cognitive functions, of attention, of the abili
concentrate, to learn and to memorize, or o
processing of sensory information. They may al
useful in the treatment, prevention, diagnosis
monitoring of the evolution of diseases invo
neurodegenerative processes which are spontaneo
which are subsequent to lesions, and of dis
involving inflammatory phenomena. The present inve
also refers to the methods of treatment invo
nicotinic receptors consisting of the administra
to animals including humans, of therapeuti
effective doses of one or more compounds o
invention. The present invention also relates t
use, for diagnostic purposes, of analogs of
derivatives in which one or more atoms have
replaced with an isotope with an atomic mass or a
number which is different to the atomic mass or t
mass number of the atoms usually encountered natura

this regard, the compounds of the invention are particularly advantageous in the case of psychi disorders or diseases or neurological disorder diseases of the central nervous system, such as example, an impairment of the ability to learn concentrate or to memorize, slight cogn impairments, senile dementia, vascular dementia, body dementia, Alzheimer's disease, Parkin disease, Huntington's chorea, Tourette's synd neuronal degeneration subsequent to a trauma strokes, to ischemia or to brain hypoxia, multis atrophy, progressive supranuclear paral amyotrophic lateral sclerosis, peripheral neuropat motor disorders such as dyskinesia, tardive dyskin hyperkinesia, dystonia and epilepsy, attention de hyperactivity disorders, schizophrenia, depres manic depressive psychosis, anxiety, pho obsessive-compulsive disorders, post-traumatic s syndrome, panic attacks, eating disorders suc anorexia, bulimia and obesity, or sleep disc including those associated with jetlag. The comp

and muscle pains such as fibromyalgia. In addition
compounds of the invention could also be used i
context of the treatment of disorders or dis
involving inflammatory processes, such as, for exa
in the gastrointestinal tract, ulcerative col
Crohn's disease, irritable bowel syndrome or dia
and, elsewhere in the body, arthritis (incl
rheumatoid arthritis) and skin inflammations su
acne. Finally, the compounds of the invention cou
useful in endocrine disorders such as pheochromoc
and smooth muscle contraction-related disorders.

The present invention also covers the use of
compounds of the invention for diagnostic purpos
for the purposes of medical imaging. It comprise
diagnostic and imaging methods consisting of
analysis, by noninvasive methods, of the distrib
of a tracer compound within the intact body o
animal, including humans, using physical means su
positon emission tomography, single-photon tomogr
magnetic resonance spectroscopy and nuclear mag

phosphorus, of sulfur, of chlorine, of iodine
technetium, such as, respectively, ^{2}H, ^{3}H, ^{11}C, ^{13}C
^{13}N, ^{15}O, ^{17}O, ^{18}F, ^{35}S, ^{36}Cl, ^{123}I, ^{125}I and ^{131}I
labeled compounds can be synthesized according t
methods described in the procedures of the pr
invention by substituting one or more reagents i
synthetic process with identical reagents conta
the label isotope(s).

The present invention relates to derivatives of fo
(I) in which:

A is, if it is present, a (C1-C6) alkyl radic
(C3-C6) alkenyl radical, a (C3-C6) alkynyl radic
(C3-C7) cycloalkyl radical or a (C5-C7) cycloal
radical; these radicals are optionally substituted
one or more substituents chosen from (C1-C5) a
(C2-C5) alkenyl, (C2-C5) alkynyl, (C3-C7) cycloa
(C5-C7) cycloalkenyl, arylalkyl, heteroarylalkyl,
heteroaryl and halogen,

C(S)NRaRb, S(O)Ra, SO_2Ra, SO_2NRaRb, ORc, SRc, O-C
-O-C(S)Ra, NRaRb, NHC(O)Ra, NHC(S)Ra, NHC
NHCONRaRb, $NHSO_2Ra$, aryl, heteroaryl, (C
heterocycloalkyl, polyfluoroalkyl, trifluorome
sulfanyl, trifluoromethoxy, linear or branched (C
alkyl, (C2-C6) alkenyl and (C2-C6) alkynyl,
substituents being optionally substituted with o
more alkyl, halogen, OH, methoxy,

R5 is an H, halogen, CF_3, CHF_2, CH_2F, linear or bra
(C1-C6) alkyl or (C3-C7) cycloalkyl radical,

Ra is linear or branched (C1-C6) alkyl, alk
alkynyl, (C3-C7) cycloalkyl, (C5-C7) cycloalk
(C4-C7) heterocycloalkyl, (C4-C7)heterocycloa
arylalkyl, heteroarylalkyl, aryl, heteroaryl
polyfluoroalkyl,

Rb is, independently of Ra, a hydrogen, linea
branched (C1-C6) alkyl, alkenyl, alkynyl, (C
cycloalkyl, (C5-C7) cycloalkenyl, (C4-C7) he

alkynyl, (C3-C7) cycloalkyl, (C5-C7) cycloal
(C4-C7) heterocycloalkyl, an arylalkyl
heteroarylalkyl,

R6 and R7 may form a saturated or unsaturated ring
5, 6 or 7 ring members, which may or may not h
hetero atom such as O, S or N and which is optic
substituted with one or more alkyls and/or halogens

R8 is an Ra or NRaRb radical,

their racemates, enantiomers and diastereoisomer
their mixtures, their tautomers and
pharmaceutically acceptable salts.

Preferably, the present invention relates
derivatives of formula (I) in which:

A is, if it is present, a (C1-C6) alkyl radic
(C3-C6) alkenyl radical, a (C3-C6) alkynyl radic
(C3-C7) cycloalkyl radical or a (C5-C7) cycloal

R4 is an aryl or heteroaryl radical being optic
substituted with one or more substituents chosen
halogen, CN, NO_2, NH_2, OH, SH, COOH, CHO, C(
C(S)NH_2, SO_2H, SO_2NH_2, NHCHO, C(O)Ra, C(O)ORa, C(O)N
C(S)NRaRb, S(O)Ra, SO_2Ra, SO_2NRaRb, ORc, SRc, O-C(
-O-C(S)Ra, NRaRb, NHC(O)Ra, NHC(S)Ra, NH(
NHCONRaRb, $NHSO_2Ra$, aryl, heteroaryl, (C
heterocycloalkyl, polyfluoroalkyl, trifluorome
sulfanyl, trifluoromethoxy, linear or branched (C
alkyl, (C2-C6) alkenyl and (C2-C6) alkynyl,
substituents being optionally substituted with o
more alkyl, halogen, OH, methoxy,

R5 is a hydrogen or Me radical,

Ra is linear or branched (C1-C6) alkyl, alk
alkynyl, (C3-C7) cycloalkyl, (C5-C7) cycloalk
(C4-C7) heterocycloalkyl, arylalkyl, heteroaryla
aryl, heteroaryl or polyfluoroalkyl,

R6 and R7 are, independently of one anothe
hydrogen, (C1-C6) alkyl, (C3-C6) alkenyl, (C
alkynyl, (C3-C7) cycloalkyl, (C5-C7) cycloalk
(C4-C7) heterocycloalkyl, an arylalkyl
heteroarylalkyl,

R6 and R7 may form a saturated or unsaturated ring
5, 6 or 7 ring members, which may or may not h
hetero atom such as O, S or N and which is optic
substituted with one or more alkyls and/or halogens

R8 is an Ra or NRaRb radical,

their racemates, enantiomers and diastereoisomer
their mixtures, their tautomers and
pharmaceutically acceptable salts.

More particularly, the present invention relate
derivatives of formula (I) in which:

separated by at least two carbon atoms,

R3 is an OH, NH_2, OMe or H radical,

R4 is an aryl or heteroaryl radical being optic
substituted with one or more substituents chosen
halogen, CN, NO_2, NH_2, OH, SH, COOH, CHO, C(
C(S)NH_2, SO_2H, SO_2NH_2, NHCHO, C(O)Ra, C(O)ORa, C(O)N
C(S)NRaRb, S(O)Ra, SO_2Ra, SO_2NRaRb, ORc, SRc, O-C(
-O-C(S)Ra, NRaRb, NHC(O)Ra, NHC(S)Ra, NHC
NHCONRaRb, $NHSO_2Ra$, aryl, heteroaryl, (C
heterocycloalkyl, polyfluoroalkyl, trifluorome
sulfanyl, trifluoromethoxy, linear or branched (C
alkyl, (C2-C6) alkenyl and (C2-C6) alkynyl,
substituents being optionally substituted with o
more alkyl, halogen, OH, methoxy,

R5 is a hydrogen,

Ra is linear or branched (C1-C6) alkyl, alk
alkynyl, (C3-C7) cycloalkyl, (C5-C7) cycloalk

cycloalkenyl, (C4-C7) heterocyclo
(hetero)arylalkyl, (hetero)aryl, (poly)fluoroa
C(O)R8, C(S)R8 or SO_2R8 radical,

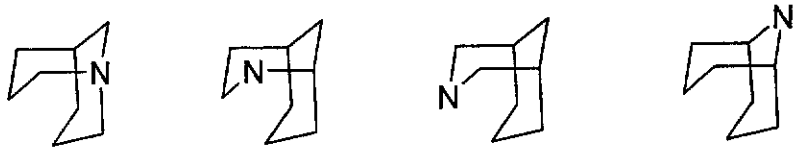
R6 and R7 are, independently of one anothe
hydrogen, (C1-C6) alkyl, (C3-C6) alkenyl, (C
alkynyl, (C3-C7) cycloalkyl, (C5-C7) cycloalk
(C4-C7) heterocycloalkyl, an arylalkyl
heteroarylalkyl,

R6 and R7 may form a saturated or unsaturated ring
5, 6 or 7 ring members, which may or may not h
hetero atom such as O, S or N and which is optic
substituted with one or more alkyls and/or halogen

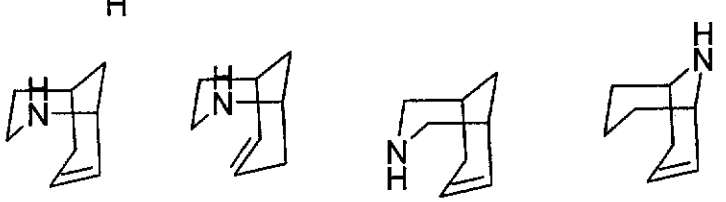
R8 is an Ra or NRaRb radical,

their racemates, enantiomers and diastereoisomer
their mixtures, their tautomers and
pharmaceutically acceptable salts.

furyl, imidazolyl, oxazolyl, pyrazinyl, pyri
tetrazolyl, oxadiazolyl, thiadiazolyl, isoxadiaz
isothiadiazolyl, isothiazolyl, isoxazolyl, triaz
indolyl, benzofuranyl, benzothienyl, azaind
pyrazolyl, indolyl; the halogen radical is e
chlorine, iodine, fluorine or bromine; the (C
azacycloalkyl radicals contain a nitrogen and 4
carbon atoms and in particular azetid
pyrrolidinyl, piperidinyl; the azacycloalkenyl rad
contain a nitrogen and 5 to 7 carbon atoms; the (C
azabicycloalkyl radicals contain 5 to 9 carbon
and are illustrated in a nonlimiting manner in
(A); the (C5-C9) azabicycloalkenyl radicals conta
to 9 carbon atoms and are illustrated in a nonlim
manner in list (B); the (C4-C7) heterocyclo
radicals contain 5 to 7 carbon atoms and one or
hetero atoms chosen from oxygen, sulfur and nitr
the polyfluoroalkyl radicals contain 1 to 6 c
atoms in a straight or branched chain, which
substituted with one or more fluorine atoms ar
particular trifluoromethyl, difluoromethyl;



By way of illustration, below are structures of (B); these structures may be linked to the main via any of their positions:



The compounds of formula (I) exhibit one or asymmetric carbons and can therefore be in the fo isomers, of racemates, of enantiomers and diastereoisomers; these are also part of the inve as are mixtures thereof.

The present invention also relates to pharmaceutical compositions containing as a principle a derivative of formula (I) in which:

A is, if it is present, a (C1-C6) alkyl radica (C3-C6) alkenyl radical, a (C3-C6) alkynyl radic (C3-C7) cycloalkyl radical or a (C5-C7) cycloal radical; these radicals are optionally substituted one or more substituents chosen from (C1-C5) a

R4 is an aryl or heteroaryl radical being optio
substituted with one or more substituents chosen
halogen, CN, NO_2, NH_2, OH, SH, COOH, CHO, C(
$C(S)NH_2$, SO_2H, SO_2NH_2, NHCHO, C(O)Ra, C(O)ORa, C(O)N
C(S)NRaRb, S(O)Ra, SO_2Ra, SO_2NRaRb, ORc, SRc, O-C(
-O-C(S)Ra, NRaRb, NHC(O)Ra, NHC(S)Ra, NH(
NHCONRaRb, $NHSO_2Ra$, aryl, heteroaryl, (C
heterocycloalkyl, polyfluoroalkyl, trifluorome
sulfanyl, trifluoromethoxy, linear or branched (C
alkyl, (C2-C6) alkenyl and (C2-C6) alkynyl,
substituents being optionally substituted with o
more alkyl, halogen, OH, methoxy,

R5 is an H, halogen, CF_3, CHF_2, CH_2F, linear or bra
(C1-C6) alkyl or (C3-C7) cycloalkyl radical,

Ra is linear or branched (C1-C6) alkyl, alk
alkynyl, (C3-C7) cycloalkyl, (C5-C7) cycloalk
(C4-C7) heterocycloalkyl, arylalkyl, heteroaryla
aryl, heteroaryl or polyfluoroalkyl,

R6 and R7 are, independently of one anothe
hydrogen, (C1-C6) alkyl, (C3-C6) alkenyl, (C
alkynyl, (C3-C7) cycloalkyl, (C5-C7) cycloalk
(C4-C7) heterocycloalkyl, an arylalkyl
heteroarylalkyl,

R6 and R7 may form a saturated or unsaturated ring
5, 6 or 7 ring members, which may or may not h
hetero atom such as O, S or N and which is optic
substituted with one or more alkyls and/or halogens

R8 is an Ra or NRaRb radical,

their racemates, enantiomers and diastereoisomers
their mixtures, their tautomers and
pharmaceutically acceptable salts.

Preferably, the present invention also relate
pharmaceutical compositions containing as a
principle a derivative of formula (I) in which:

in the 1-position of the pyrazole are necess
separated by at least two carbon atoms,

R3 is an OH, NH_2, OMe or H radical,

R4 is an aryl or heteroaryl radical being optio
substituted with one or more substituents chosen
halogen, CN, NO_2, NH_2, OH, SH, COOH, CHO, C(O
$C(S)NH_2$, SO_2H, SO_2NH_2, NHCHO, C(O)Ra, C(O)ORa, C(O)N
C(S)NRaRb, S(O)Ra, SO_2Ra, SO_2NRaRb, ORc, SRc, O-C(
-O-C(S)Ra, NRaRb, NHC(O)Ra, NHC(S)Ra, NHC
NHCONRaRb, $NHSO_2Ra$, aryl, heteroaryl, (C
heterocycloalkyl, polyfluoroalkyl, trifluorome
sulfanyl, trifluoromethoxy, linear or branched (C
alkyl, (C2-C6) alkenyl and (C2-C6) alkynyl,
substituents being optionally substituted with o
more alkyl, halogen, OH, methoxy,

R5 is a hydrogen or Me radical,

Rc is a linear or branched (C1-C6) alkyl, (C
alkenyl, (C3-C6) alkynyl, (C3-C7) cycloalkyl, (C
cycloalkenyl, (C4-C7) heterocycloalkyl, (het
arylalkyl, (hetero)aryl, (poly)fluoroalkyl, C(
C(S)R8 or SO_2R8 radical,

R6 and R7 are, independently of one anothe
hydrogen, (C1-C6) alkyl, (C3-C6) alkenyl, (C
alkynyl, (C3-C7) cycloalkyl, (C5-C7) cycloalk
(C4-C7) heterocycloalkyl, an arylalkyl
heteroarylalkyl,

R6 and R7 may form a saturated or unsaturated ring
5, 6 or 7 ring members, which may or may not h
hetero atom such as O, S or N and which is optic
substituted with one or more alkyls and/or halogens

R8 is an Ra or NRaRb radical,

R1 is an NR_6R_7, (C4-C7) azacycloalkyl, (
azacycloalkenyl, (C5-C9) azabicycloalkyl or (C
azabicycloalkenyl group; these groups are optic
substituted with one or more substituents chosen
(C1-C5) alkyl, (C3-C5) cycloalkyl and halogen,

A-R1 is such that the nitrogen of R1 and the nit
in the 1-position of the pyrazole are necess
separated by at least two carbon atoms,

R3 is an OH, NH_2, OMe or H radical,

R4 is an aryl or heteroaryl radical being optic
substituted with one or more substituents chosen
halogen, CN, NO_2, NH_2, OH, SH, COOH, CHO, C(
$C(S)NH_2$, SO_2H, SO_2NH_2, NHCHO, C(O)Ra, C(O)ORa, C(O)N
C(S)NRaRb, S(O)Ra, SO_2Ra, SO_2NRaRb, ORc, SRc, O-C(
-O-C(S)Ra, NRaRb, NHC(O)Ra, NHC(S)Ra, NH
NHCONRaRb, $NHSO_2Ra$, aryl, heteroaryl, (C
heterocycloalkyl, polyfluoroalkyl, trifluorome
sulfanyl, trifluoromethoxy, linear or branched (C

containing 5, 6 or 7 ring members, which may or ma
have a hetero atom such as O, S or N, this ring
optionally substituted with one or more alkyl a
halogen radicals,

