part acetophenone derivatives) according to general procedure A, and 2-amino-3-(4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (111 mg, 44%). MS (ISP) 507.5 [$(M+H)^+$]; mp 269°C.

Example 8.19

2-(3-Methyl-4-trifluoromethyl-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(3-methyl-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (149 mg, 0.5 mmol), prepared from 3-methyl-4-trifluoromethyl-acetophenone (synthesis: see part acetophenone derivatives) according to general procedure A, and 2-amino-3-(4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (93 mg, 44%). MS (ISP) 422.1 [$(M+H)^+$]; mp 225°C.

Example 8.20

2-(4-Chloro-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(4-chloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (125 mg, 0.5 mmol), prepared from commercially available 4-chloro-acetophenone according to general procedure A, and 2-amino-3-(2-methyl-4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (46 mg, 24%). MS (ISP) 389.2 [$(M+H)^+$]; mp 232°C.

Example 8.21

2-(4-Chloro-3-methyl-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(4-chloro-3-methyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (132 mg, 0.5 mmol), prepared from commercially available 4-chloro-3-methyl-acetophenone according to general procedure A, and 2-amino-3-(2-methyl-4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (87 mg, 0.5 mmol) according to general

procedure B yielded the title compound as an orange solid (49 mg, 24%). MS (ISP) 403.4 [(M+H)$^+$]; mp 246°C.

Example 8.22

2-(3-Chloro-4-fluoro-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(3-chloro-4-fluoro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (134 mg, 0.5 mmol), prepared from commercially available 3-chloro-4-fluoro-acetophenone according to general procedure A, and 2-amino-3-(2-methyl-4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (52 mg, 26%). MS (ISP) 407.3 [(M+H)$^+$]; mp 255°C.

Example 8.23

2-(4-Dichloro-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(3,4-dichloro-phenyl)-4,4,4-trifluoro-butane-1,3-dione (143 mg, 0.5 mmol), prepared from commercially available 3,4-dichloro-acetophenone according to general procedure A, and 2-amino-3-(2-methyl-4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (57 mg, 27%). MS (ISP) 423.2 [(M+H)$^+$]; mp 271°C.

Example 8.24

8-(2-Methyl-pyridin-4-yl)-4-trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine

Reaction of 1-(4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (142 mg, 0.5 mmol), prepared from commercially available 4-trifluoromethyl-acetophenone according to general procedure A, and 2-amino-3-(2-methyl-4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (46 mg, 22%). MS (ISP) 423.2 [(M+H)$^+$]; mp 257°C.

Example 8.25

8-(2-Methyl-pyridin-4-yl)-4-trifluoromethyl-2-(3-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine

Reaction of 1-(3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (142 mg, 0.5 mmol), prepared from commercially available 3-trifluoromethyl-acetophenone according to general procedure A, and 2-amino-3-(2-methyl-4-pyridinyl)-1H-imidazole

[synthesis: see part amino-imidazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (59 mg, 28%). MS (ISP) 423.2 [$(M+H)^+$]; mp 234°C.

Example 8.26

2-(3-Fluoro-4-trifluoromethyl-phenyl)-8-(2-methyl-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(3-fluoro-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (151 mg, 0.5 mmol), prepared from commercially available 3-fluoro-4-trifluoromethyl-acetophenone according to general procedure A, and 2-amino-3-(2-methyl-4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as a red solid (59 mg, 27%). MS (ISP) 441.2 [$(M+H)^+$]; mp 252°C.

Example 8.27

2-(4-Ethoxy-3-trifluoromethyl-phenyl)-8-(2-methyl-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(4-ethoxy-3-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (164 mg, 0.5 mmol), prepared from 4-ethoxy-3-trifluoromethyl-acetophenone (synthesis: see part acetophenone derivatives) according to general procedure A, and 2-amino-3-(2-methyl-4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (41 mg, 18%). MS (ISP) 467.4 [$(M+H)^+$]; mp 249°C.

Example 8.28

8-(2-Methyl-pyridin-4-yl-2-[4-(2,2,2-trifluoro-ethoxy)-3-trifluoromethyl-phenyl]-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-[4-(2,2,2,-trifluoro-ethoxy)-3-trifluoromethyl-phenyl]-4,4,4-trifluoro-butane-1,3-dione (191 mg, 0.5 mmol), prepared from 4-(2,2,2-trifluoro-ethoxy)-3-trifluoromethyl-acetophenone (synthesis: see part acetophenone derivatives) according to general procedure A, and 2-amino-3-(2-methyl-4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (51 mg, 20%). Orange solid. MS (ISP) 521.4 [$(M+H)^+$]; mp 219°C.