Rc is a linear or branched (C1-C6) alkyl, (C
alkenyl, (C3-C6) alkynyl, (C3-C7) cycloalkyl, (C
cycloalkenyl, (C4-C7) heterocycloalkyl, (hetero)
alkyl, (hetero)aryl, (poly)fluoroalkyl, C(O)R8, C
or SO_2R8 radical,

R6 and R7 are, independently of one anothe
hydrogen, (C1-C6) alkyl, (C3-C6) alkenyl, (C
alkynyl, (C3-C7) cycloalkyl, (C5-C7) cycloalk
(C4-C7) heterocycloalkyl, an arylalkyl
heteroarylalkyl,

R6 and R7 may form a saturated or unsaturated ring
5, 6 or 7 ring members, which may or may not ha
hetero atom such as O, S or N and which is optio
substituted with one or more alkyls and/or halogens

heteroaryl and halogen,

R1 is an NR6R7, (C4-C7) azacycloalkyl, (C azacycloalkenyl, (C5-C9) azabicycloalkyl or (C azabicycloalkenyl group; these groups are optic substituted with one or more substituents chosen (C1-C5) alkyl, (C3-C5) cycloalkyl and halogen,

A-R1 is such that the nitrogen of R1 and the nit in the 1-position of the pyrazole are necess separated by at least two carbon atoms,

R3 is an H, halogen, OH, SH, NH_2, ORc, SRc, SORa, NHCHO, NRaRb, NHC(O)Ra, NHC(S)Ra or $NHSO_2Ra$ radical

R4 is an aryl or heteroaryl radical being optic substituted with one or more substituents chosen halogen, CN, NO_2, NH_2, OH, SH, COOH, CHO, C($C(S)NH_2$, SO_2H, SO_2NH_2, NHCHO, C(O)Ra, C(O)ORa, C(O)N C(S)NRaRb, S(O)Ra, SO_2Ra, SO_2NRaRb, ORc, SRc, O-C(-O-C(S)Ra, NRaRb, NHC(O)Ra, NHC(S)Ra, NH

cycloalkyl, (C5-C7) cycloalkenyl, (C1-C7) h
cycloalkyl, arylalkyl, heteroarylalkyl,
heteroaryl or polyfluoroalkyl,

Ra and Rb may form a saturated or unsaturated
containing 5, 6 or 7 ring members, which may or ma
have a hetero atom such as O, S or N, this ring
optionally substituted with one or more alkyl a
halogen radicals,

Rc is a linear or branched (C1-C6) alkyl, (C
alkenyl, (C3-C6) alkynyl, (C3-C7) cycloalkyl, (C
cycloalkenyl, (C4-C7) heterocycloalkyl, (het
arylalkyl, (hetero)aryl, (poly)fluoroalkyl, C(
C(S)R8 or SO_2R8 radical,

R6 and R7 are, independently of one anothe
hydrogen, (C1-C6) alkyl, (C3-C6) alkenyl, (C
alkynyl, (C3-C7) cycloalkyl, (C5-C7) cycloalk
(C4-C7) heterocycloalkyl, an arylalkyl
heteroarylalkyl,

(C3-C6) alkenyl radical, a (C3-C6) alkynyl radic
(C3-C7) cycloalkyl radical or a (C5-C7) cycloal
radical; these radicals are optionally substituted
one or more substituents chosen from (C1-C5) a
(C2-C5) alkenyl, (C2-C5) alkynyl, (C3-C7) cycloa
(C5-C7) cycloalkenyl, arylalkyl, heteroarylalkyl,
heteroaryl and halogen,

R1 is an NR6R7, (C4-C7) azacycloalkyl, (C
azacycloalkenyl, (C5-C9) azabicycloalkyl or (C
azabicycloalkenyl group; these groups are optic
substituted with one or more substituents chosen
(C1-C5) alkyl, (C3-C5) cycloalkyl and halogen,

A-R1 is such that the nitrogen of R1 and the nit
in the 1-position of the pyrazole are necess
separated by at least two carbon atoms,

R3 is an OH, NH_2, OMe or H radical,

(C4-C7) heterocycloalkyl, arylalkyl, heteroaryla
aryl, heteroaryl or polyfluoroalkyl,

Rb is, independently of Ra, a hydrogen, linea
branched (C1-C6) alkyl, alkenyl, alkynyl, (C
cycloalkyl, (C5-C7) cycloalkenyl, (C4-C7) he
cycloalkyl, arylalkyl, heteroarylalkyl,
heteroaryl or polyfluoroalkyl,

Ra and Rb may form a saturated or unsaturated
containing 5, 6 or 7 ring members, which may or ma
have a hetero atom such as O, S or N, this ring
optionally substituted with one or more alkyl a
halogen radicals,

Rc is a linear or branched (C1-C6) alkyl, (C
alkenyl, (C3-C6) alkynyl, (C3-C7) cycloalkyl, (C
cycloalkenyl, (C4-C7) heterocycloalkyl, (het
arylalkyl, (hetero)aryl, (poly)fluoroalkyl, C(
C(S)R8 or SO_2R8 radical,

More particularly, the present invention relates
use as a medicinal product of pyrazole derivativ
formula (I) in which:

A is, if it is present, a (C1-C6) alkyl radic
(C3-C6) alkenyl radical, a (C3-C6) alkynyl radic
(C3-C7) cycloalkyl radical or a (C5-C7) cycloal
radical; these radicals are optionally substituted
one or more substituents chosen from (C1-C5) a
(C2-C5) alkenyl, (C2-C5) alkynyl, (C3-C7) cycloa
(C5-C7) cycloalkenyl, arylalkyl, heteroarylalkyl,
heteroaryl and halogen,

R1 is an NR6R7, (C4-C7) azacycloalkyl, (C
azacycloalkenyl, (C5-C9) azabicycloalkyl or (C
azabicycloalkenyl group; these groups are optic
substituted with one or more substituents chosen
(C1-C5) alkyl, (C3-C5) cycloalkyl and halogen,

more alkyl, halogen, OH, methoxy,

R5 is a hydrogen,

Ra is linear or branched (C1-C6) alkyl, alk
alkynyl, (C3-C7) cycloalkyl, (C5-C7) cycloalk
(C4-C7) heterocycloalkyl, arylalkyl, heteroaryla
aryl, heteroaryl or polyfluoroalkyl,

Rb is, independently of Ra, a hydrogen, linea
branched (C1-C6) alkyl, alkenyl, alkynyl, (C
cycloalkyl, (C5-C7) cycloalkenyl, (C4-C7) he
cycloalkyl, arylalkyl, heteroarylalkyl,
heteroaryl or polyfluoroalkyl,

Ra and Rb may form a saturated or unsaturated
containing 5, 6 or 7 ring members, which may or ma
have a hetero atom such as O, S or N, this ring
optionally substituted with one or more alkyl a
halogen radicals,

R_8 is an Ra or NRaRb radical,

their racemates, enantiomers and diastereoisomer
their mixtures, their tautomers and
pharmaceutically acceptable salts.

Among the compounds of formula (I) which are u
according to the invention, mention may be made o
following compounds:

1-[2-(3-Methoxy-4-phenylpyrazol-1-yl)ethyl]piperid

1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-4-phenyl-1H-
pyrazol-1-ol

3-(3-Benzyloxy-4-phenylpyrazol-1-ylmethyl)-1-
azabicyclo[2.2.2]octane

3-(3-Methoxy-4-phenylpyrazol-1-ylmethyl)-1-
azabicyclo[2.2.2]octane

1-[2-(7-Azabicyclo[2.2.1]hept-7-yl)ethyl]-4-phenyl-1H-pyrazol-3-ol

1-[2-(2-Azabicyclo[2.2.2]oct-2-yl)ethyl]-4-phenyl-1H-pyrazol-3-ol

1-[2-(2-Azabicyclo[2.2.1]hept-2-yl)ethyl]-4-phenyl-1H-pyrazol-3-ol

1-[2-Dimethylaminoethyl]-4-phenyl-1H-pyrazol-3-ol

1-[3-Dimethylaminopropyl]-4-phenyl-1H-pyrazol-3-ol

1-[2-((2S,6R)-2,6-Dimethylpiperidin-1-yl)ethyl]-4-phenyl-1H-pyrazol-3-ol

1-[2-Diethylaminoethyl]-4-phenyl-1H-pyrazol-3-ol

1-(2-Diisopropylaminoethyl)-4-phenyl-1H-pyrazol-3-ol

4-Phenyl-1-(2-pyrrolidin-1-ylethyl)-1H-pyrazol-3-ol

1-(2-Dimethylaminopropyl)-4-phenyl-1H-pyrazol-3-ol

1-(1-Methylpiperidin-3-ylmethyl)-4-phenyl-1H-pyrazol-3-ol

5-Methyl-4-phenyl-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol

4-(3-Aminophenyl)-1-(2-dimethylaminoethyl)-1H-pyrazol-3-ol

N-{3-[3-Hydroxy-1-(2-dimethylaminoethyl)-1H-pyrazol-4-yl]phenyl}acetamide

4-(4-Aminophenyl)-1-(2-dimethylaminoethyl)-1H-pyrazol-3-ol

1-(2-Dimethylaminoethyl)-4-(4'-fluorobiphenyl-3-yl)-pyrazol-3-ol

4-Phenyl-1-(2-piperidin-1-ylpropyl)-1H-pyrazol-3-ol

3-(4-Phenylpyrazol-1-ylmethyl)-1-azabicyclo[2.2.2]-octane

4-(5-Chlorothiophen-2-yl)-1-(2-piperidin-1-ylethyl)-pyrazol-3-ol

4-(3-Methoxyphenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol

4-(2-Methoxyphenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol

4-(3-Hydroxyphenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol

4-(4-Hydroxyphenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol

4-(2-Fluorophenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol

4-(2-Chlorophenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol

1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(4-chlorophenyl)-pyrazol-3-ol

1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(3-chlorophenyl)-pyrazol-3-ol

1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(3-fluorophenyl)-pyrazol-3-ol

1-(1-Methylpyrrolidin-3-yl)-4-phenyl-1H-pyrazol-3-o

1-[2-(1-Methylpyrrolidin-2-yl)ethyl]-4-phenyl-1H-pyrazol-3-ol

4-Benzo[b]thiophen-2-yl-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol

4-Phenyl-1-piperidin-3-yl-1H-pyrazol-3-ol

1-(2-Piperidin-1-ylethyl)-4-thiophen-3-yl-1H-pyrazol-3-ol

1-(2-Piperidin-1-ylethyl)-4-p-tolyl-1H-pyrazol-3-ol

1-(1-Azabicyclo[2.2.2]oct-2-ylmethyl)-4-phenyl-1H-pyrazol-3-ol

(S)-1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-phenyl-1H-pyrazol-3-ol

(R)-1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-phenyl-1H-pyrazol-3-ol

4-Phenyl-1-pyrrolidin-3-ylmethyl-1H-pyrazol-3-ol

1-[(1R,4S)-2-(2-Azabicyclo[2.2.1]hept-2-yl)ethyl]-4-phenyl-1H-pyrazol-3-ol

1-((R)-1-Methylpyrrolidin-2-ylmethyl)-4-phenyl-1H-pyrazol-3-ol

1-((S)-1-Methylpyrrolidin-3-yl)-4-phenyl-1H-pyrazol-3-ol

1-((R)-1-Methylpyrrolidin-3-yl)-4-phenyl-1H-pyrazol-3-ol

1-[1-(7-Azabicyclo[2.2.1]hept-2-yl)ethyl]-4-phenyl-1H-pyrazol-3-ol

1-(1-Azabicyclo[2.2.1]hept-3-yl)-4-phenyl-1H-pyrazol-3-ol

4-Phenyl-1-piperidin-2-ylmethyl-1H-pyrazol-3-ol

1-(S)-1-Azabicyclo[2.2.2]oct-3-yl-4-(4-chlorophenyl
1H-pyrazol-3-ol

1-(R)-1-Azabicyclo[2.2.2]oct-3-yl-4-(3-chlorophenyl
1H-pyrazol-3-ol

1-(S)-1-Azabicyclo[2.2.2]oct-3-yl-4-(3-chlorophenyl
1H-pyrazol-3-ol

1-(R)-1-Azabicyclo[2.2.2]oct-3-yl-4-(3-fluorophenyl
1H-pyrazol-3-ol

1-(S)-1-Azabicyclo[2.2.2]oct-3-yl-4-(3-fluorophenyl
1H-pyrazol-3-ol

4-(5-Bromothiophen-2-yl)-1-(2-piperidin-1-ylethyl)-
pyrazol-3-ol

4-(5-Phenylthiophen-2-yl)-1-(2-piperidin-1-ylethyl)
pyrazol-3-ol

4-(6-Chloropyridin-2-yl)-1-(2-piperidin-1-ylethyl)-
pyrazol-3-ol

4-(1H-Indol-6-yl)-1-(2-piperidin-1-ylethyl)-1H-pyra
3-ol

4-(1H-Indol-5-yl)-1-(2-piperidin-1-ylethyl)-1H-pyra
3-ol

4-(1H-Indol-3-yl)-1-(2-piperidin-1-ylethyl)-1H-pyra
3-ol

4-(1-Methyl-1H-indol-3-yl)-1-(2-piperidin-1-ylethyl
1H-pyrazol-3-ol

N-{4-[3-Hydroxy-1-(2-piperidin-1-ylethyl)-1H-pyrazo
4-yl]phenyl}methanesulfonamide

N-{3-[3-Hydroxy-1-(2-piperidin-1-ylethyl)-1H-pyrazo
4-yl]phenyl}methanesulfonamide

yl)-1H-pyrazol-3-ol

1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-4-(5-chloro-thiophen-2-yl)-1H-pyrazol-3-ol

1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-4-(4-chloro-phenyl)-1H-pyrazol-3-ol

1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-4-(3-chloro-phenyl)-1H-pyrazol-3-ol

1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-4-(3-fluoro-phenyl)-1H-pyrazol-3-ol

1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-4-(3-hydroxyphenyl)-1H-pyrazol-3-ol

1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-4-(4-hydroxy-phenyl)-1H-pyrazol-3-ol

1-[2-(2-Azabicyclo[2.2.1]hept-2-yl)ethyl]-4-(3-chl
4-hydroxyphenyl)-1H-pyrazol-3-ol

1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-4-(3-chloro-
4-hydroxyphenyl)-1H-pyrazol-3-ol

1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(3-hydroxyphenyl
pyrazol-3-ol

1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(4-hydroxyphenyl
pyrazol-3-ol

1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(3-chloro-4-hydr
phenyl)-1H-pyrazol-3-ol

2-[1-(2-Piperidin-1-ylethyl)-1H-pyrazol-4-yl]benza

N-Methyl-2-[1-(2-piperidin-1-ylethyl)-1H-pyrazol-4
benzamide

1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-phenyl-1H-pyrazole-
3-thiol

4-[1-(1-Azabicyclo[2.2.2]oct-3-yl)-1H-pyrazol-4-yl]-
2-chlorophenol

4-[1-(1-Azabicyclo[2.2.2]oct-3-yl)-1H-pyrazol-4-yl]-
phenol

3-[4-(4-Chlorophenyl)pyrazol-1-ylmethyl]-1-azabicyclo-
[2.2.2]octane

4-[1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-1H-pyrazol-
4-yl]phenol

4-[1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-1H-pyrazol-
4-yl]-2-chlorophenol

3-(3-Cyclopropylmethoxy-4-phenylpyrazol-1-ylmethyl)-
1-azabicyclo[2.2.2]octane

4-[1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-4-yl]-2-chlorophenol

N-[1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-4-phenyl-1H-pyrazol-3-yl]methanesulfonamide

1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-4-phenyl-1H-pyrazole-3-thiol

1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-4-phenyl-1H-pyrazol-3-ylamine

2-[2-(4-Phenylpyrazol-1-yl)ethyl]-2-azabicyclo-[2.2.1]heptane

2-{2-[4-(4-Chlorophenyl)pyrazol-1-yl]ethyl}-2-azabicyclo[2.2.1]heptane

4-{1-[2-(2-Azabicyclo[2.2.1]hept-2-yl)ethyl]-1H-pyrazol-4-yl}phenol

chlorophenyl)-1H-pyrazol-3-yl]methanesulfonamide

1-[2-(2-Azabicyclo[2.2.1]hept-2-yl)ethyl]-4-(4-chlo
phenyl)-1H-pyrazol-3-ylamine

1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(4-chlorophenyl)-
pyrazole-3-thiol

N-[1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-4-(4-chlor
phenyl)-1H-pyrazol-3-yl]methanesulfonamide

1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-4-(4-chloro-
phenyl)-1H-pyrazol-3-ylamine

1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-4-(4-chloro-
phenyl)-1H-pyrazole-3-thiol