Example 8.29

2-(3-Methyl-4-trifluoromethyl-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(3-methyl-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (149 mg, 0.5 mmol), prepared from 3-methyl-4-trifluoromethyl-acetophenone (synthesis: see part acetophenone derivatives) according to general procedure A, and 2-amino-3-(2-methyl-4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (44 mg, 20%). Orange solid. MS (ISP) 437.4 [$(M+H)^+$]; mp 243°C.

Example 8.30

2-(3-Ethoxy-4-trifluoromethyl-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(3-ethoxy-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (164 mg, 0.5 mmol), prepared from 3-ethoxy-4-trifluoromethyl-acetophenone (synthesis: see part acetophenone derivatives) according to general procedure A, and 2-amino-3-(4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (70 mg, 31%). MS (ISP) 453.4 [$(M+H)^+$]; mp 212°C.

Example 8.31

2-(3-Ethoxy-4-trifluoromethyl-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(3-ethoxy-4-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (164 mg, 0.5 mmol), prepared from 3-ethoxy-4-trifluoromethyl-acetophenone (synthesis: see part acetophenone derivatives) according to general procedure A, and 2-amino-3-(4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (30 mg, 13%). MS (ISP) 467.2 [$(M+H)^+$]; mp 177°C.

Example 8.32

8-Pyridin-4-yl-2-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-[3-(2,2,2,-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-4,4,4-trifluoro-butane-1,3-dione (191 mg, 0.5 mmol), prepared from 3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-acetophenone (synthesis: see part acetophenone derivatives) according to general procedure A, and 2-amino-3-(4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (84 mg, 33%). MS (ISP) 507.4 [$(M+H)^+$]; mp 233°C.

Example 8.33

8-(2-Methyl-pyridin-4-yl)-2-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-[3-(2,2,2,-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-4,4,4-trifluoro-butane-1,3-dione (191 mg, 0.5 mmol), prepared from 3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-acetophenone (synthesis: see part acetophenone derivatives) according to general procedure A, and 2-amino-3-(2-methyl-4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (140 mg, 54%). MS (ISP) 521.3 $[(M+H)^+]$; mp 189°C.

Example 8.34

2-(3,4-Bis-trifluoromethyl-phenyl)-8-pyridin-4-yl-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(3,4-bis-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (176 mg, 0.5 mmol), prepared from 3,4-bis-trifluoromethyl-acetophenone [CAS No. 129604-25-7] according to general procedure A, and 2-amino-3-(4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as an orange solid (80 mg, 34%). MS (ISP) 477.2 $[(M+H)^+]$; mp 211°C.

Example 8.35

2-(3,4-Bis-trifluoromethyl-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(3,4-bis-trifluoromethyl-phenyl)-4,4,4-trifluoro-butane-1,3-dione (200 mg, 0.57 mmol), prepared from 3,4-bis-trifluoromethyl-acetophenone [CAS No. 129604-25-7] according to general procedure A, and 2-amino-3-(2-methyl-4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (99 mg, 0.57 mmol) according to general procedure B yielded the title compound as an orange solid (28 mg, 10%). Orange solid. MS (ISP) 491.3 $[(M+H)^+]$; mp 218°C.

Example 8.36

2-(4-Bromo-phenyl)-8-(2-methyl-pyridin-4-yl)-4-trifluoromethyl-imidazo[1,5-a]pyrimidine

Reaction of 1-(4-bromo-phenyl)-4,4,4-trifluoro-butane-1,3-dione (148 mg, 0.5 mmol), prepared from commercially available 4-bromo-acetophenone according to general procedure A, and 2-amino-3-(2-methyl-4-pyridinyl)-1H-imidazole [synthesis: see part amino-imidazole derivatives] (87 mg, 0.5 mmol) according to general procedure B

yielded the title compound as an orange solid (42 mg, 19%). MS (ISP) 435.3 [$(M+H)^+$]; mp 249°C.