1-(1-Methylperhydroazepin-3-yl)-4-phenyl-1H-pyrazol
3-ol

1-(2-Methylaminocyclopentyl)-4-phenyl-1H-pyrazol-3-

pyrazol-3-ol

4-Phenyl-1-pyrrolidin-3-ylmethyl-1H-pyrazol-3-ol

1-((2R) 1-Methylpyrrolidin-2-ylmethyl)-4-phenyl-1H-pyrazol-3-ol

4-Phenyl-1-(piperidin-3-yl)-1H-pyrazol-3-ol

1-(1-Methylpiperidin-2-ylmethyl)-4-phenyl-1H-pyrazol

1-(1-Methylazepan-3-yl)-4-phenyl-1H-pyrazol-3-ol

4-Phenyl-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol

4-(Thiophen-2-yl)-1-(2-piperidin-1-ylethyl)-1H-pyra
3-ol

4-(3,4-Dichlorophenyl)-1-(2-piperidin-1-ylethyl)-1H
pyrazol-3-ol

4-(4-Methylphenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol

1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(1H-indol-5-yl)-1 pyrazole

(+)-1-(Azabicyclo[2.2.2]oct-3-yl)-4-(1H-indol-5-yl) pyrazole

(-)-1-(Azabicyclo[2.2.2]oct-3-yl)-4-(1H-indol-5-yl) pyrazole

1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(5-chlorothiophen yl)-1H-pyrazol-3-ol

1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(5-chlorothiophen yl)-1H-pyrazol-3-ol

1-(1-Azabicyclo[2.2.2]oct-2-ylmethyl)-4-phenyl-1H-pyrazol-3-ol

(+)-1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-phenyl-1H-pyrazol-3-ol

(-)-1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-4-phenyl-pyrazol-1-ol

(+)-1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-4-phenyl-pyrazol-1-ol

1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-4-(4-chlorophenyl)-1H-pyrazol-3-ol

(-)-1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(4-chlorophe 1H-pyrazol-3-ol

(+)-1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(4-chlorophe 1H-pyrazol-3-ol

(-)-1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(4-fluorophe 1H-pyrazol-3-ol

chlorophenol

(-)-4-[1-(1-Azabicyclo[2.2.2]oct-3-yl)-1H-pyrazol-4-yl]-2-chlorophenol

(+)-4-[1-(1-Azabicyclo[2.2.2]oct-3-yl)-1H-pyrazol-4-yl]-2-chlorophenol

(+)-1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-pyridin-2-yl-pyrazol-3-ol

(-)-1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-pyridin-2-yl-pyrazol-3-ol

(+)-1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-phenyl-1H-pyrazol-3-ylamine

(-)-1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-phenyl-1H-pyrazol-3-ylamine

and (In) for R3 = S(O)Ra, SO_2Ra. The definitio
various substituents are the same as those of fo
(I), unless otherwise indicated.

For easy reading, groups GP, GP', GP", GP"', GP^{iv} an
are groups which protect functions sensitive to
reaction conditions and are introduced as define
T.W. Greene et al., Protective Groups in Or
Synthesis, Wiley-Interscience, third edition (1
capable of being unaffected by the subsequent ste
the synthesis and of being deprotected under condi
which do not affect the rest of the molecule.

The derivatives of formula (I) for which R3
hydroxyl (Ia) can be obtained from derivative
formula (II) (I with R3 = OGP) for which GP
hydroxyl function-protecting group.

residue such as methyl, allyl, cyclohex-2-enyl, t
or tetrahydropyran-2-yl. The GP group is prefera
benzyl or a cyclohex-2-enyl. The deprotection of t
group is carried out according to the methods desc
in T.W. Greene et al., Protective Groups in Or
Synthesis, Wiley-Interscience, third edition (1999)

For example, when the GP group is a benzyl,
deprotection is carried out by hydrolysis in
presence of concentrated hydrochloric acid i
alcohol such as ethanol, methanol or isopropanol
temperature of between 20°C and the boiling temper
of the reaction medium, preferably in ethanol, a
boiling temperature of the reaction medium.

Alternatively, the debenzylation can be carried o
the following successive operations:

a) Formation of the hydrochloride of the compound
deprotected in the presence of hydrochloric aci
aqueous solution or in solution in an organic so

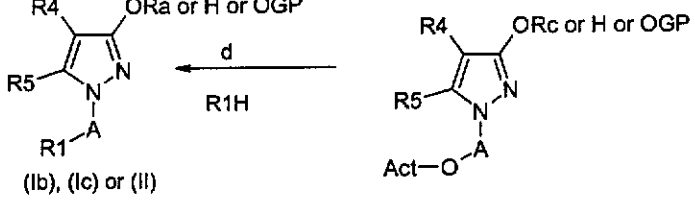
reaction medium. The reaction can also be carrie
with ammonium formate, in the presence of a cat
such as palladium-on-charcoal, in an alcohol su
ethanol, methanol or isopropanol, at a temper
between 20°C and the boiling temperature of
reaction medium, preferably in methanol at the bo
temperature of the reaction medium.

When the GP group is a cyclohexenyl, the deprote
is carried out by hydrolysis in acid medium,
example in the presence of a solution of hydroch
acid in an ether or an alcohol, in a solvent su
methanol or ethanol at a temperature of between
and the boiling temperature of the reaction medium.

The derivatives of formula I for which R3 is OR
being different to C(O)R8, C(S)R8, SO_2R8), H, NH_2 o
(Ib), (Ic), (Id) or (II) can be obtained accordi
three different synthetic pathways.

and the boiling temperature of the reaction mediu
in the presence of potassium tert-butoxide,
solvent such as dimethylformamide, at a temperatu
between 20°C and the boiling temperature of
reaction medium. The reaction can also be carrie
in the presence of potassium carbonate and, option
of potassium iodide, in a solvent such as ace
methyl ethyl ketone, acetonitrile or dimethylforma
preferably in methyl ethyl ketone, at the bo
temperature of the reaction medium.

The compounds (IV) are commercial or can be obt
from the corresponding alcohols of formula R1-A-
methods known to those skilled in the art such as
described in J. March, Advanced Organic Chemi
Wiley-Interscience, fourth edition (1992)
R.C. Larock, Comprehensive Organic Transformations
Publishers (1989). The alcohols of formula R1-A-O
commercial or can be obtained by adapting me
described in the literature using the basic ge
knowledge of those skilled in the art.



The compounds of formula (Ib), (Ic) or (II) ca obtained in three or four steps from the pyrazol formula (III) according to the following protocol:

a) Alkylation of the pyrazole (III) with a compou formula (V) GP'O-A-X in which GP' is a hyd function-protecting group, as defined in T.W. G and al., Protective Groups in Organic Synthesis, W Interscience, third edition (1999), capable of unaltered during the alkylation step and of deprotected under conditions which do not affec rest of the molecule (for example, the GP' group m a silyl-containing group such as tert-butyldime silyl, triisopropylsilyl or diphenylmethylsilyl, aralkyl, alkylidene, cycloalkylidene, heteroalky

acetonitrile or dimethylformamide, preferably in t
ethyl ketone, at the boiling temperature of
reaction medium.

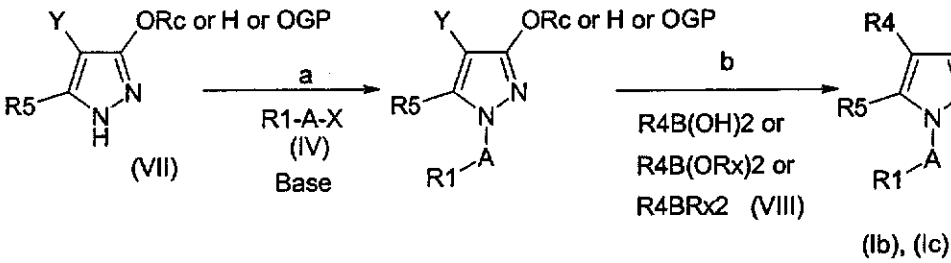
b) Production of the intermediates of formula
after cleavage of the GP' protective group accordi
the methods described in T.W. Greene and
Protective Groups in Organic Synthesis, W
Interscience, third edition (1999), and not affe
the other functions carried by the molecule.
example, when the GP' group is a tetrahydropyran-
the deprotection of the alcohol may be carried o
acid medium, for example in the presence of aq
hydrochloric acid, in a solvent such as ethanc
methanol, at a temperature of between 20°C and
boiling temperature of the reaction medium, prefe
in the presence of aqueous hydrochloric acid
ethanol, at a temperature in the region of 20°C.

a') Alternatively, when A is an ethyl or (C
cycloalkyl radical, these radicals being optio

dichloromethane, at a temperature of between -20
the boiling temperature of the reaction me
preferably at a temperature of between -10°C
temperature in the region of 20°C.

d) Substitution of the activated alcohol residue w
primary or secondary amine of formula R1H. The rea
is carried out in basic medium, for example in
presence of potassium carbonate, in a polar sol
such as dimethylformamide or acetonitrile,
temperature of between 20°C and the boiling temper
of the reaction medium, preferably
dimethylformamide, at a temperature in the regi
80°C.

The compounds (V) are commercial or can be obt
from the corresponding alcohols of formula GP'O-A-
methods known to those skilled in the art as desc
in J. March, Advanced Organic Chemistry, W
Interscience, fourth edition (1992) or R.C. La
Comprehensive Organic Transformations, VCH Publi



The compounds of formula (Ib), (Ic), and (II) c
obtained in two steps from the compounds of fo
(VII) for which Y = Br, I or Cl (preferably Br or

a) Alkylation of the 4-halopyrazole of formula
with a compound of formula (IV) as defined above
reaction is carried out under an inert atmosphere
example under argon or under nitrogen, in basic m
in an aprotic solvent, for example in the presen
sodium hydride, in an aprotic solvent such
dimethylformamide, at a temperature of between 20°
the boiling temperature of the reaction medium,
the presence of potassium tert-butoxide, in a so

tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$)
(diphenylphosphino)ferrocenyl palladium ($PdCl_2dppf$
a solvent such as dimethylformamide, dimethoxyet
tetrahydrofuran, dioxane, toluene, xylene or eth
optionally in the presence of water, at a temper
of between 20°C and the boiling temperature o
reaction medium (Kotha S. et al., Tetrahedron
58, 9633).

The boronic acids, alkyl or cycloalkyl boronate
(hetero)aryldialkyl boron of formula (VIII)
commercial or are obtained using or adapting me
described in the literature, for example
G.W. Kabalka et al., Tetrahedron Letters 1986,
3843, J.F. Nicoud et al., Tetrahedron Letters
34, 8237, J.M. Tour et al., J. Amer. Chem. Soc.
116, 11723, or T.J.J. Mueller et al., Synthesis
9, 1163.

The intermediates of formula (III), when there
radical ORc (Rc being different to C(O)R8, C(

(III)

The pyrazoles of formula (III) can be obtained in steps from the compounds of formula (IX) accordi the following protocol:

a) Condensation of an (aryl)alkyl (hetero)aryl ac for which Rx = alkyl or aralkyl, of formula (IX), an aminomethylenation agent or a carbonylation age formula (X) for which Ry is a Cl, O-alkyl, O-ar or O-CO-alkyl radical, preferably for which Ry O-alkyl radical. The aminomethylenation reaction c carried out in the presence of a reagent suc N,N,N',N',N",N"-hexamethylmethanetriamine, C-met N,N,N',N'-tetramethylmethanediamine or C-tert-bu N,N,N',N'-tetramethylmethanediamine, in the absenc solvent or in a solvent such as tetrahydrofura dioxane at a temperature of between 20°C and boiling temperature of the reaction medium, prefe in the presence of C-tert-butoxy-N,N,N',N'-tetrame methanediamine in tetrahydrofuran at a temperatu

boiling temperature of the reaction medium.

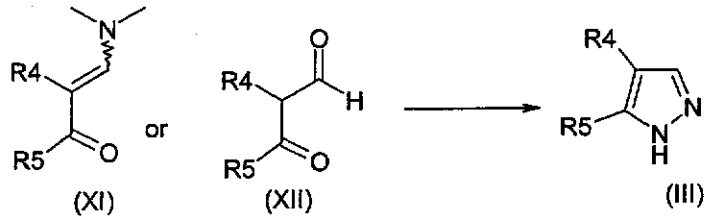
c) Protection of the nitrogen in the 1-position o
1H-pyrazol-3-ol with a protective group such a
acetyl, alkyloxycarbonyl or tosyl, preferably wi
acetyl group. The reaction is carried out wit
acetylating, alkyloxycarbonylating or tosylating a
preferably with acetic anhydride without solvent
the presence of a solvent such as pyridine,
temperature of between 20°C and the boiling temper
of the reaction medium, preferably at a temperatu
the region of 100°C.

d) Protection of the hydroxyl group of the pyrazo
introduction of the -Rc residue onto the hydroxy
the pyrazole, followed by deprotection of the nit
in the 1-position of the pyrazole. The protectio
the hydroxyl group of the pyrazole and the introdu
of the -Rc residue onto the hydroxyl of the pyr
can be carried out, for example, by alkylation o
hydroxyl group of the pyrazole with the compound

the region of 85°C. The deprotection of the nitrog
the 1-position of the pyrazole is carried out acco
to the methods described in T.W. Greene et
Protective Groups in Organic Synthesis, W
Interscience, third edition (1999). For example,
the protective group is an acetyl, the deprotectio
be carried out in the presence of a base such as s
hydroxide or potassium carbonate, in an alcohol su
ethanol or methanol, to which a solvent suc
tetrahydrofuran or dioxane is optionally added,
temperature of between 20°C and the boiling temper
of the reaction medium, preferably in the presen
sodium hydroxide in a mixture of ethanol
tetrahydrofuran, at a temperature in the regio
20°C.

The compounds of formula (IX) are commercial or c
obtained using or adapting methods described in
literature.

obtained according to the reaction scheme repre
below:



(XI) (XII) (III)

The compounds of formula (III) can be obtained fro
compounds of formula (XI) or (XII) and hydra
generally in monohydrate form. The reaction is ca
out, for example, in an alcohol such as eth
propanol or isopropanol, at a temperature in the r
of 20°C and the boiling temperature of the rea
medium, preferably in ethanol, at the bo
temperature of the reaction medium.

The compounds of formula (XI) or (XII) are comme
or can be obtained using or adapting methods desc
in the literature.

a) Protection of the compounds of formula (VII)
example with a tosyl, mesyl or acetyl group, prefe
with a tosyl group. This reaction is carried
according to the processes known to those skill
the art and described in T.W. Greene et al., Prote
Groups in Organic Synthesis, Wiley-Interscience,
edition (1999). For example, when the protective
is a tosyl, the reaction is carried out with
chloride in basic medium, for example in the pre
of sodium hydride or of potassium tert-butoxide
aprotic solvent such as dimethylformamide
temperature between -10°C and the boiling temper
of the reaction medium.

b) Introduction of the R4 group by Suzuki coupli
by two consecutive Stille reactions. The introdu
of the R4 group by Suzuki coupling is carried out
the protected 4-halopyrazole obtained in the prec
step and a boronic acid, an alkyl or cyclo
boronate or a (hetero)aryldialkyl boron of fo
(VIII) for which Rx is an alkyl or cycloalkyl rad
under an inert atmosphere, in the presence o

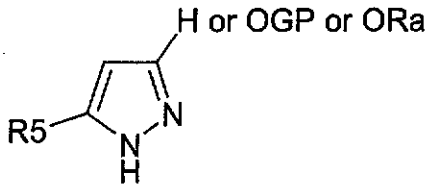
as tetrahydrofuran at a temperature of between
the boiling temperature of the reaction me
according to A.I. Scott et al., Tetrahedron Lett.
37, 3247. The second Stille reaction is carrie
using the organotin above and a halogenated arc
derivative of formula R4-Z for which Z is a Br, I
radical (preferably Br or I), with a palladium
(catalyst) such as tris(dibenzylidene)dipall
(Pd2dba3) and tristrifurylphosphine, in a solvent
as dioxane at a temperature of between 20°C an
boiling temperature of the reaction medium, acc
to U. Hacksell et al., Bioorg. & Med. Chem. I
1994, 2837.

c) Cleavage of the protective group introduced i
first step. This reaction is carried out accordi
the processes known to those skilled in the ar
described in T.W. Greene et al., Protective Grou
Organic Synthesis, Wiley-Interscience, third ed
(1999). For example, when the protective group
tosyl, the reaction can be carried out

form, with a 2-(hetero)aryl-3-oxopropionitrile
formula (XIII) in acid medium, for example in
presence of acetic acid, in an alcohol such as eth
propanol or isopropanol, at a temperature of be
20°C and the boiling temperature of the rea
medium, preferably in ethanol, at the bo
temperature of the reaction medium.

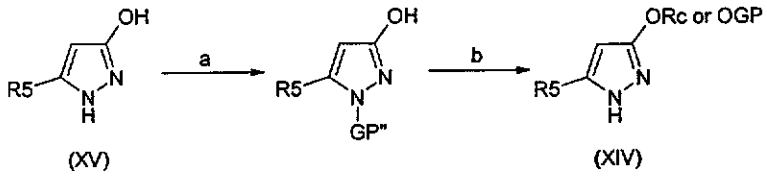
The compounds of formula (XIII) can be obtained
or adapting methods described in the literature.