Example 9: Preparation of 5-phenyl-3-pyridinyl-7-difluoromethyl-pyrazolo[1,5-a]pyrimidines (General Procedure B)

A stirred mixture of a 3-amino-4-pyridinyl-pyrazole (1 eq.) and a 1-phenyl-4,4,4-difluoro-butane-1,3-dione (1 eq.), prepared according to general procedure A, in acetic acid was heated under reflux conditions for about 3.5 h. The reaction mixture was evaporated and the product was isolated by column chromatography (e.g. heptane/ethyl acetate) and further purified by crystallization. If the product precipitates during the reaction it can be isolated by filtration and further purified by crystallization.

Ex.	dione	compound name	MS (ISP) / mp
9.1	S1.7	7-Difluoromethyl-3-pyridin-4-yl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine	MS (ISP) 391.2 [$(M+H)^+$] mp 222°C
9.2	S1.7	7-Difluoromethyl-3-(2-methyl-pyridin-4-yl)-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine	MS (ISP) 405.4 [$(M+H)^+$] mp 213°C
9.3	S1.19	7-Difluoromethyl-5-(3-methyl-4-trifluoromethyl-phenyl)-3-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine	MS (ISP) 405.4 [$(M+H)^+$] mp 236°C
9.4	S1.19	7-Difluoromethyl-3-(2-methyl-pyridin-4-yl)-5-(3-methyl-4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine	MS (ISP) 419.3 [$(M+H)^+$] mp 221°C
9.5	S1.30	7-Difluoromethyl-5-(4-methoxy-phenyl)-3-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine	MS (ISP) 353.2 [$(M+H)^+$] mp 206°C

Example 9.1

7-Difluoromethyl-3-pyridin-4-yl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine

Reaction of 4,4-difluoro-1-(4-trifluoromethyl-phenyl)-butane-1,3-dione (133 mg, 0.5 mmol), prepared from commercially available 4-trifluoromethyl-acetophenone

according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (130 mg, 67%). MS (ISP) 391.2 [$(M+H)^+$]; mp 222°C.

Example 9.2

7-Difluoromethyl-3-(2-methyl-pyridin-4-yl)-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine

Reaction of 4,4-difluoro-1-(4-trifluoromethyl-phenyl)-butane-1,3-dione (133 mg, 0.5 mmol), prepared from commercially available 4-trifluoromethyl-acetophenone according to general procedure A, and 3-amino-4-(2-methyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2-methyl-pyridine, as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (159 mg, 79%). MS (ISP) 405.4 [$(M+H)^+$]; mp 213°C.

Example 9.3

7-Difluoromethyl-5-(3-methyl-4-trifluoromethyl-phenyl)-3-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine

Reaction of 4,4-difluoro-1-(3-methyl-4-trifluoromethyl-phenyl)-butane-1,3-dione (140 mg, 0.5 mmol), prepared from 3-methyl-4-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (140 mg, 69%). MS (ISP) 405.4 [$(M+H)^+$]; mp 236°C.

Example 9.4

7-Difluoromethyl-3-(2-methyl-pyridin-4-yl)-5-(3-methyl-4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine

Reaction of 4,4-difluoro-1-(3-methyl-4-trifluoromethyl-phenyl)-butane-1,3-dione (140 mg, 0.5 mmol), prepared from 3-methyl-4-trifluoromethyl-acetophenone (synthsesis: see part acetophenone derivatives) according to general procedure A, and 3-amino-4-(2-methyl-4-pyridinyl)-pyrazole [prepared from 4-cyanomethyl-2-methyl-pyridine, CAS No. 130138-46-4, as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (87 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (164 mg, 78%). MS (ISP) 419.3 [$(M+H)^+$]; mp 221°C.

Example 9.5

7-Difluoromethyl-5-(4-methoxy-phenyl)-3-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine

Reaction of 4,4-difluoro-1-(4-methoxy-phenyl)-butane-1,3-dione (114 mg, 0.5 mmol), prepared from commercially available 4-methoxy-acetophenone according to general procedure A, and 3-amino-4-(4-pyridinyl)-pyrazole [CAS No. 216661-87-9; prepared from 4-cyanomethyl-pyridine as described in Bioorg. Med. Chem. Lett. 12 (2002) 3537 – 3541] (80 mg, 0.5 mmol) according to general procedure B yielded the title compound as a yellow solid (120 mg, 68%). MS (ISP) 353.2 [$(M+H)^+$]; mp 206°C.

Compounds of formula I and their pharmaceutically acceptable salts (hereinafter: Pharmaceutical Compound) have pharmacological activity and are useful as pharmaceuticals. In particular, Pharmaceutical Compounds exhibit metabotropic glutamate receptor antagonist activity. In particular, Pharmaceutical Compounds are active at the mGluR2 receptor.

The mGluR interaction of the Pharmaceutical Compounds may be demonstrated, e.g. in an in vitro binding assay, e.g. as follows:

[^{3}H]-LY354740 binding on mGlu2 transfected CHO cell membranes.

Transfection and cell culture: cDNA encoding the rat mGlu2 receptor protein in pBluescript II was subcloned into the eukaryotic expression vector pcDNA I-amp from Invitrogen (NV Leek, The Netherlands). This vector construct (pcD1mGR2) was co-transfected with a psvNeo plasmid encoding the gene for neomycin resistance, into CHO cells by a modified calcium phosphate method described by Chen & Okayama (1988). The cells were maintained in Dulbecco's Modified Eagle medium with reduced L-glutamine (2 mM final concentration) and 10 % dialysed foetal calf serum from Gibco BRL (Basel, Switzerland). Selection was made in the presence of G-418 (1000 µg/ml final). Clones were identified by reverse transcription of 5 µg total RNA, followed by PCR using mGlu2 receptor specific primers 5'-atcactgcttgggtttctggcactg-3' and 5'-agcatcactgtgggtggcataggagc-3' in 60 mM Tris HCl (pH 10), 15 mM $(NH4)_2SO_4$, 2 mM $MgCl_2$, 25 units/ml Taq Polymerase with 30 cycles annealing at 60°C for 1 min., extention at 72°C for 30 s, and 1 min. 95°C denaturation.

Membrane preparation: Cells, cultured as above, were harvested and washed three times with cold PBS and frozen at –80°C. The pellet was resuspended in cold 20 mM HEPES-NaOH buffer containing 10 mM EDTA (pH 7.4), and homogenised with a polytron (Kinematica, AG, Littau, Switzerland) for 10 s at 10 000 rpm. After centrifugation for 30 min. at 4°C, the pellet was washed once with the same buffer, and once with cold 20 mM

HEPES-NaOH buffer containing 0.1 mM EDTA, (pH 7.4). Protein content was measured using the Pierce method (Socochim, Lausanne, Switzerland) using bovine serum albumin as standard.

[^{3}H]-LY354740 binding: After thawing, the membranes were resuspended in cold 50mM Tris-HCl buffer containing 2 mM $MgCl_2$ and 2 mM $CaCl_2$, (pH 7) (binding buffer). The final concentration of the membranes in the assays was 25 µg protein/ml. Inhibition experiments were performed with membranes incubated with 10 nM [^{3}H]-LY354740 at room temperature, for 1 hour, in the presence of various concentrations of the compound to be tested. Following the incubations, membranes were filtered onto Whatmann GF/C glass fiber filters and washed 5 times with cold binding buffer. Non specific binding was measured in the presence of 10 µM DCG IV. After transfer of the filters into plastic vials containing 10 ml of Ultima-gold scintillation fluid (Packard, Zürich, Switzerland), the radioactivity was measured by liquid scintillation in a Tri-Carb 2500 TR counter (Packard, Zürich, Switzerland).

Data analysis: The inhibition curves were fitted with a four parameter logistic equation giving IC_{50} values, and Hill coefficients.

The compounds show activities, as measured in the above assay, of 5 µM or less, typically 0.5 µM or less, and ideally of 0.1 µM or less. The below table shows exemplary K_i values:

Compound no.	mGluR2 K_i [µM]	Example	mGluR2 K_i [µM]
1.13	0.043	4.35	0.045
1.19	0.032	4.43	0.048
2.2	0.072	4.9	0.047
3.2	0.076	5.20	0.043
4.24	0.043	7.1	0.0439

Activity specifically as medicament in Alzheimer's disease may be demonstrated in accordance with standard test methods, e.g. an asymptotic performance in an operant delayed match to position (DMTP) task, modified from the procedure originally published by Dunnett, Psychopharmacology (Berl) 87:357-63 (1985) [Higgins et al., Europ. J. Neuroscience 15:1827-1840 (2002); Higgins et al., Europ. J. Neuroscience 15:911-922 (2002); Higgins et al., Neuropharmacology 44:324-241 (2003)].