The intermediates (VII) for which there is an H, O
ORc (Rc being different to C(O)R8, C(S)R8, SO_2R8) i
3-position of the pyrazole are obtained from
derivative of formula (XIV)



(XIV)

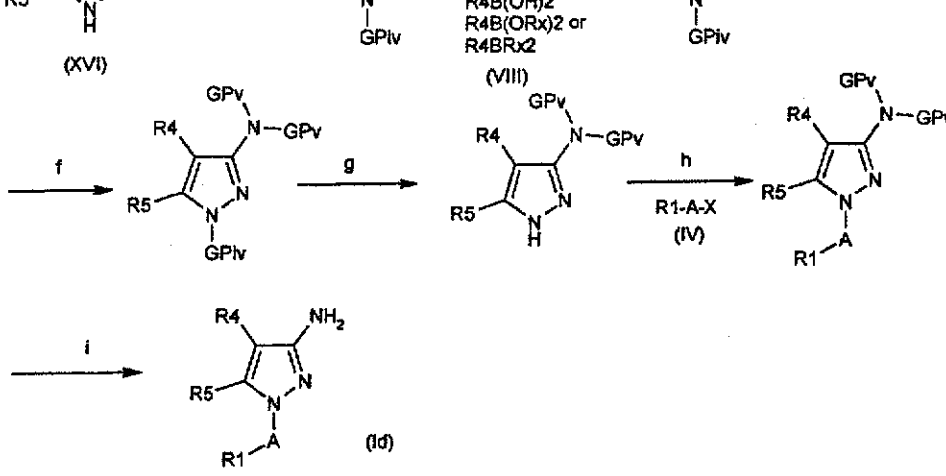
The intermediates (XIV) for which
radical or an ORc radical (Rc being differe
C(O)R8, C(S)R8, SO_2R8) in the 3-position of the py
can be obtained in two steps from compounds of f
(XV) according to the following protocol:



(XV) (XIV)

a) Protection of the nitrogen in the 1-position
1H-pyrazol-3-ol with a protective group such
acetyl, alkyloxycarbonyl or tosyl, preferably wi
acetyl group. The reaction is carried out wit
acetylating, alkyloxycarbonylating or tosylating
preferably with acetic anhydride without solvent
the presence of a solvent such as pyridine,
temperature of between 20°C and the boiling temper
of the reaction medium, preferably at a temperatu
the region of 100°C.

between 20°C and the boiling temperature of the
reaction medium, preferably in methyl ethyl keton
the boiling temperature of the reaction medium. Wh
is a CHF_2 group, the alkylation can be carried out
methyl chlorodifluoroacetate, in basic medium,
example in the presence of a base such as pota
carbonate, in a solvent such as dimethylformamide,
temperature of between 20°C and the boiling temper
of the reaction medium, preferably at a temperatu
the region of 65°C. The deprotection of the nitrog
the pyrazole is carried out according to the me
described in T.W. Greene et al., in Protective G
in Organic Synthesis, Wiley-Interscience, third ed
(1999). For example, when the protective group
acetyl, the deprotection can be carried out in
presence of a base such as sodium hydroxid
potassium carbonate, in an alcohol such as ethano
methanol, with a solvent such as tetrahydrofura
dioxane being optionally added, at a temperatur
between 20°C and the boiling temperature of
reaction medium, preferably in the presence of s



a) Protection of the 4-halo-3-nitropyrazoles of fo
(XVI), for example with a 2-trimethylsilanylet
methyl group. This reaction is carried out accordi
the processes known to those skilled in the art
described in T.W. Greene et al., Protective Group
Organic Synthesis, Wiley-Interscience, third ed
(1999). For example, the reaction is carried out
2-trimethylsilanylethoxymethyl chloride in
medium, for example in the presence of sodium hy

palladium ($PdCl_2dppf$), in a solvent such
dimethylformamide, dimethoxyethane, tetrahydrof
dioxane, toluene, xylene or ethanol, optionally i
presence of water at a temperature of between 20°
the boiling temperature of the reaction me
Alternatively, the introduction of the R4 group c
carried out by means of two consecutive S
reactions. The first Stille reaction is carried
under an inert atmosphere using the protected 4-ha
nitropyrazole obtained in the preceding step
bis(tributyltin) in the presence of cuprous iodid
a palladium salt (catalyst) such as palladium diac
($Pd(OAc)_2$) and of triphenylphosphine, in a solvent
as tetrahydrofuran, at a temperature of between
and the boiling temperature of the reaction me
according to AI. Scott et al., Tetrahedron Lett.
37, 3247. The second Stille reaction is carried
using the preceding organotin and a haloge
aromatic derivative of formula R4-Z for which Z
Br, I or Cl radical (preferably Br or I), wi
palladium salt (catalyst) such as tris(dibenzylid

group GP^v is an amine-protecting group as define
T.W. Greene et al., Protective Groups in Or
Synthesis, Wiley-Interscience, third edition (1999
resistant to the conditions for deprotecting the
GP^{iv}. For example, the group GP^v may be an ally
benzyl or a para-methoxybenzyl. The group GP
introduced according to the processes known to
skilled in the art and described in T.W. Greene et
Protective Groups in Organic Synthesis, W
Interscience, third edition (1999). For example,
the protective group GP^v is an allyl, the reactio
carried out with allyl bromide in the presence
base such as cesium carbonate, in an aprotic sol
such as acetonitrile or dimethylformamide, a
temperature of between 20°C and the boiling tempera
of the reaction medium.

g) Cleavage of the protective group GP^{iv} introduce
the first step, according to the processes know
those skilled in the art and described in T.W. Gr

medium, or in the presence of potassium salt bas
in a solvent such as dimethylformamide,
temperature of between 20°C and the boiling temper
of the reaction medium. The reaction can als
carried out in the presence of potassium carbonate
optionally, of potassium iodide, in a solvent su
acetone, methyl ethyl ketone, acetonitrile
dimethylformamide, preferably in methyl ethyl ke
at the boiling temperature of the reaction medium.

i) Cleavage of the protective group GP^v introduc
step f), according to the processes known to
skilled in the art and described in T.W. Greene et
Protective Groups in Organic Synthesis, W
Interscience, third edition (1999). For example,
the protective group GP^v is an allyl, the reactio
be carried out with a palladium salt such
tetrakistriphenylphosphine palladium ($Pd(PPh_3)_4$) i
presence of an acid such as N,N-dimethylbarbi
acid, in an aprotic solvent such as dichloromethan

The compounds (Ie) can be obtained from the comp
(Id) according to the protocols known to those sk
in the art and described, for example, in J. M
Advanced Organic Chemistry, Wiley-Interscience, f
edition (1992), R.C. Larock, Comprehensive Or
Transformations, VCH Publishers (1989) or Bra
P. Mundy and Michael G. Ellerd, Name Reactions
Reagents in Organic Synthesis, A. Wiley-Intersc
Publication (1988).

The compounds (If) can be obtained from the comp
(Ia) by reaction with a thionating agent, such as
example, Lawesson's reagent, and according to
protocols described, for example, in J. March, Adv
Organic Chemistry, Wiley-Interscience, fourth ed
(1992).
The compounds (Ig) can be obtained from the comp
(If) according to the protocols known to those sk
in the art and described, for example, in J. M
Advanced Organic Chemistry, Wiley-Interscience, f

does not affect the rest of the molecule, as desc
in Protective Groups in Organic Synthesis, T.W. Gr
Ed. by Wiley, third edition (1999). This reaction
for example, be carried out with boron tribromide
solvent such as dichloromethane at a temperatur
between -5°C and the boiling temperature of
reaction medium.

The compounds of formula (I) for which the R4 gro
substituted with one or more NH_2 radicals ca
obtained by reduction of the corresponding
compounds according to a protocol as describe
J. March, Advanced Organic Chemistry, W
Interscience, fourth edition (1992) or R.C. La
Comprehensive Organic Transformations, VCH Publi
(1989). For example, this reaction can be carrie
by hydrogenation in the presence of a catalyst su
palladium-on-charcoal and, optionally, of an acid
as hydrochloric acid, in an alcohol such as eth
methanol or isopropanol, at a hydrogen pressur
between 1 bar and 20 bar and at a temperatur

water and of an alcohol such as methanol or ethan
a temperature between 20°C and the boiling temper
of the reaction medium, preferably in ethanol a
boiling temperature of the reaction medium.
functionalization of the resulting amino derivativ
carried out according to methods which do not a
the rest of the molecule, known to those skilled i
art and described, for example, in J. March, Adv
Organic Chemistry, Wiley-Interscience, fourth ed
(1992), R.C. Larock, Comprehensive Or
Transformations, VCH Publishers (1989), Bradfor
Mundy and Michael G. Ellerd, Name Reactions
Reagents in Organic Synthesis, A. Wiley-Intersc
Publication (1988) or Hartwig J.F., Angew. Chem.
Ed. Engl. 1998, 2047.

The compounds of formula (Ib), (Ic) or (II) for
the R4 group is substituted with one or more ar
heteroaryl radicals can be obtained from
corresponding halogenated compounds (prefe
brominated or iodinated) and from suitable bo

The compounds of formula (I) can be optic
transformed into addition salts with an inorgan
organic acid by reaction of such an acid in an or
solvent such as an alcohol, a ketone or an ether
chlorinated solvent. These salts are also part o
invention.

As examples of pharmaceutically acceptable s
mention may be made of the following s
benzenesulfonate, hydrobromide, hydrochloride, cit
ethanesulfonate, fumarate, gluconate, iodate, mal
isethionate, methanesulfonate, nitrate, oxa
palmoate, phosphate, salicylate, succinate, sul
tartrate, theophylline acetate and p-toluenesulfona

The compounds of the invention have been t
with regard to their ability to bind nico
receptors containing the α7 subunit by means
binding assay on rat brain membrane prepara
according to the methods described below:

above composition and frozen at -20 C. On the d
the assay, the membranes were thawed, centrifuge
24 000 g for 20 minutes, and then resuspended
final concentration of 2-5 mg of proteins/m
Dulbecco phosphate buffer at pH 7.4 containing 0.0
bovine serum albumin.

Measurement of the affinity for receptors conta
the α7 subunit:

The binding of the compounds of the inventio
receptors containing the α7 subunit was measure
competition with respect to [^{3}H]-methyllycacon
([^{3}H]-MLA), a radiolabeled tracer which recognize
receptors (Davies et al., Neuropharmacology 1999,
679-690), according to conventional methods adapte
the 96-well-plate format. The ability of the comp
of the invention to displace the binding of [^{3}H]-M
rat hippocampal membranes was determined in dupl
after incubation for 2 hours at ambient tempera
Each well contained a sample of approximately 150

Data analysis

For each compound tested, the residual radioactivi
the filters was expressed in counts per minutes
determinations in duplicate were averaged and
concentration of compound which inhibits by hal
specific binding of the radioactive tracer (IC_{50}
calculated by curvilinear regression using spe
software (GraphPad Prism). The apparent aff
constants Ki for the compounds of the invention
calculated using the Cheng and Prusoff equation (
and Prusoff, Biochem. Pharmacol. 1973, *22*, 3099-310

The compounds of the invention which were studie
this assay exhibit a Ki value of less than 10 μM.

The following examples illustrate the invention
nonlimiting manner.

Example 1

phase is washed with 3 times 25 cm³ of water, d
then dried over anhydrous magnesium sulfate, fil
and concentrated to dryness under reduced pressu
kPa), so as to give an oily residue which is pur
by chromatography on silica gel (particle size
μm), eluting with a mixture of ethyl acetate
cyclohexane (67 /33 by volume). After concentrati
the fractions under reduced pressure, 0.3 g
colorless oil is obtained, which is dissolved in
of acetone and 30 cm³ of an approximately 3M soluti
hydrochloric ether are added. The white precip
formed is filtered and then dried under vacuum (7
at a temperature of 60°C. 0.325 g of 1-[2-(3-met
4-phenylpyrazol-1-yl)ethyl]piperidine dihydrochl
is thus obtained in the form of a white solid
melts at 208°C (with decomposition).

^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
(mt: 1H); from 1.60 to 1.90 (mt: 5H); 2.94 (mt:
from 3.40 to 3.60 (mt: 4H); 3.95 (s: 3H); 4.47 (t
6.5 Hz: 2H); 7.29 (broad t, J = 7.5 Hz: 1H);

water and extracted with 250 cm³ of ethyl acetate. The
organic phase is washed with 3 times 25 cm³ of w
and is then dried over anhydrous magnesium sul
filtered and concentrated to dryness under re
pressure (3 kPa), so as to give a light brown
residue, which is purified by chromatography on s
gel (particle size 15-35 μm), eluting with a mixtu
dichloromethane and methanol (98.5/1.5 by vol
After concentration of the fractions under re
pressure, 0.3 g of 3-methoxy-4-phenylpyrazol
obtained in the form of a pale yellow powder
melts at 150°C.

The 1-(3-hydroxy-4-phenylpyrazol-1-yl)ethanone ca
prepared in the following way:

3.4 cm³ of acetic anhydride are added, over 10 min
to a solution of 6.4 g of 4-phenyl-1H-pyrazol-3-
64 cm³ of pyridine preheated to 100°C. After a fu
30 minutes at 100°C, the mixture is cooled and p
into 600 cm³ of a water-ice mixture. The precip

pyrazol-1-ylmethyl)-1-azabicyclo[2.2.2]octane

0.08 g of palladium-on-charcoal (10%) in 20 cm
ethanol is stirred in an autoclave under a hyd
pressure of 500 kPa, at a temperature of 20°C, f
hours. The reaction medium is then filtered
Celite® and concentrated to dryness under re
pressure (3 kPa), so as to give a pasty residue,
is covered with 50 cm^3 of acetone and tritu
overnight. After filtration of the solid which
appeared and drying under vacuum (70 Pa)
temperature of 60°C, 0.265 g of
azabicyclo[2.2.2]oct-3-ylmethyl)-4-phenyl-1H-pyrazo
ol dihydrochloride is obtained in the form
hygroscopic beige crystals which melt at around
(with decomposition).

^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
1.65 to 1.95 (mt: 4H); from 1.95 to 2.15 (mt: 1H);
2.40 to 2.60 (mt: 1H); 2.96 (broad dd, J = 12.5 an
Hz: 1H); from 3.10 to 3.40 (mt: 5H); 4.03 (dd, J =
and 7.5 Hz: 1H); 4.10 (dd, J = 13.5 and 7.5 Hz:
7.15 (broad t, J = 7.5 Hz: 1H); 7.34 (broad t,

region of 50°C, 11.78 g of 3-chlorometh
azabicyclo[2.2.2]octane hydrochloride are adde
small portions, and the mixture is then heated f
hours at a temperature in the region of 50°C.
mixture is cooled to ambient temperature and 25 c
water are then added slowly, and the mixture is
run into 300 cm^3 of water and extracted with two
300 cm^3 of ethyl acetate. The pooled organic phase
washed with 3 times 100 cm^3 of water, and then
over anhydrous magnesium sulfate, filtered
concentrated to dryness under reduced pressure (3
The oily residue obtained is purified by chromatog
on alumina, eluting with a mixture of ethyl acetat
methanol (90/10 by volume). After concentration o
fractions under reduced pressure, 2.81 g of a brow
are obtained, which oil is dissolved in 200 c
ethanol and 6.25 cm^3 of an approximately 6M aq
hydrochloric acid solution are added. The solutio
concentrated to dryness under reduced pressure (3
The residue is taken up with 200 cm^3 of ethanol
redried, twice. 3.01 g of 3-(3-benzylo

following way:

A suspension of 5.7 g of 1-(3-hydroxy-4-phenylpyr
1-yl)ethanone, 3.9 g of potassium carbonate and 3.
(5.3 g) of benzyl bromide in 250 cm^3 of 2-butano
stirred at the boiling temperature of the rea
medium for two and a quarter hours. The insc
inorganic material is removed by filtration and
filtrate is concentrated to dryness under re
pressure (3 kPa). The residue is dissolved in 50 c
tetrahydrofuran, 50 cm^3 of methanol and 1 cm^3 of
sodium hydroxide solution are added and the mixtu
stirred for a quarter of an hour at ambient temper
and then concentrated to dryness under reduced pre
(3 kPa). The residue is taken up with 5 cm^3 of wate
extracted with 250 cm^3 of ethyl acetate. The or
phase is dried over anhydrous magnesium sul
filtered and concentrated to dryness under re
pressure (3 kPa), so as to give a white solid res
which is triturated in a mixture of isopropyl ethe
petroleum ether. After filtration and air-drying,

temperature in the region of 50 C. The mixtu
cooled to ambient temperature, 10 cm^3 of water are
added slowly, and the mixture is concentrated
reduced pressure (3 kPa). The residue is taken up
25 cm^3 of water and extracted with 3 times 100 c
ethyl acetate. The pooled organic phases are w
with 3 times 25 cm^3 of water, and then dried, fil
and concentrated to dryness under reduced pressu
kPa). The oily residue obtained is purifie
chromatography on alumina, eluting with a mixtu
ethyl acetate and methanol (90/10 by volume).
concentration of the fractions under reduced pres
0.3 g of a brown oil is obtained, which is dissolv
40 cm^3 of acetone, and 35 cm^3 of approximatel
hydrochloric ether are added. The solution
concentrated to dryness under reduced pressure (3
and the pasty residue is washed with two times 50 c
ethyl ether and then triturated in 50 cm^3 of ethyl
overnight. After filtration of the solid obtaine
drying under vacuum (70 Pa) at a temperature of
0.25 g of 3-(3-methoxy-4-phenylpyrazol-1-ylmethy

A suspension of 0.163 g of 3-(3-benzyloxy-4-ph
pyrazol-1-yl)-1-azabicyclo[2.2.2]octane, 0.38 cm^3
hydrochloric acid and 0.024 g of palladium-on-cha
(at 10%) in 20 cm^3 of ethanol is stirred in an auto
under a hydrogen pressure of 1 000 kPa,
temperature of 20°C for 8 hours. The reaction medi
then filtered over Celite ® and concentrated to dr
under reduced pressure (3 kPa), so as to gi
hygroscopic oily residue, which is dissolved in 1
of water and lyophilized. 0.083 g of 1-(1-azabic
[2.2.2]oct-3-yl)-4-phenyl-1H-pyrazol-1-ol dih
chloride is thus obtained in the form of an amor
brown solid.