Pharmaceutical Compounds and prodrugs thereof, e.g. esters, N-oxides, phosphate esters, glycoamide esters and glyceride conjugates, are accordingly useful as mGluR

antagonists, e.g. in the treatment or prevention of diseases and conditions in which activation of mGluR plays a role or is implicated. Such conditions include in particular acute and/or chronic neurological disorders.

At present, eight different members of these mGluRs are known and of these some even have sub-types. On the basis of structural parameters, the different influences on the synthesis of secondary metabolites and the different affinity to low-molecular weight chemical compounds, these eight receptors can be sub-divided into three sub-groups: mGluR1 and mGluR5 belong to group I, mGluR2 and mGluR3 belong to group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III.

Ligands of metabotropic glutamate receptors belonging to the group II can be used for the treatment or prevention of acute and/or chronic neurological disorders.

Acute and/or chronic neurological disorders include psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits like mild cognitive impairment, age-related cognitive decline, vascular dementia, Parkinsons's disease, memory impairment associated with depression or anxiety, Down's syndrome, stroke, traumatic brain injury, and attention deficit disorder. Other treatable indications are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are acute and chronic pain, Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficient functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychotic episodes, opiate addiction, anxiety, vomiting, dyskinesia and depression.

In one embodiment, the acute and/or chronic neurological disorder is Alzheimer's disease. In another embodiment, the acute and/or chronic neurological disorder is mild cognitive impairment.

As used herein, a mammal in need of treatment of an acute and/or chronic neurological disorder means a mammal, e.g. a human that is suffering from, or is at risk of suffering from, an acute and/or chronic neurological disorder.

As used herein, the terms "treat", treating "and treatment", and the like, as applied to an acute and/or chronic neurological disorder, refer to methods that slow, ameliorate, reduce or reverse such a disorder or any symptoms associated with said disorder, as

currently afflicting the subject, as well as methods that prevent such a disorder or any symptoms thereof, from occurring.

Pharmaceutical Compounds can be used as medicaments, e.g. in the form of pharmaceutical compositions. The pharmaceutical compositions can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, the administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

Pharmaceutical Compounds can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical compositions. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, e.g., as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, e.g., 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, e.g., water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary. Suitable carriers for suppositories are, e.g., natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

In addition, the pharmaceutical compositions may contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They may also contain still other therapeutically valuable substances.

As mentioned earlier, medicaments containing Pharmaceutical Compound and a therapeutically inert excipient are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more Pharmaceutical Compound and, if desired, one or more other therapeutically valuable substances into a galenical dosage form together with one or more therapeutically inert carriers.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/ kg/day being

preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

In accordance with the foregoing the present invention also provides:

(a) A pharmaceutical compound for use as a metabotropic glutamate receptor antagonist, for example for use in any of the particular indications as hereinbefore set forth;

(b) A pharmaceutical composition comprising a pharmaceutical compound as under (a) as active ingredient together with a pharmaceutically acceptable diluent or carrier therefor;

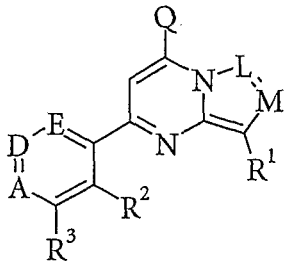
(c) A pharmaceutical composition for the treatment or prevention of a disease or condition in which metabotropic glutamate receptor activation plays a role or is implicated comprising a pharmaceutical compound as under (a) and a carrier;

(d) Use of a pharmaceutical compound as under (a) for the manufacture of a medicament for the treatment or prevention of a disease or condition in which metabotropic glutamate receptor activation plays a role or is implicated;

(e) A process for the preparation of a compound as under (a).

Claims

1. A compound of formula I



(I)

wherein

A is $=C(R^4)-$,

D is $=C(R^5)-$,

E is $=C(R^6)-$,

or one of A, D and E is =N-,

L is =N- or =C(H)-,

M is $=C(R^7)-$, when L is =N-, or M is =N-, when L is =C(H)-,

Q is CF_3 of CHF_2,

R^1 is –CN, unsubstituted pyridinyl, pyridinyl substituted by (C_1-C_4)-alkyl or by (C_1-C_4)-alkanol, or is the corresponding pyridine-N-oxide,

R^2 is hydrogen, halogen, (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl,

R^3 is hydrogen, halogen, (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl,

R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

R^6 is hydrogen or halogen, and

R^7 is hydrogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by CN,

with the proviso that when A is $=C(R^4)-$, D is =C(H)-, E is =C(H)-, L is =N-, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and (a) M is =C(H)-, R^4 is not hydrogen, chloro or methoxy; or (b) M is $=C(CH_3)-$, R^4 is not hydrogen,

and their pharmaceutically acceptable addition salts.