^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
1.65 to 2.05 (mt: 4H); 2.41 (mt: 1H); 3.26 (mt:
3.40 (mt: 1H); 3.77 (mt: 2H); 4.68 (mt: 1H);
(broad t, J = 7.5 Hz: 1H); 7.34 (broad t, J = 7.
2H); 7.69 (broad d, J = 7.5 Hz: 2H); 8.22 (s: 1H);
10.15 to 10.75 (broad unresolved peak: 1H);
(unresolved peak: 1H).

concentrated under reduced pressure (3 kPa).
residue is taken up with 10 cm^3 of water and extr
with 50 cm^3 of ethyl acetate. The organic phas
washed with 3 times 10 cm^3 of water, and is then d
filtered and concentrated to dryness under re
pressure (3 kPa). The oily residue obtained is pur
by preparative HPLC on 10μ C8 Kromasil, eluting w
mixture of acetonitrile and water (50/50 by volume
then of acetonitrile and ammoniacal methanol (7M)
by volume). After concentration of the fractions
reduced pressure, 0.163 g of 3-(3-benzy
4-phenylpyrazol-1-yl)-1-azabicyclo[2.2.2]octane
obtained in the form of a yellow oil, which is us
it is in the following step.

The 3-[(methanesulfonyl)oxy]-1-azabicyclo[2.2.2]o
can be obtained according to the method describe
S.M. Jenkins et al., J. Med. Chem. 1992, *35*, 2392-2

Example 6

^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
(mt: 4H); 1.84 (mt: 4H); 3.17 (mt: 2H); from 3.
3.55 (mt: 4H); 4.41 (t, J = 6.5 Hz: 2H); 7.15 (bro
J = 7.5 Hz: 1H); 7.34 (broad t, J = 7.5 Hz: 2H);
(broad d, J = 7.5 Hz: 2H); 8.05 (s: 1H);
(unresolved peak: 1H); 10.49 (unresolved peak: 1H).
IR spectrum (KBr): 3431; 2934; 2638; 2422; 1608;
1572; 1528; 1452; 1210; 1179; 1013; 760; 692; 67
511 cm^{-1}.

The 1-[2-(3-benzyloxy-4-phenylpyrazol-1-yl)ethyl
hydroazepine can be prepared in the following way:

A suspension of 1 g of 1-[(toluene-4-sulfonyl)ox
(3-benzyloxy-4-phenylpyrazol-1-yl)ethyl, 0.29 cm
perhydroazepine and 0.88 g of potassium carbonat
25 cm^3 of acetonitrile is stirred for 3 hours
temperature in the region of 80°C, and then 0.15 c
perhydroazepine is added and the heating is cont
for 2 hours. The mixture is concentrated to dr
under reduced pressure (3 kPa). The residue is tak

59 cm^3 of triethylamine are added dropwise, at am
temperature, to a suspension of 13.7 g
2-(3-benzyloxy-4-phenylpyrazol-1-yl)ethanol h
chloride in 400 cm^3 of dichloromethane. The rea
mixture is cooled to around 5°C and a solutio
22.5 g of toluene-4-sulfonyl chloride in 200 c
dichloromethane is added, over 0.5 hours.
stirring for 16 hours at ambient temperature,
mixture is concentrated to dryness under re
pressure (3 kPa). The residue is taken up with 10
of water and extracted with (500 + 250) cm^3 of
acetate. The pooled organic phases are washed w
times 100 cm^3 of water, and then dried over anhy
magnesium sulfate, filtered and concentrated to dr
under reduced pressure (3 kPa). The oily re
obtained is purified by chromatography on silica
(particle size 15-35 μm), eluting with dichlorome
and then a mixture of dichloromethane and met
(95/5 by volume). After concentration of the frac
under reduced pressure, 19 g of 1-[(tolue

it is in the following step.

The 3-benzyloxy-4-phenyl-1-[2-(tetrahydropyran-oxy)ethyl]-1H-pyrazole can be prepared in the foll way:

3.07 g of sodium hydride (at 75% by mass in l petroleum jelly) are added gradually, under an atmosphere and at ambient temperature, to a soluti 16 g of 3-benzyloxy-4-phenylpyrazole in 110 cm anhydrous dimethylformamide. After stirring for quarters of an hour at a temperature in the regi 50°C, a solution of 11.06 cm^3 (15.31 g) of 2-(2-b ethoxy)tetrahydropyran in 40 cm^3 of anhy dimethylformamide is added dropwise, and the mixtu then heated for three quarters of an hour temperature in the region of 50°C. 25 cm^3 of wate then added slowly to the mixture, which is ther into 90 cm^3 of water and extracted with 3 times 30 of ethyl acetate. The pooled organic phases are w

7.5 Hz: 2H); 7.50 (broad d, J = 7.5 Hz: 2H);
(broad d, J = 7.5 Hz: 2H); 8.05 (s: 1H).

Example 7

1-[2-(2-Methylpiperidin-1-yl)ethyl]-4-phenyl-1H-pyrazol-3-ol dihydrochloride

A suspension of 0.58 g of 1-[2-(3-benzyloxy-4-ph
pyrazol-1-yl)ethyl]-2-methylpiperidine, 1.29 cm^3 c
hydrochloric acid and 0.082 g of palladium-on-cha
(at 10%) in 20 cm^3 of ethanol is stirred in an auto
under a hydrogen pressure of 1 000 kPa, a
temperature of 20°C for 8 hours. The reaction medi
then filtered over Celite® and concentrated to dr
under reduced pressure (3 kPa). The residue
triturated in 40 cm^3 of acetone and isolate
filtration. 0.54 g of 1-[2-(2-methylpiperidin-1
ethyl]-4-phenyl-1H-pyrazol-3-ol dihydrochloride is
obtained in the form of a beige powder which melt
118°C (with decomposition).

25 cm³ of acetonitrile is stirred for 6 hours
temperature in the region of 80°C. The mixtur
concentrated to dryness under reduced pressure (3
The residue is taken up with 50 cm³ of wate
extracted with 200 cm³ of ethyl acetate. The or
phase is washed with 3 times 25 cm³ of water, a
then dried, filtered and concentrated to dryness
reduced pressure (3 kPa). The oily residue obtain
purified by chromatography on silica gel (particle
15-35 μm), eluting with a mixture of dichlorome
and methanol (97/3 by volume). After concentrati
the fractions under reduced pressure, 0.65 g of
(3-benzyloxy-4-phenylpyrazol-1-yl)ethyl]-2-methyl-
piperidine is obtained in the form of a colo
viscous oil, which is used as it is in the foll
step.
Mass spectrum (EI): m/z 375 ($M^{+\cdot}$), m/z 112 (base pea

Example 8

few drops of CD_3COOD d4; δ in ppm): from 2.00 to
(mt: 4H); 3.29 (unresolved peak: 4H); 3.52 (t,
6 Hz: 2H); 4.40 (t, J = 6 Hz: 2H); 4.94 (broad d
48 Hz: 1H); 7.14 (broad t, J = 7.5 Hz: 1H); 7.33
t, J = 7.5 Hz: 2H); 7.65 (broad d, J = 7.5 Hz:
7.99 (s: 1H).
IR spectrum (KBr): 3054; 2963; 2633; 2531; 1608;
1528; 1452; 1177; 1031; 1015; 764; 698 and 509 cm^{-1}

The 1-[2-(3-benzyloxy-4-phenylpyrazol-1-yl)et
4-fluoropiperidine can be prepared in the foll
way:

A suspension of 1 g de 1-[(toluene-4-sulfonyl)
2-(3-benzyloxy-4-phenylpyrazol-1-yl)ethyl, 0.702
4-fluoropiperidine hydrobromide and 1.18 g of pota
carbonate in 25 cm^3 of acetonitrile is stirrec
6 hours at a temperature in the region of 80°C
mixture is concentrated to dryness under re
pressure (3 kPa). The residue is taken up with 50
water and extracted with 200 cm^3 of ethyl acetate

pyrazol-3-ol dihydrochloride

A suspension of 0.57 g of 1-[2-(3-benzyloxy-4-ph pyrazol-1-yl)ethyl]-3-methylpiperidine, 1.27 cm^3 hydrochloric acid and 0.081 g of palladium-on-cha (at 10%) in 20 cm^3 of ethanol is stirred in an autc under a hydrogen pressure of 1 000 kPa, temperature of 20°C for 8 hours. The reaction medi then filtered over Celite® and concentrated to dr under reduced pressure (3 kPa). The residu triturated in 75 cm^3 of acetone and isolate filtration. 0.198 g of 1-[2-(3-methylpiperidin-1 ethyl]-4-phenyl-1H-pyrazol-3-ol dihydrochloride is obtained in the form of a pale yellow powder melts at 220°C (with decomposition).

^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6 with addition few drops of CD_3COOD, δ in ppm): 0.89 (d, J = 7 Hz: 1.05 (mt: 1H); from 1.60 to 2.00 (mt: 4H); 2.58 1H); 2.83 (very broad t, J = 12 Hz: 1H); from 3. 3.55 (mt: 4H); 4.39 (t, J = 6.5 Hz: 2H); 7.13 (

then dried, filtered and concentrated to dryness
reduced pressure (3 kPa). The oily residue obtain
purified by chromatography on silica gel (particle
15-35 μm), eluting with a mixture of dichlorome
and methanol (97/3 by volume). After concentrati
the fractions under reduced pressure, 0.58 g of
(3-benzyloxy-4-phenylpyrazol-1-yl)ethyl]-3-methyl-
piperidine is obtained in the form of a colo
viscous oil, which is used as it is in the foll
step.
Mass spectrum (EI): m/z 375 ($M^{+\cdot}$), m/z 112 (base pe

Example 10

1-[2-(3,6-Dihydro-2H-pyridin-1-yl)ethyl]-4-phenyl-1
pyrazol-3-ol dihydrochloride

A solution of 0.6 g of 1-[2-(3-benzyloxy-4-ph
pyrrol-1-yl)ethyl]-1,2,3,6-tetrahydropyridine in
mixture of 5 cm^3 of 37% hydrochloric acid and of
of ethanol is heated at 80°C for 6 hours and

IR spectrum (KBr): 3422; 2948; 2688; 2579; 1607; 1452; 1184; 1023; 768; 699; 667; 670 and 511 cm^{-1}.

The 1-[2-(3-benzyloxy-4-phenylpyrrol-1-yl)et 1,2,3,6-tetrahydropyridine can be prepared in following way:

A suspension of 1 g of 1-[(toluene-4-sulfonyl)ox (3-benzyloxy-4-phenylpyrazol-1-yl)ethyl, 0.36 cm 1,2,3,6-tetrahydropyridine and 0.88 g of pota carbonate in 25 cm^3 of acetonitrile is stirred hours at a temperature in the region of 80°C. mixture is concentrated to dryness under re pressure (3 kPa). The residue is taken up with 50 c water and extracted with 200 cm^3 of ethyl acetate organic phase is washed with 3 times 25 cm^3 of w and is then dried, filtered and concentrated to dr under reduced pressure (3 kPa). The oily re obtained is purified by chromatography on silica (particle size 15-35 μm), eluting with a mixtur

temperature and then concentrated to dryness under
reduced pressure (3 kPa). The residue obtained
0.078 g of palladium-on-charcoal (at 10%) are susp
in 20 cm^3 of ethanol and stirred in an autoclave un
hydrogen pressure of 1 000 kPa, at a temperatu
20°C for 8 hours. The reaction medium is then fil
over Celite® and concentrated to dryness under re
pressure (3 kPa). The residue is triturated in 25 c
acetone and isolated by filtration. 0.466 g of 1-[
azabicyclo[2.2.1]hept-7-yl)ethyl]-4-phenyl-1H-pyraz
3-ol dihydrochloride is thus obtained in the form
white powder which melts at 228°C (with decompositi

^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
(unresolved peak: 4H); 2.00 (unresolved peak: 4H);
(mt: 2H); 3.93 (broad s: 2H); 4.43 (broad t,
6.5 Hz: 2H); 7.15 (broad t, J = 7.5 Hz: 1H);
(broad t, J = 7.5 Hz: 2H); 7.65 (broad d, J = 7.5
2H); 8.08 (s: 1H); from 10.35 to 10.55 (
unresolved peak: 1H); 10.47 (unresolved peak: 1H).

under reduced pressure (3 kPa). The oily re
obtained is purified by chromatography on silic
(particle size 15-35 μm), eluting with a mixtu
dichloromethane and methanol (98/2 by volume).
concentration of the fractions under reduced pres
0.6 g of 7-[2-(3-benzyloxy-4-phenylpyrazol-1-yl)et
7-azabicyclo[2.2.1]heptane is obtained in the form
colorless viscous oil, which is used as it is i
following step.
Mass spectrum (CI): m/z 374 ($[M+H]^+$) (base peak).

Example 12

1-[2-(2-Azabicyclo[2.2.2]oct-2-yl)ethyl]-4-phenyl-1
pyrazol-3-ol dihydrochloride

2 cm^3 of 6M hydrochloric acid is added to a soluti
0.9 g of 2-[2-(3-benzyloxy-4-phenylpyrazol-1-yl)et
2-azabicyclo[2.2.2]octane in 50 cm^3 of ethanol, an
mixture is stirred for a quarter of an hour at am
temperature and then concentrated to dryness

(broad d, J = 7.5 Hz: 2H); 8.04 (s: 1H);
(unresolved peak: 1H).
IR spectrum (KBr): 2949; 2870; 2629; 2184; 1608;
1510; 1455; 1198; 870; 761; 692; 670 and 510 cm^{-1}.

The 2-[2-(3-benzyloxy-4-phenylpyrazol-1-yl)ethy
azabicyclo[2.2.2]octane can be prepared in
following way:
A suspension of 1 g of 1-[(toluene-4-sulfonyl)ox
(3-benzyloxy-4-phenylpyrazol-1-yl)ethyl, 0.563
2-azabicyclo[2.2.2]octane hydrochloride and 0.88
potassium carbonate in 25 cm^3 of acetonitrile is st
for 8 hours at a temperature in the region of 80°C
mixture is concentrated to dryness under re
pressure (3 kPa). The residue is taken up with 30
water and extracted with 200 cm^3 of ethyl acetate
organic phase is washed with twice 30 cm^3 of water
is then dried, filtered and concentrated to dr
under reduced pressure (3 kPa). The oily re
obtained is purified by chromatography on silica

pyrazol-3-ol dihydrochloride

1.6 cm^3 of 6M hydrochloric acid are added to a sol of 0.7 g of 2-[2-(3-benzyloxy-4-phenylpyraz yl)ethyl]-2-azabicyclo[2.2.1]heptane in 50 cm ethanol, and the mixture is stirred for a quarter hour at ambient temperature and then concentrat dryness under reduced pressure (3 kPa). The re obtained and 0.10 g of palladium-on-charcoal (at are suspended in 20 cm^3 of ethanol and stirred autoclave under a hydrogen pressure of 1 000 kPa, temperature of 20°C for 8 hours. The reaction medi then filtered over Celite® and concentrated to dr under reduced pressure (3 kPa). The residu triturated in 40 cm^3 of acetone and isolate filtration. 0.565 g of 1-[2-(2-azabicyclo[2.2.1] 2-yl)ethyl]-4-phenyl-1H-pyrazol-3-ol dihydrochlori thus obtained in the form of a beige powder which at 173°C (with decomposition).

(3-benzyloxy-4-phenylpyrazol-1-yl)ethyl] 0.91 g
2-azabicyclo[2.2.1]heptane hydrochloride and 0.88
potassium carbonate in 25 cm^3 of acetonitrile is st
for 8 hours at a temperature in the region of 80°C
mixture is concentrated to dryness under re
pressure (3 kPa). The residue is taken up with 30 c
water and extracted with 200 cm^3 of ethyl acetate
organic phase is washed with two times 30 cm^3 of w
and is then dried, filtered and concentrated to dr
under reduced pressure (3 kPa). The oily re
obtained is purified by chromatography on silica
(particle size 15-35 μm), eluting with a mixtur
dichloromethane and methanol (95/5 by volume).
concentration of the fractions under reduced pres
0.75 g of 2-[2-(3-benzyloxy-4-phenylpyrazol-1
ethyl]-2-azabicyclo[2.2.1]heptane is obtained in
form of a colorless viscous oil, which is used as
in the following step.
Mass spectrum (EI): m/z 373 ($M^{+\cdot}$), m/z 110 (base pea

^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
(d, J = 5 Hz: 6H); 3.51 (mt: 2H); 4.38 (t, J = 6.
2H); 7.16 (broad t, J = 7.5 Hz: 1H); 7.35 (broad
= 7.5 Hz: 2H); 7.65 (broad d, J = 7.5 Hz: 2H); 8.0
1H); 10.27 (unresolved peak: 1H); from 10.30 to
(very broad unresolved peak: 1H).
IR spectrum (KBr): 3311; 2985; 2558; 2463; 1629;
1508; 1467; 1409; 1190; 985; 760; 687 and 673 cm^{-1}.
The [2-(3-benzyloxy-4-phenylpyrazol-1-yl)ethy
methylamine dihydrochloride can be prepared in
following way:

0.154 g of sodium hydride (at 75% by mass in l
petroleum jelly) is added gradually, under an
atmosphere and at ambient temperature, to a soluti
0.25 g of 3-benzyloxy-4-phenylpyrazole in 3 cm
anhydrous dimethylformamide, followed,
disappearance of the foams, by 0.5 g of (2-bromoet
dimethylamine hydrobromide. After stirring for 2
at ambient temperature, water is slowly added and
mixture is extracted with ethyl acetate. The or

7.30 to 7.50 (mc: 3H); 7.52 (broad d, J = 7.5 Hz:
7.65 (broad d, J = 7.5 Hz: 2H); 8.17 (s: 1H);
(unresolved peak: 1H).

The (2-bromoethyl)dimethylamine hydrobromide ca
obtained according to the method describe
L.H. Amundsen et al., J. Am. Chem. Soc. 1941, *63*,
307.

Example 15

1-[3-Dimethylaminopropyl]-4-phenyl-1H-pyrazol-3-ol
dihydrochloride

The process is carried out as in example 2, but
0.274 g of [3-(3-benzyloxy-4-phenylpyrazol-1
propyl]dimethylamine dihydrochloride and 0.04
palladium-on-charcoal (at 10%). 0.209 g of
dimethylaminopropyl]-4-phenyl-1H-pyrazol-3-ol dih
chloride is thus obtained in the form of a beige p
which melts at around 208°C (with decomposition).

ethyl acetate. The pooled organic phases are dried
magnesium sulfate, and then concentrated to dr
under reduced pressure (3 kPa). The residue obtain
dissolved in 25 cm^3 of ethanol, an excess o
approximately 3M hydrochloric ether solution is a
and the mixture is returned to dryness. 0.274
[3-(3-benzyloxy-4-phenylpyrazol-1-
yl)propyl]dimethylamine dihydrochloride is
obtained in the form of a pasty white solid used
is in the following step.

The [3-(3-benzyloxy-4-phenylpyrazol-1-yl)propy
methylamine oxalate can be prepared in the foll
way:

0.106 g of sodium hydride (at 75% by mass in l
petroleum jelly) is added gradually, under an
atmosphere and at ambient temperature, to a soluti
0.25 g of 3-benzyloxy-4-phenylpyrazole in 15 cu
anhydrous dimethylformamide. After stirring for
quarters of an hour at a temperature in the regi
50°C, 0.316 g of (3-chloropropyl)dimethyl

6.5 Hz: 2H); 5.33 (s: 2H); 7.10 (broad t, J = 7.
1H); from 7.30 to 7.45 (mt: 3H); 7.43 (broad t, J
Hz: 2H); 7.51 (broad d, J = 7.5 Hz: 2H); 7.65 (bro
J = 7.5 Hz: 2H); 8.09 (s: 1H).

Example 16

1-[2-((2S,6R)-2,6-Dimethylpiperidin-1-yl)ethyl]-4-phenyl-1H-pyrazol-3-ol dihydrochloride

The process is carried out as in example 2, but 0.123 g of (2S,6R)-1-[2-(3-benzyloxy-4-phenylpyr 1-yl)ethyl]-2,6-dimethylpiperidine dihydrochloride 0.014 g of palladium-on-charcoal (at 10%). 0.075 1-[2-((2S,6R)-2,6-dimethylpiperidin-1-yl)ethyl]-4-phenyl-1H-pyrazol-3-ol dihydrochloride is thus obt in the form of a beige powder which melts at a 206°C (with decomposition).

^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$ d6, at a temper of 403K, δ in ppm): 1.36 (d, J = 6.5 Hz: 6H); 1.57 1H); from 1.65 to 1.90 (mt: 5H); 3.28 (unresolved

benzyloxy-4-phenylpyrazol-1-yl)ethyl]-2,6-dimethyl
piperidine dihydrochloride is thus obtained in the
of a colorless paste used as it is in the foll
step.

The (2S,6R)-1-[2-(3-benzyloxy-4-phenylpyrazol-1
ethyl]-2,6-dimethylpiperidine can be prepared in
following way:

0.211 g of sodium hydride (at 75% by mass in l
petroleum jelly) is added gradually, under an
atmosphere and at ambient temperature, to a soluti
0.25 g of 3-benzyloxy-4-phenylpyrazole in 20 c
anhydrous dimethylformamide. After stirring for
quarters of an hour at a temperature in the regi
50°C, 0.636 g of (2S,6R)-1-(2-chloroethyl)
dimethylpiperidine hydrochloride is added in
portions, and the mixture is then stirred for 16
at ambient temperature. The mixture is run into 15
of water and extracted with twice 150 cm^3 of
acetate. The pooled organic phases are washed

benzyloxy-4-phenylpyrazol-1-yl)ethyl] 2,6-dimethyl
piperidine is obtained in the form of a colorles
used as it is in the following step. ^{1}H NMR spe
(300 MHz, $(CD_3)_2SO$ d6, δ in ppm): 1.08 (d, J = 6.
6H); 1.17 (broad double t, J = 12 and 3 Hz: 2H);
(mt: 1H); 1.53 (broad d, J = 12 Hz: 2H); 1.62 (mt:
2.48 (mt: 2H); 2.95 (t, J = 6.5 Hz: 2H); 3.98 (t
6.5 Hz: 2H); 5.32 (s: 2H); 7.15 (tt, J = 7.5
1.5 Hz: 1H); from 7.30 to 7.45 (mt: 1H); 7.34 (bro
J = 7.5 Hz: 2H); 7.42 (broad t, J = 7.5 Hz: 2H);
(broad d, J = 7.5 Hz: 2H); 7.66 (broad d, J = 7.
2H); 8.10 (s: 1H).

The (2S,6R)-1-(2-chloroethyl)-2,6-dimethylpiperi
amine hydrochloride can be obtained according to
method described by R. Dahlbom et al.,
Pharmaceutica Suecica 1969, *6* (3), 413-418.

Example 17

1-[2-Diethylaminoethyl]-4-phenyl-1H-pyrazol-3-ol
dihydrochloride

The [2-(3-benzyloxy-4-phenylpyrazol-1-yl)ethyl]die
amine dihydrochloride can be obtained in the foll
way:

The process is carried out as in example 15, but
0.31 g of [2-(3-benzyloxy-4-phenylpyrazol-1
ethyl]diethylamine oxalate. 0.31 g of [2-(3-benzy
4-phenylpyrazol-1-yl)ethyl]diethylamine dihydrochl
is thus obtained in the form of a colorless gum us
it is in the following step.

The [2-(3-benzyloxy-4-phenylpyrazol-1-yl)ethyl]die
amine oxalate can be obtained in the following way:

The process is carried out as in example 15, but
0.211 g of sodium hydride (at 75% by mass in l
petroleum jelly) and 0.516 g of (2-chloroethyl)die
amine hydrochloride. 0.376 g of [2-(3-benzylo
phenylpyrazol-1-yl)ethyl]diethylamine oxalate is

diisopropylamine dihydrochloride and 0.025 g palladium-on-charcoal (at 10%). 0.122 g of 1-[2-d propylaminoethyl]-4-phenyl-1H-pyrazol-3-ol dihydrochloride is thus obtained in the form of a powder which melts at around 220°C decomposition).

^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): (broad d, J = 7 Hz: 6H); 1.34 (broad d, J = 7 Hz: 3.47 (unresolved peak: 2H); 3.71 (mt: 2H); 4.40 (t, J = 6.5 Hz: 2H); 7.14 (broad t, J = 7.5 Hz: 7.33 (broad t, J = 7.5 Hz: 2H); 7.65 (broad d, 7.5 Hz: 2H); 8.12 (s: 1H); 9.96 (unresolved peak: 10.49 (broad s: 1H).

IR spectrum (KBr): 2984; 2654; 2507; 2469; 1607; 1531; 1453; 1193; 759; 693; 673 and 511 cm^{-1}.

The [2-(3-benzyloxy-4-phenylpyrazol-1-yl)ethyl]d propylamine dihydrochloride can be obtained in following way:

which melts at 134°C.

^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6 with additio
few drops of CD_3COOD d4, δ in ppm): 1.21 (d, J =
12H); 3.39 (broad t, J = 6.5 Hz: 2H); 3.57 (mt:
4.30 (t, J = 6.5 Hz: 2H); 5.35 (s: 2H); 7.17 (br
J = 7.5 Hz: 1H); 7.35 (mt: 3H); 7.41 (broad t,
7.5 Hz: 2H); 7.49 (broad d, J = 7.5 Hz: 2H);
(broad d, J = 7.5 Hz: 2H); 8.10 (s: 1H).

Example 19

4-Phenyl-1-(2-pyrrolidin-1-ylethyl)-1H-pyrazol-3-o
dihydrochloride

The process is carried out as in example 2, but
0.285 g of 3-benzyloxy-4-phenyl-1-(2-pyrrolid
ylethyl)-1H-pyrazole dihydrochloride and 0.037
palladium-on-charcoal (at 10%). 0.101 g of 4-phen
(2-pyrrolidin-1-ylethyl)-1H-pyrazol-3-ol dih
chloride is thus obtained in the form of a beige p
which melts at around 173°C (with decomposition).

0.54 g of 3-benzyloxy-4-phenyl-1-(2-pyrro
1-ylethyl)-1H-pyrazole oxalate. 0.285 g of 3-benzy
4-phenyl-1-(2-pyrrolidin-1-ylethyl)-1H-pyrazole
dihydrochloride is thus obtained in the form of a
gum used as it is in the following step.

The 3-benzyloxy-4-phenyl-1-(2-pyrrolidin-1-ylethyl
pyrazole oxalate can be obtained in the following

The process is carried out as in example 15, but
0.211 g of sodium hydride (at 75% by mass in
petroleum jelly) and 0.51 g of 1-(2-chloroet
pyrrolidine hydrochloride. 0.354 g of 3-benzy
4-phenyl-1-(2-pyrrolidin-1-ylethyl)-1H-pyrazole ox
is thus obtained in the form of a white powder
melts at 144°C.
^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
(mt: 4H); 3.10 (mt: 4H); 3.46 (mt: 2H); 4.33 (t,
6.5 Hz: 2H); 5.35 (s: 2H); 7.18 (broad t, J = 7.
1H); 7.36 (mt: 3H); 7.43 (broad t, J = 7.5 Hz:

under reduced pressure (3 kPa). The residue is tak
with 30 cm^3 of water and extracted with 250 cm^3 of
acetate. The organic phase is washed with 3 times
of water, and dried, filtered and concentrate
dryness under reduced pressure (3 kPa). The
residue obtained is purified by chromatograph
silica gel, eluting with a mixture of ethyl acetat
methanol (90/10, then 75/25 by volume).
concentration of the fractions under reduced pres
0.36 g of an oil is obtained, which is dissolv
15 cm^3 of acetone, and 5 cm^3 of an approximatel
hydrochloric ether solution are added. The precip
which has appeared is triturated overnight and
isolated by filtration. 0.308 g of 3-(3-metho
phenylpyrazol-1-yl)-1-azabicyclo[2.2.2]octane
hydrochloride is thus obtained in the form
hygroscopic beige powder which melts at around
(with decomposition).
^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
1.65 to 2.05 (mt: 4H); 2.42 (mt: 1H); 3.28 (mt:

piperidine hydrochloride, and [illegible] g
mixture of dichloromethane and methanol (95/
volume). 0.175 g of 1-[2-(3-difluoromethoxy-4-ph
pyrazol-1-yl)ethyl]piperidine hydrochloride is
obtained in the form of a white solid which mel
around 174°C (with decomposition).

^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
(unresolved peak: 1H); from 1.60 to 1.90 (mt: 5H);
(unresolved peak: 2H); 3.47 (very broad d, J = 1
2H); 3.54 (unresolved peak: 2H); 4.55 (broad t,
6.5 Hz: 2H); 7.29 (tt, J = 7.5 and 2.5 Hz: 1H);
(t, J = 72 Hz: 1H); 7.44 (broad t, J = 7.5 Hz:
7.59 (broad d, J = 7.5 Hz: 2H); 8.30 (s: 1H);
10.00 to 10.20 (unresolved peak: 1H).

IR spectrum (KBr): 3100; 2931; 2644; 2543; 1609;
1507; 1482; 1456; 1364; 1181; 1125; 1100; 1076;
694 and 513 cm^{-1}.

The 3-difluoromethoxy-4-phenyl-1H-pyrazole can
prepared in the following way:

1H-pyrazole is obtained in the form of a yellow
which melts at 125°C. Mass spectrum (EI): m/z 210
(base peak), m/z 160 $[M - CF_2]^{+\cdot}$.

Example 22

4-Phenyl-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-yla
dihydrochloride

10 cm^3 of 1N hydrochloric ether solution is adde
excess, to a solution of 0.2 g of 4-phenyl-
piperidin-1-ylethyl)-1H-pyrazol-3-ylamine in 10 c
methanol, and the mixture is concentrated to dr
under reduced pressure (3 kPa). The residue prov
after trituration in ethyl ether, 0.244 g of 4-ph
1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ylamine
dihydrochloride in the form of white crystals
melt at around 120°C.
^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
1.25 to 1.55 (mt: 1H); from 1.60 to 1.90 (mt: 5H);
(unresolved peak: 2H); 3.44 (unresolved peak: 2H);

taken up with 40 cm³ of 0.5N sodium hydroxide so
and extracted with 50 cm³ of ethyl acetate. The or
phase is dried over magnesium sulfate, filtered
concentrated to dryness under reduced pressure (3
The yellow oily residue is purified by chromatog
on basic alumina, eluting successively with a mi
of ethyl acetate and dichloromethane (50/50 by vo
and then with pure ethyl acetate. 0.2 g of 4-phen
(2-piperidin-1-ylethyl)-1H-pyrazol-3-ylamine is
obtained in the form of a white solid which mel
96°C and has an Rf of 0.4 (ethyl acetate, alu
oxide plate reference 105731, Merck).

^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
(mt: 2H); 1.49 (mt: 4H); 2.39 (broad t, J = 5 Hz:
2.64 (t, J = 6.5 Hz: 2H); 3.98 (t, J = 6.5 Hz:
4.63 (s: 2H); 7.15 (tt, J = 7.5 and 1.5 Hz: 1H);
(broad t, J = 7.5 Hz: 2H); 7.49 (broad d, J = 7.
2H); 7.74 (s: 1H).

removal of the gel by filtration, the organic p
concentrated to dryness under reduced pressure (3
The oily residue obtained is purified by chromatog
on basic alumina, eluting with a mixture
dichloromethane and ethyl acetate (80/20 by vol
After concentration of the fractions under re
pressure, a colorless oil is obtained, whic
dissolved in 10 cm^3 of ethyl ether, and 1 cm^3
approximately 6N solution of hydrochloric dioxa
added, and the mixture is then concentrated to dr
under reduced pressure (3 kPa). The residu
triturated in acetone and isolated by filtra
0.045 g of 4-phenyl-1-(2-piperidin-1-ylethyl
pyrazol-3-ylamine dihydrochloride is thus obtain
the form of a white solid which melts at around
(with decomposition).
^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
1.25 to 1.50 (unresolved peak: 1H); from 1.60 to
(mt: 5H); 1.6 (s: 3H); 2.94 (unresolved peak: 2H);
3.40 to 3.65 (mt: 4H); 4.42 (t, J = 6.5 Hz: 2H);
(broad t, J = 7.5 Hz: 1H); 7.37 (broad t, J = 7.

H NMR spectrum (100 MHz, $(CD_3)_2SO$ d6, at a temp of 373 K, δ in ppm): 1.42 (mt: 2H); 1.52 (mt: 4H); (t, J = 5 Hz: 4H); 3.6 (t, J = 6.5 Hz: 2H); 4.17 = 6.5 Hz: 2H); 7.24 (broad t, J = 7.5 Hz: 1H); (broad t, J = 7.5 Hz: 2H); 7.49 (broad d, J = 7. 2H); 7.96 (s: 1H); 8.30 (broad d, J = 5 Hz: 1H); (unresolved peak: 1H).