2. The compound according to claim 1 wherein:

A is $=C(R^4)-$,

D is $=C(R^5)-$,

E is $=C(R^6)-$,

or one of A, D and E is =N-,

L is =N- or =C(H)-,

M is $=C(R^7)-$, when L is =N-, or M is =N-, when L is =C(H)-,

Q is CF_3,

R^1 is –CN, unsubstituted pyridinyl, pyridinyl substituted by (C_1-C_4)-alkyl or the corresponding pyridine-N-oxide,

R^2 is hydrogen, halogen, (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl,

R^3 is hydrogen, halogen, (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl,

R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

R^6 is hydrogen or halogen, and

R^7 is hydrogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by CN,

with the proviso that when A is $=C(R^4)-$, D is =C(H)-, E is =C(H)-, L is =N-, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and (a) M is =C(H)-, R^4 is not hydrogen, chloro or methoxy; or (b) M is $=C(CH_3)-$, R^4 is not hydrogen,

and their pharmaceutically acceptable addition salts.

3. The compound according to claim 1 wherein A is $=C(R^4)-$, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine.

4. The compound according to claim 1 wherein D is $=C(R^5)-$, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine.

5. The compound according to claim 1 wherein E is $=C(R^6)-$, wherein R^6 is hydrogen or halogen.

6. The compound according to claim 1 wherein L is =N-.

7. The compound according to claim 1 wherein L is =C(H)-.

8. The compound according to claim 1 wherein M is =C(R^7)-, wherein R^7 is hydrogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by CN.

9. The compound according to claim 8 wherein R^7 is hydrogen.

10. The compound according to claim 8 wherein R^7 is unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN.

11. The compound according to claim 1 wherein R^1 is –CN.

12. The compound according to claim 1 wherein R^1 is unsubstituted pyridinyl, pyridinyl substituted by (C_1-C_4)-alkyl or the corresponding pyridine-N-oxide.

13. The compound according to claim 1 wherein

A is =C(R^4)-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

D is =C(R^5)-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

E is =C(R^6)-, wherein R^6 is hydrogen or halogen,

L is =N- or =C(H)-,

M is =C(R^7)-, wherein R^7 is hydrogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by CN, when L is =N-; or M is =N-, when L is =C(H)-,

R^1 is –CN, unsubstituted pyridinyl, pyridinyl substituted by (C_1-C_4)-alkyl, or the corresponding pyridine-N-oxide,

R^2 is hydrogen, halogen, (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl,

R^3 is hydrogen, halogen, (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl,

with the proviso that when A is =C(R^4)-, D is =C(H)-, E is =C(H)-, L is =N-, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and (a) M is =C(H)-, R^4 is not hydrogen, chloro or methoxy; or (b) M is =C(CH_3)-, R^4 is not hydrogen.

14. The compound according to claim 1 wherein

A is $=C(R^4)$-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

D is $=C(R^5)$-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

E is $=C(R^6)$-, wherein R^6 is hydrogen or halogen,

L is =N-,

M is $=C(R^7)$-, wherein R^7 is hydrogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by CN,

R^1 is –CN, unsubstituted pyridinyl, pyridinyl substituted (C_1-C_4)-alkyl, or the corresponding pyridine-N-oxide,

R^2 is hydrogen, halogen or (C_1-C_4)-alkyl

R^3 is hydrogen, halogen or (C_1-C_4)-alkyl

with the proviso that when A is $=C(R^4)$-, D is =C(H)-, E is =C(H)-, L is =N-, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and (a) M is =C(H)-, R^4 is not hydrogen, chloro or methoxy; or (b) M is $=C(CH_3)$-, R^4 is not hydrogen.