IR spectrum (KBr): 34434; 3218; 2955; 2799; 1683; 1607; 1325; 1289; 765; 698 and 592 cm^{-1}.

Example 24

N-[4-Phenyl-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3- acetamide oxalate

0.1 cm^3 of acetic anhydride is added to a soluti 0.27 g of 4-phenyl-1-(2-piperidin-1-ylethyl pyrazol-3-ylamine in 5 cm^3 of chloroform, and mixture is then stirred at ambient temperature 100 hours. After the mixture has been concentrat dryness under reduced pressure (3 kPa), 15 cm^3

(broad d, δ = 7.5 Hz: 2H); 8.11 (broad s: 1H);
(unresolved peak: 1H).

IR spectrum (KBr): 3258; 3026; 2952; 2683; 2540;
1640; 1525; 1447; 1373; 1202; 1008; 765 and 700 cm

Example 25

N-[4-Phenyl-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3
methanesulfonamide

0.06 cm^3 of methanesulfonyl chloride is added
solution of 0.18 g of 4-phenyl-1-(2-piperic
ylethyl)-1H-pyrazol-3-ylamine in 5 cm^3 of chlorc
and the mixture is then stirred at ambient tempe
for 22 hours. 0.04 cm^3 of methanesulfonyl chlori
added to the mixture and the stirring is continu
ambient temperature for 3 hours. 15 cm^3 of a satu
sodium hydrogen carbonate solution are added t
mixture, which is extracted with 25 cm^3 of
acetate. The organic phase is dried over magn
sulfate, filtered and concentrated to dryness

unresolved peak: 1H).

IR spectrum (KBr): 3105; 2928; 1610; 1440; 1321; 976; 765; 699; 524 and 518 cm^{-1}.

Example 26

1-(2-Dimethylaminopropyl)-4-phenyl-1H-pyrazol-3-ol dihydrochloride

1 cm^3 of a 4N hydrochloric solution in dioxane is gradually, at a temperature in the region of 20°C, solution of 0.42 g of {2-[3-(cyclohex-2-enyl 4-phenylpyrazol-1-yl]-1-methylethyl}dimethylamine 5 cm^3 of methanol, with stirring. After stirring f hours at a temperature in the region of 20°C, reaction mixture is concentrated to dryness reduced pressure (2.7 kPa) and dried at 40°C reduced pressure (2.7 kPa) so as to give 0.37 1-(2-dimethylaminopropyl)-4-phenyl-1H-pyrazol-3-ol dihydrochloride in the form of a white solid

is then brought to 50°C for 15 hours. After addition of a further 0.14 g of sodium hydride a in liquid petroleum jelly and a further 0.7 (2-chloro-1-methylethyl)dimethylamine hydrochlo the reaction is continued for 15 hours at 50°C, ar reaction medium is then cooled to a temperature i region of 20°C and concentrated to dryness reduced pressure (2.7 kPa). The residue obtain taken up in 100 cm^3 of water; the resulting aq phase is extracted with 3 times 30 cm dichloromethane, and the organic phase is dried magnesium sulfate and concentrated to dryness reduced pressure (2.7 kPa). 1.2 g of a brown o obtained, which is purified by flash chromatograp silica under an argon pressure (50 kPa) [el dichloromethane/methanol (95/5 by volume)]. concentration of the fractions to dryness under re pressure (2.7 kPa), 0.42 g of {2-[3-(cyclo enyloxy)-4-phenylpyrazol-1-yl]-1-methylethyl}dimeth amine is obtained in the form of an oil [TLC: el

reaction medium is concentrated to dry
reduced pressure (2.7 kPa), which results in a re
which is solubilized in 100 cm^3 of ethyl acetate
organic solution is washed with two times 20 c
water and with 20 cm^3 of water saturated with s
chloride, dried over magnesium sulfate, filtered
evaporated to dryness under reduced pressure (2.7
The solid obtained is taken up with 5 cm^3 of
acetate under hot conditions with stirring; 40 c
diisopropyl ether are added to the solution, whi
brought to the reflux of the solvent for 15 minute
then cooled to a temperature in the region of 20
first crystallization crop is filtered off, washed
10 cm^3 of diisopropyl ether and 10 cm^3 of pentane
dried under reduced pressure (2.7 kPa) to give 1
of 3-(cyclohex-2-enyloxy)-4-phenyl-1H-pyrazole in
form of a white powder. The crystallization filtra
evaporated to dryness under reduced pressure (2.7
and taken up with 20 cm^3 of diisopropyl ether
20 cm^3 of pentane are added; a second crystalliz
crop is filtered off and dried under reduced pre

brought to the reflux of the solvent [illegible]
further 15 cm^3 of cyclohexene are then added an
reaction is continued at the reflux of the solven
5 hours. The catalyst is filtered off over supe
and the solution is evaporated to dryness under re
pressure (2.7 kPa) to give 0.48 g of a solid whi
triturated in 10 cm^3 of a mixture of diisopropyl
and pentane. After filtration, 0.3 g of a sol
obtained, which is used again in reaction with 10
ethanol, 10 cm^3 of cyclohexene and 0.1 g of palla
on-charcoal at 10% with stirring and at the refl
the solvent for 15 hours. The catalyst is filtere
over supercel, and the filtrate is evaporate
dryness under reduced pressure (2.7 kPa) to give
of a solid which is purified by flash chromatograp
silica under an argon pressure (50 kPa) [el
dichloromethane/methanol/38% aqueous ammonia sol
(88/10/2 by volume)]. After concentration of
fractions under reduced pressure (2.7 kPa), 0.15 g
yellowish solid is obtained, which is taken up in
of methanol at a temperature in the region of

methylpiperidine can be prepared in the following w

0.4 g of sodium hydride at 75% in liquid petr
jelly is added gradually, at a temperature ir
region of 20°C, to a solution of 1 g of 3-benzy
4-phenyl-1H-pyrazole in 10 cm^3 of dimethylform
under an argon atmosphere and with stirring, and
mixture is then brought to 50°C for 10 minutes.
the addition of 1.5 g of 3-chlorometh
methylpiperidine hydrochloride, the reaction medi
heated at 80°C for 15 hours, and is then cooled
temperature in the region of 20°C and poured
100 cm^3 of water. The mixture is extracted
dichloromethane; the organic phase is dried
magnesium sulfate, filtered and evaporated to dr
under reduced pressure (2.7 kPa) to give 1.6 g
brown oil which is purified by flash chromatograp
silica under an argon pressure (50 kPa) [el
dichloromethane/methanol (95/5 by volume)].
concentration of the fractions to dryness under re

for 15 hours at a temperature in the region of
the reaction mixture is concentrated to dryness
reduced pressure (2.7 kPa). The residue is tritu
in diisopropyl ether, filtered, and dried under re
pressure (2.7 kPa) at 40°C for 2 hours to give 0
of 5-methyl-4-phenyl-1-(2-piperidin-1-ylethyl
pyrazol-3-ol dihydrochloride in the form of a
solid which melts at 222°C. Mass spectrum (CI): m/
(MH^+).

The 1-{2-[3-(cyclohex-2-enyloxy)-5-methyl-4-ph
pyrazol-1-yl]ethyl}piperidine can be prepared in
following way:

0.2 g of sodium hydride at 75% in liquid petr
jelly is added gradually, at a temperature in
region of 20°C, to a solution of 0.46 g of 3-(cycl
2-enyloxy)-5-methyl-4-phenyl-1H-pyrazole in 15 c
dimethylformamide with stirring and under an
atmosphere. After heating for 5 minutes at 50°C, 0
of 1-(2-chloroethyl)piperidine hydrochloride is

can be prepared in the following way:

0.54 cm^3 of 5N sodium hydroxide is added gradually, temperature in the region of 20°C, to a solution, stirring, of 0.8 g of 1-[3-(cyclohex-2-enylox methyl-4-phenylpyrazol-1-yl]ethanone in a mixtur 20 cm^3 of methanol and 20 cm^3 of tetrahydrofuran. stirring for 6 hours at a temperature in the regi 20°C, the reaction mixture is concentrated to dr under reduced pressure (2.7 kPa), and the resid taken up with 100 cm^3 of dichloromethane and 10 c water; the organic phase is separated by settling dried over magnesium sulfate, filtered and concent to dryness under reduced pressure (2.7 kPa) to 0.46 g of 3-(cyclohex-2-enyloxy)-5-methyl-4-pheny pyrazole in the form of a yellow gum [TLC: el cyclohexane/ethyl acetate (70/30 by vol Rf = 0.19]. Mass spectrum (EI) : m/z (254 $M^{+\cdot}$), m/ $[(M-C_6H_8)^{+\cdot}]$.

After concentration of the fractions to dryness
reduced pressure (2.7 kPa), 0.8 g of 1-[3-(cyclohexenyloxy)-5-methyl-4-phenylpyrazol-1-yl]ethanone obtained in the form of a yellow oil [TLC: eluent cyclohexane/ethyl acetate (70/30 by volume) Rf = 0.74]. Mass spectrum (EI): m/z 296 ($M^{+\cdot}$), m/z [$(216-C_2H_2O)^{+\cdot}$].

The 1-(3-hydroxy-5-methyl-4-phenylpyrazol-1-yl)ethanone can be prepared in the following way:

0.85 cm^3 of acetic anhydride is added to a solution of 1.74 g of 5-methyl-4-phenyl-1H-pyrazol-3-ol (CAS 64754-67-2) in 17 cm^3 of pyridine with stirring which has been brought to 100°C. After heating at this temperature for 30 minutes, the reaction medium is cooled to a temperature in the region of 20°C and then poured into 100 cm^3 of a mixture of ice and water. The solution is extracted with 2 times 50 cm^3 of ethyl acetate; the organic phases are pooled, washed with twice 100 cm^3 of water, dried over magnesium sul

reaction medium is then filtered over Superco
filtrate is evaporated under reduced pres
(2.7 kPa). The reaction crude is taken up
dichloromethane and the resulting mixture is wa
successively with a saturated aqueous hydr
carbonate solution, water and a saturated aqu
sodium chloride solution. The aqueous phases are po
and evaporated under reduced pressure (2.7 kPa).
residue obtained is taken up with methanol and
suspension is filtered. After evaporation of
filtrate under reduced pressure (2.7 kPa), the resi
solid is triturated in 3N hydrochloric ethanol.
precipitate formed is filtered off and dried u
vacuum (2.7 kPa) to give 110 mg of 4-(3-aminopheny
(2-dimethylaminoethyl)-1H-pyrazol-3-ol trihydrochlo
in the form of a beige solid.
IR spectrum (KBr): 3432; 2839; 2689; 2586; 1627; 1
1523; 1462; 1178; 786 and 696 cm^{-1}.
^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
(s: 6H); 3.45 (t, J = 6.5 Hz: 2H); 4.41 (t, J = 6.5
2H); 7.10 (broad d, J = 8 Hz: 1H); 7.42 (t, J = 8

(2-bromoethyl)dimethylamine hydrobromide in 50 c
dimethylformamide is added. The reaction mixtur
stirred for 15 h at a temperature in the regio
20°C, and 1.5 h at 50°C, and is then cooled
temperature in the region of 20°C and poured
400 cm^3 of water. The aqueous phase is extracted
with ethyl acetate. The organic phases are po
washed successively with water and a saturated aq
sodium chloride solution, dried over magnesium sul
filtered and evaporated under reduced pre
(2.7 kPa) to give an orange-colored oil whic
purified by flash chromatography on silica unde
argon pressure (50 kPa) [eluent: ethyl acetate,
ethyl acetate/methanol (90/10 by volume)].
concentration of the fractions under reduced pres
1.7 g of {2-[3-benzyloxy-4-(3-nitrophenyl)pyraz
yl]ethyl}dimethylamine are obtained in the form
orange-colored oil. Mass spectrum (EI): m/z 366
m/z 91 ($C_7H_7^+$), m/z 71 ($C_4H_9N^{+\cdot}$), m/z 58 ($C_3H_8N^+$).

successively with water and a saturated aq
chloride solution, dried over magnesium sul
filtered and evaporated under reduced pre
(2.7 kPa) to give an oil which is triturate
diisopropyl ether. The precipitate formed is fil
and dried under vacuum (2.7 kPa) to give 3.47
3-benzyloxy-4-(3-nitrophenyl)-1H-pyrazole in the
of a yellow solid.
^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
(s: 2H); 7.36 (broad t, J = 7.5 Hz: 1H); 7.44 (bro
J = 7.5 Hz: 2H); 7.55 (broad d, J = 7.5 Hz: 2H);
(t, J = 8 Hz: 1H); 8.00 (dd, J = 8 and 2 Hz: 1H);
(broad d, J = 8 Hz: 1H); 8.33 (s: 1H); 8.62 (t,
2 Hz: 1H); from 12.00 to 12.80 (very broad unres
peak: 1H).

The 1-[3-hydroxy-4-(3-nitrophenyl)pyrazol-1-yl]eth
can be prepared in the following way:

A solution of 3.8 g of dimethylammonium
nitrophenyl)-1H-pyrazol-3-olate in 40 cm^3 of pyri

A solution, with stirring, of 9.3 g of benzyl est
3-dimethylamino-2-(3-nitrophenyl)acrylic acid
1.4 cm^3 of hydrazine monohydrate in 100 cm^3 of et
is heated for 3 h at the reflux of the solvent
then cooled in an ice bath. The solid forme
filtered off, washed with water, and dried under v
(2.7 kPa) to give 4.44 g of dimethylammonium
nitrophenyl)-1H-pyrazol-3-olate in the form o
orange-colored solid.
IR spectrum (KBr): 3346; 3199; 3071; 2855; 2685;
1583; 1538; 1469; 1350; 934; 766; 747 and 681 cm^{-1}.

The benzyl ester of 3-dimethylamino-2-(3-nitrophe
acrylic acid can be prepared in the following way:

11.5 cm^3 of C-tert-butoxy-N,N,N',N'-tetramethylmet
diamine is added to a solution of 10 g of benzyl
of 2-(3-nitrophenyl)acrylic acid in 100 cm
tetrahydrofuran and the mixture is heated for 15
the reflux of the solvent. After cooling

N-{3-[3-Hydroxy-1-(2-dimethylaminoethyl)-1H-pyrazol-4-yl]phenyl}acetamide dihydrochloride

1.8 cm^3 of 3N hydrochloric diethyl ether are added to a solution of 400 mg of N-{3-[3-benzyloxy-1-(2-dimethylaminoethyl)-1H-pyrazol-4-yl]phenyl}acetamide in 20 cm^3 of ethanol. After stirring for 15 min at a temperature in the region of 20°C, the solution is evaporated to dryness under reduced pressure (2.7 kPa). The residue is taken up in 20 cm^3 of ethanol and the solution obtained is introduced into an autoclave. 50 mg of palladium-on-charcoal at 10% are added, and the mixture is then placed under hydrogen (5 bar). After stirring for 2 h at a temperature in the region of 20°C, the reaction medium is filtered over supercel and the filtrate is evaporated. The yellow oil obtained (440 mg) is dissolved in 20 cm^3 of ethanol and the mixture again in reaction with 50 mg of palladium-on-charcoal at 10%, under hydrogen (5 bar), at 40°C and with stirring for 4 h. The reaction medium is then fil

pyrazol-4-yl]phenyl}acetamide [illegible]

following way:

0.116 cm^3 of acetyl chloride is added to a soluti
500 mg of 3-[3-benzyloxy-1-(2-dimethylaminoethyl
pyrazol-4-yl]phenylamine and 0.418 cm^3 of triethyl
in 20 cm^3 of dichloromethane under an argon atmos
and with stirring, while maintaining the temperatu
the medium at 5°C. After stirring for 15 h
temperature in the region of 20°C, a further 0.1 c
triethylamine and 0.1 cm^3 of acetyl chloride are
to the reaction mixture and the reaction is cont
for 2 h. The reaction medium is then w
successively twice with water and a saturated aq
sodium chloride solution, dried over magnesium sul
filtered and evaporated under reduced pre
(2.7 kPa) to give 540 mg of N-{3-[3-benzyloxy-
dimethylaminoethyl)-1H-pyrazol-4-yl]phenyl}acetamid
the form of a yellow oil.

settling out, washed successively with water a
saturated aqueous sodium chloride solution, dried
magnesium sulfate, filtered and evaporated
reduced pressure (2.7 kPa) to give 1 g of
benzyloxy-1-(2-dimethylaminoethyl)-1H-pyrazol-4-
yl]phenylamine in the form of an orange-colored
Mass spectrum (EI): m/z 336 ($M^{+\cdot}$), m/z 265 [(M - C_7
m/z 91($C_7H_7^+$), m/z 71($C_4H_9N^{+\cdot}$), m/z 58 ($C_3H_8N^+$).