15. The compound according to claim 1 wherein

A is $=C(R^4)$-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

D is $=C(R^5)$-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

E is $=C(R^6)$-, wherein R^6 is hydrogen or halogen,

L is =N-,

M is $=C(R^7)$-, wherein R^7 is hydrogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

R^1 is –CN,

R^2 is hydrogen, halogen or (C_1-C_4)-alkyl

R^3 is hydrogen, halogen or (C_1-C_4)-alkyl

with the proviso that when A is =C(R^4)-, D is =C(H)-, E is =C(H)-, L is =N-, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and (a) M is =C(H)-, R^4 is not hydrogen, chloro or methoxy; or (b) M is =C(CH_3)-, R^4 is not hydrogen.

16. The compound according to claim 1 wherein

A is =C(R^4)-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine,

D is =C(R^5)-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine

E is =C(R^6)-, wherein R^6 is hydrogen or halogen

L is =N-,

M is =C(R^7)-, wherein R^7 is hydrogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN,

R^1 is –CN, and

R^2 and R^3 are hydrogen,

with the proviso that when A is =C(R^4)-, D is =C(H)-, E is =C(H)-, L is =N-, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and M is =C(H)-, R^4 is not hydrogen, chloro or methoxy.

17. The compound according to claim 1 wherein

A is =C(R^4)-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine,

D is =C(R^5)-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine

E is =C(R^6)-, wherein R^6 is hydrogen or halogen

L is =N-,

M is =C(R^7)-, wherein R^7 is hydrogen,

R^1 is –CN, and

R^2 and R^3 are hydrogen,

with the proviso that when A is =C(R^4)-, D is =C(H)-, E is =C(H)-, L is =N-, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and M is =C(H)-, R^4 is not hydrogen, chloro or methoxy.

18. The compound according to claim 1 wherein

A is =C(R^4)-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine,

D is $=C(R^5)$-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine

E is $=C(R^6)$-, wherein R^6 is hydrogen,

L is =N-,

M is $=C(R^7)$-, wherein R^7 is hydrogen,

R^1 is –CN, and

R^2 and R^3 are hydrogen,

with the proviso that when A is $=C(R^4)$-, D is =C(H)-, E is =C(H)-, L is =N-, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and M is =C(H)-, R^4 is not hydrogen, chloro or methoxy.

19. The compound according to claim 1 wherein

A is $=C(R^4)$-, wherein R^4 is hydrogen, Cl, F, methyl or trifluoromethyl, or 2-trifluoroethoxy,

D is $=C(R^5)$-, wherein R^5 is hydrogen, Cl, F, methyl or trifluoromethyl,

E is $=C(R^6)$-, wherein R^6 is hydrogen,

L is =N-,

M is $=C(R^7)$-, wherein R^7 is hydrogen,

R^1 is –CN, and

R^2 and R^3 are hydrogen,

with the proviso that when A is $=C(R^4)$-, D is =C(H)-, E is =C(H)-, L is =N-, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and M is =C(H)-, R^4 is not hydrogen, chloro or methoxy.

20. The compound according to claim 1 wherein

A is $=C(R^4)$-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine,

D is $=C(R^5)$-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine

E is $=C(R^6)$-, wherein R^6 is hydrogen or halogen

L is =N-,

M is $=C(R^7)$-, wherein R^7 is unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN,

R^1 is –CN, and

R^2 and R^3 are hydrogen,

with the proviso that when A is $=C(R^4)$-, D is =C(H)-, E is =C(H)-, L is =N-, R^1 is –CN, R^2 is hydrogen, R^3 is hydrogen, and M is $=C(CH_3)$-, R^4 is not hydrogen.

21. The compound according to claim 1 wherein

A is =C(R^4)-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine ,

D is =C(R^5)-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine,

E is =C(R^6)-, wherein R^6 is hydrogen or halogen,

L is =N-,

M is =C(R^7)-, wherein R^7 is hydrogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN

R^1 is unsubstituted pyridinyl, pyridinyl substituted by (C_1-C_4)-alkyl, or the corresponding pyridine-N-oxide,

R^2 is hydrogen, halogen or (C_1-C_4)-alkyl, and

R^3 is hydrogen, halogen or (C_1-C_4)-alkyl.

22. The compound according to claim 1 wherein

A is =C(R^4)-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine,

D is =C(R^5)-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine,

E is =C(R^6)-, wherein R^6 is hydrogen or halogen,

L is =N-,

M is =C(R^7)-, wherein R^7 is hydrogen,

R^1 is unsubstituted pyridinyl, pyridinyl substituted by (C_1-C_4)-alkyl, or the corresponding pyridine-N-oxide,

R^2 and R^3 are hydrogen.

23. The compound according to claim 1 wherein

A is =C(R^4)-, wherein R^4 is hydrogen, halogen, (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy,

D is =C(R^5)-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine,

E is =C(R^6)-, wherein R^6 is hydrogen or halogen,

L is =N-,

M is =C(R^7)-, wherein R^7 is hydrogen,

R^1 is unsubstituted pyridin-4-yl or pyridin-4-yl substituted by (C_1-C_4)-alkyl,

R^2 and R^3 are hydrogen.

24. The compound according to claim 1 wherein

A is $=C(R^4)$-, wherein R^4 is (C_1-C_4)-alkyl substituted by fluorine,

D is $=C(R^5)$-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine,

E is $=C(R^6)$-, wherein R^6 is hydrogen,

L is =N-,

M is $=C(R^7)$-, wherein R^7 is hydrogen,

R^1 is unsubstituted pyridin-4-yl or pyridin-4-yl substituted by (C_1-C_4)-alkyl,

R^2 and R^3 are hydrogen.

25. The compound according to claim 1 wherein

A is $=C(R^4)$-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy substituted by fluorine,

D is $=C(R^5)$-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine,

E is $=C(R^6)$-, wherein R^6 is hydrogen or halogen,

L is =C(H)-,

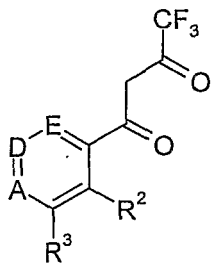
M is =N-,

R^1 is –CN, unsubstituted pyridinyl, pyridinyl substituted by (C_1-C_4)-alkyl, or the corresponding pyridine-N-oxide,

R^2 is hydrogen, halogen or (C_1-C_4)-alkyl, and

R^3 is hydrogen, halogen or (C_1-C_4)-alkyl.

26. A process for the preparation of a compound of formula I as claimed in claim 1, comprising reacting a compound of formula II



(II)

wherein

A is $=C(R^4)$-, wherein R^4 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_1-C_4)-alkoxy or (C_1-C_4)-alkoxy

substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

D is =C(R^5)-, wherein R^5 is hydrogen, halogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by fluorine, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by fluorine,

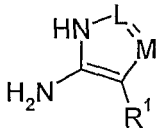
E is =C(R^6)-, wherein R^6 is hydrogen or halogen,

or one of A, D and E is =N-,

R^2 is hydrogen, halogen, (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl, and

R^3 is hydrogen, halogen, (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl,

with a compound of formula III



(III)

wherein

L is =N- or =C(H)-,

M is =C(R^7)-, when L is =N-, or M is =N-, when L is =C(H)-,

R^1 is –CN, unsubstituted pyridinyl, pyridinyl substituted by (C_1-C_4)-alkyl or the corresponding pyridine-N-oxide, and

R^7 is hydrogen, unsubstituted (C_1-C_4)-alkyl or (C_1-C_4)-alkyl substituted by CN, unsubstituted (C_3-C_6)-cycloalkyl or (C_3-C_6)-cycloalkyl substituted by CN.

27. The compound according to claim 1 for use as a metabotropic glutamate receptor antagonist.

28. A pharmaceutical composition comprising the compound according to claim 1 as active ingredient together with a pharmaceutically acceptable diluent or carrier therefore.

29. A pharmaceutical composition for the treatment or prevention of a disease or condition in which metabotropic glutamate receptor activation plays a role or is implicated comprising the compound according to claim 1 and a carrier.

30. Use of the compound according to claim 1 for the manufacture of a medicament for the treatment or prevention of a disease or condition in which metabotropic glutamate receptor activation plays a role or is implicated.

31. Use according to claim 30 wherein the disease is selected from the group consisting of acute and/or chronic neurological disorders comprising psychosis, schizophrenia,

Alzheimer's disease, cognitive disorders and memory deficits comprising mild cognitive impairment, age-related cognitive decline, vascular dementia, Parkinsons's disease, memory impairment associated with depression or anxiety, Down's syndrome, stroke, traumatic brain injury, and attention deficit disorder, restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia, acute and chronic pain, Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments, muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychotic episodes, opiate addiction, anxiety, vomiting, dyskinesia and depression.

32. The invention as hereinbefore described.