Example 31

4-(4-Aminophenyl)-1-(2-dimethylaminoethyl)-1H-pyraz
3-ol dihydrochloride

1.2 cm^3 of 3N hydrochloric diethyl ether are added
solution of 250 mg of {2-[3-benzyloxy-4-(4-n
phenyl)pyrazol-1-yl]ethyl}dimethylamine in 20 cu
ethanol. After stirring for 20 minutes at a temper
in the region of 20°C, the solution is evaporate
dryness under reduced pressure (2.7 kPa). The re

The {2-[3-benzyloxy-4-(4-nitrophenyl)pyrazol-1
ethyl}dimethylamine can be prepared in the foll
way:

A solution of 3 g of 3-benzyloxy-4-(4-nitrophenyl
pyrazole in 50 cm^3 of dimethylformamide is added
suspension of 980 mg of sodium hydride (at 7
liquid petroleum jelly) in 50 cm^3 of dimethylform
under an argon atmosphere and with stirring.
heating for 30 min at 50°C, the mixture is stirre
1 h at a temperature in the region of 20°C and is
cooled in an ice bath and a solution of 4.7
(2-bromoethyl)dimethylamine hydrobromide in 50 c
dimethylformamide is added. The reaction mediu
stirred for 15 h at a temperature in the region of
and is then poured into 400 cm^3 of water. The ac
phase is extracted twice with ethyl acetate.
organic phases are pooled, washed successively
water twice and a saturated aqueous sodium chl

hydroxy-4-(4-nitrophenyl)pyrazol-1-yl]ethanone

50 cm^3 of methyl ethyl ketone with stirring. mixture is heated at the reflux of the solvent 2.5 h, cooled to a temperature in the region of and filtered. The filtrate is evaporated under re pressure (2.7 kPa) and the residue is taken up 25 cm^3 of tetrahydrofuran and 25 cm^3 of methanol, 2 cm^3 of 10N sodium hydroxide are then added. stirring for 30 min at a temperature in the regi 20°C, the reaction medium is evaporated under re pressure (2.7 kPa). The reaction crude is taken u dichloromethane. The organic phase is w successively with water and a saturated aqueous s chloride solution, dried over magnesium sul filtered and evaporated under reduced pre (2.7 kPa) to give an oil which is triturate diisopropyl ether. The precipitate formed is filt and dried under vacuum (2.7 kPa) to give 3 3-benzyloxy-4-(4-nitrophenyl)-1H-pyrazole in the of an ochre solid.

of 1-(3-hydroxy-4-(4-nitrophenyl)pyrazol-1-yl)et
in the form of a yellow solid.

IR spectrum (KBr): 3370; 3128; 2980; 2587; 1721;
1600; 1509; 1341; 1224; 1111; 855; 757 and 643 cm^{-1}

The dimethylammonium 4-(4-nitrophenyl)-1H-pyr
3-olate can be prepared in the following way:

A solution, with stirring, of 10.7 g of methyl est
3-dimethylamino-2-(4-nitrophenyl)acrylic acid an
2.1 cm^3 of hydrazine monohydrate in 120 cm^3 of et
is heated for 3 h at the reflux of the solvent,
cooled in an ice bath. The solid formed is filt
rinsed with diisopropyl ether, and dried under v
(2.7 kPa) to give 5 g of dimethylammonium 4-(4-n
phenyl)-1H-pyrazol-3-olate in the form of an or
colored solid.
IR spectrum (KBr): 3188; 3089; 2909; 2728; 2423;
1589; 1567; 1538; 1501; 1345; 1330; 1212; 1112;
880; 761 and 581 cm^{-1}.

IR spectrum (CCl_4): 2949; 1095; 1048; 1219; 1095; 1219; 1095; 1048 and 855 cm^{-1}.

Example 32

1-(2-Dimethylaminoethyl)-4-(4'-fluorobiphenyl-3-yl) pyrazol-3-ol dihydrochloride

1.2 cm^3 of 3N hydrochloric diethyl ether are added solution of 300 mg of {2-[3-benzyloxy-4-(4'-fl biphenyl-3-yl)pyrazol-1-yl]ethyl}dimethylamine in 2 of ethanol. After stirring for 30 min at a temper in the region of 20°C, the solution is evaporat dryness under reduced pressure (2.7 kPa). The re is taken up with 20 cm^3 of ethanol. The sol obtained is introduced into an autoclave and 14 palladium-on-charcoal at 10% are added, and it is placed under hydrogen (7 bar). After stirring fo at 30°C, the reaction medium is filtered over supe and the filtrate is evaporated. Diisopropyl eth added to the residue, resulting in a suspension,

following way:

860 mg of 4-fluorophenylboronic acid, 1.3
potassium phosphate and 330 mg of bis(triph
phosphine)palladium chloride are added to a st
solution of 620 mg of {2-[3-benzyloxy-
bromophenyl)pyrazol-1-yl]ethyl}dimethylamine in
of toluene under an argon atmosphere. After heati
the reflux of the solvent for 15 h, the reaction m
is cooled to a temperature in the region of 20°C,
acetate and water are added, and the mixtur
filtered over supercel. The filtrate is separat
settling out and the organic phase is then w
successively with 0.5N sodium hydroxide, water
saturated aqueous sodium chloride solution; it is
over magnesium sulfate, filtered and evaporated
reduced pressure (2.7 kPa). The brown oil obt
(1.3 g) is purified by flash chromatography on al
CRB1 under an argon pressure (50 kPa) [el
cyclohexane/ethyl acetate (80/20 by volume)].
concentration of the fractions under reduced pres

cooled in an ice bath and a solut
(2-bromoethyl)dimethylamine hydrobromide in 100 c
dimethylformamide is added. The reaction mediu
stirred for 15 h at a temperature in the regi
20°C, and for 3 h at 50°C, and is then cooled
temperature in the region of 20°C and poured int
cm^3 of water. The aqueous phase is extracted twice
ethyl acetate. The organic phases are pooled, w
successively with water twice and a saturated aq
sodium chloride solution, dried over magnesium sul
filtered and evaporated under reduced pressure
kPa) to give an orange-colored oil which is purifi
flash chromatography on silica under an argon pre
(50 kPa) [eluent: ethyl acetate, ethyl acetate/met
(90/10 by volume)]. After concentration of
fractions under reduced pressure, 2.4 g of {
benzyloxy-4-(3-bromophenyl)pyrazol-1-yl]ethyl}dime
amine are obtained in the form of an orange-co
oil.

Mass spectrum (CI): m/z 400 (MH^+), m/z 322
Br + 2H)$^+$].

dichloromethane. The organic phase is
successively with water twice and a saturated aq
sodium chloride solution, dried over magnesium sul
filtered and evaporated under reduced pre
(2.7 kPa) to give an oil which is purified by
chromatography on silica under an argon pre
(50 kPa) [eluent: cyclohexane/ethyl acetate (80/
volume)]. After concentration of the fractions
reduced pressure, 3.3 g of 3-benzyloxy-
bromophenyl)-1H-pyrazole are obtained in the form
cream solid.

^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
(s: 2H); from 7.25 to 7.40 (mt: 3H); 7.42 (broad t
7.5 Hz: 2H); 7.51 (broad d, J = 7.5 Hz: 2H); 7.71
J = 7.5 and 2 Hz: 1H); 7.93 (broad s: 1H); 8.1
1H); 12.25 (unresolved peak: 1H).

The 1-[4-(3-bromophenyl)-3-hydroxypyrazol-1-yl]eth
can be prepared in the following way:

A solution, with stirring, of [illegible] g of methyl
of 2-(3-bromophenyl)-3-dimethylaminoacrylic acid a
2.1 cm^3 of hydrazine monohydrate in 100 cm^3 of et
is heated at the reflux of the solvent for 3 h
reaction mixture is evaporated to dryness under re
pressure (2.7 kPa) and the residue is triturate
diisopropyl ether. The solid formed is filtered a
dried under vacuum (2.7 kPa) to give 5.1
dimethylammonium 4-(3-bromophenyl)-1H-pyrazol-3-
in the form of a cream solid. The filtrat
evaporated under reduced pressure (2.7 kPa),
residue is triturated in diisopropyl ether, and
solid formed is filtered and dried under v
(2.7 kPa), resulting in 4.3 g of 4-(3-bromophenyl
pyrazol-3-ol in the form of a cream solid.
IR spectrum (KBr): 3099; 2768; 2668; 1620; 1590;
1241; 1081; 787; 712 and 689 cm^{-1}.

The methyl ester of 2-(3-bromophenyl)-3-dimethyla
acrylic acid can be prepared in the following way:

4-Biphenyl-3-yl-1-(2-dimethylaminoethyl)-1H-pyrazo
3-ol dihydrochloride

1 cm^3 of 3N hydrochloric diethyl ether is added
solution of 121 mg of {2-[3-benzyloxy-4-biph
3-ylpyrazol-1-yl]ethyl}dimethylamine in 20 cm
ethanol. After stirring for 30 min at a temperatu
the region of 20°C, the solution is evaporate
dryness under reduced pressure (2.7 kPa). The re
is taken up with 20 cm^3 of ethanol. The sol
obtained is introduced into an autoclave, 11 m
palladium-on-charcoal at 10% are added, and it is
placed under hydrogen (7 bar). After stirring fo
at 30°C, the reaction medium is filtered over supe
and the filtrate is evaporated. Diisopropyl eth
added to the residue, resulting in a suspension
is heated at the reflux of the solvent and fil
under hot conditions. The resulting solid is
under vacuum (2.7 kPa) to give 69 mg of 4-biph

330 mg of {2-[3-benzyloxy-1-(3-bromophenyl)pyra
yl]ethyl}dimethylamine in 25 cm^3 of toluene unde
argon atmosphere. After heating at the reflux o
solvent for 15 h, 168 mg of phenylboronic acid, 2
of potassium phosphate and 148 mg of bis(triph
phosphine)palladium chloride are added to the rea
medium and the reaction is continued at the
temperature for 15 h. The mixture is then cooled
temperature in the region of 20°C, ethyl acetate
water are added, and it is filtered over supercel
filtrate is separated by settling out, and the or
phase is then washed successively with 0.5N s
hydroxide, water and a saturated aqueous s
chloride solution; it is dried over magnesium sul
filtered and evaporated under reduced pre
(2.7 kPa). The brown oil obtained (1.2 g) is pur
by flash chromatography on alumina CTB1 under an
pressure (50 kPa) [eluent: cyclohexane/ethyl ac
(80/20 by volume)]. After concentration of
fractions under reduced pressure, 300 mg of an or
colored oil are obtained, which is again used

pyrazol-3-ol dihydrochloride

0.06 cm^3 of 12N hydrochloric acid is added to a sol of 200 mg of {2-[3-benzyloxy-4-(4'-fluorobiph 4-yl)pyrazol-1-yl]ethyl}dimethylamine in 20 cm ethanol. The mixture is introduced into an autoc 28 mg of palladium-on-charcoal at 10% are added, a is then placed under hydrogen (5 bar). After sti for 4 h at 40°C, the reaction medium is filtered supercel and the filtrate is evaporated. The resid triturated in diisopropyl ether. The solid obta dissolved in 20 cm^3 of ethanol, is used again reaction in an autoclave with 10 mg of palladiu charcoal at 10% and under hydrogen (7 bar). stirring for 5 h at 35°C, the reaction mixtur filtered over supercel and the filtrate is evapor The residue is triturated in diisopropyl e filtered and dried under vacuum (2.7 kPa) to give of 1-(2-dimethylaminoethyl)-4-(4'-fluorobiphenyl-4 1H-pyrazol-3-ol dihydrochloride in the form of a solid.

bromophenyl)pyrazol-1-yl]ethyl}dimethylamine in 2
of toluene under an argon atmosphere. After heati
the reflux of the solvent for 15 h, the rea
mixture is cooled to a temperature in the regio
20°C, ethyl acetate and water are added, and i
filtered over supercel. The filtrate is separate
settling out, and the organic phase is then w
successively with 0.5N sodium hydroxide, water a
saturated aqueous sodium chloride solution; it is
over magnesium sulfate, filtered and evaporated
reduced pressure (2.7 kPa). The brown oil obt
(800 mg) is purified by flash chromatography on al
CTB1 under an argon pressure (50 kPa) [el
cyclohexane/ethyl acetate (80/20 by volume)].
concentration of the fractions under reduced pre
(2.7 kPa), 220 mg of {2-[3-benzyloxy-4-(4'-fl
biphenyl-4-yl)pyrazol-1-yl]ethyl}dimethylamine
obtained in the form of a yellow oil.
Mass spectrum (EI): m/z 415 ($M^{+\cdot}$), m/z 344 [
$C_4H_9N)^+$], m/z 91 ($C_7H_7^+$), m/z 58 ($C_3H_8N^+$).

phase is extracted twice with ethyl acetate
organic phases are pooled, washed successively
water twice and a saturated aqueous sodium chl
solution, dried over magnesium sulfate, filtered
evaporated under reduced pressure (2.7 kPa) to g
brown oil which is purified by flash chromatograp
silica under an argon pressure (50 kPa) [eluent:
acetate, ethyl acetate/methanol (90/10 by volu
After concentration of the fractions under re
pressure, 2.3 g of {2-[3-benzyloxy-
bromophenyl)pyrazol-1-yl]ethyl}dimethylamine
obtained in the form of a yellow oil.
Mass spectrum (EI): m/z 399 ($M^{+\cdot}$), m/z 328 [
$C_4H_9N)^+$], m/z 91 ($C_7H_7^{+\cdot}$), m/z 58 ($C_3H_8N^+$).

The 3-benzyloxy-4-(4-bromophenyl)-1H-pyrazole ca
prepared in the following way:

3.88 g of potassium carbonate and 3.1 cm^3 of b
bromide are added to a suspension of 6.58 g de
benzyloxy-4-(4-bromophenyl)pyrazol-1-yl]ethanone

phenyl) in pyridine in the form of a brown
filtrate is evaporated under reduced pressure (2.7
and the residue is taken up with dichloromethane
organic solution is washed with water and a satu
aqueous sodium chloride solution, dried over magn
sulfate, filtered and evaporated under reduced pre
(2.7 kPa). The resulting solid is triturate
diisopropyl ether, filtered and dried under v
(2.7 kPa) to give a further 2.3 g of 3-benzyloxy-
bromophenyl)-1H-pyrazole in the form of a beige sol
^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$ d6, δ in ppm):
(s: 2H); 7.35 (broad t, J = 7.5 Hz: 1H); 7.42 (
t, J = 7.5 Hz: 2H); 7.50 (broad d, J = 7.5 Hz:
7.51 (broad d, J = 8.5 Hz: 2H); 7.65 (broad d,
8.5 Hz: 2H); 8.09 (s: 1H).

The 1-[4-(4-bromophenyl)-3-hydroxypyrazol-1-yl]eth
can be prepared in the following way:

A solution of 6 g of 4-(4-bromophenyl)-1H-pyrazol
in 50 cm^3 of pyridine, under an argon atmosphere

1.9 cm^3 of hydrazine monohydrate in 100 cm^3 of ethan
heated at the reflux of the solvent for 3 h.
reaction mixture is evaporated to dryness under re
pressure (2.7 kPa) and the residue is triturate
diisopropyl ether. The solid formed is filtered a
dried under vacuum (2.7 kPa) to give 6 g of
bromophenyl)-1H-pyrazol-3-ol in the form of a
solid.
IR spectrum (KBr): 3299; 3123; 2958; 2674; 1606;
1517; 1488; 1399; 1163; 1080; 1008; 824 and 509 cm

The ethyl ester of 2-(4-bromophenyl)-3-dimethyla
acrylic acid can be prepared in the following way:

13.5 cm^3 of C-tert-butoxy-N,N,N',N'-tetramethylmet
diamine are added to a solution of 10 g of ethyl
of 2-(4-bromophenyl)acrylic acid in 100 cm
tetrahydrofuran and the mixture is heated at the r
of the solvent for 3 h. After stirring for 15 h
temperature in the region of 20°C, the reaction mi

of dioxane. After boiling for [illegible]
the region of 20°C, the suspension is filtered, an
solid is rinsed once with dioxane and then three
with diisopropyl ether, and is dried under v
(2.7 kPa) to give 55 mg of 1-(2-piperidin-1-ylethy
pyridin-2-yl-1H-pyrazol-3-ol dihydrochloride in
form of a white powder.

IR spectrum (KBr): 3037; 2943; 2644; 2541; 1633;
1577; 1454; 1179; 782 and 685 cm^{-1}.

^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
(mt: 1H); from 1.60 to 1.90 (mt: 5H); 2.95 (mt:
from 3.35 to 3.55 (mt: 4H); 4.57 (t, J = 6.5 Hz:
7.58 (mt: 1H); 8.15 (broad d, J = 7 Hz: 1H);
(broad t, J = 7 Hz: 1H); 8.61 (broad d, J = 5 Hz:
8.69 (broad s: 1H); 10.64 (unresolved peak: 1H).

The 2-[3-(cyclohex-2-enyloxy)-1-(2-piperidin-
ethyl)-1H-pyrazol-4-yl]pyridine can be prepared i
following way:

cyclohexane/ethyl acetate (90/10 by volume)].
concentration of the fractions under reduced pres
1.6 g of 2-[3-(cyclohex-2-enyloxy)-1-(2-piper
1-ylethyl)-1H-pyrazol-4-yl]pyridine are obtained i
form of a pale yellow oil.
Mass spectrum (EI): m/z 352 ($M^{+\cdot}$), m/z 271 [(M - C_6
m/z 111 ($C_7H_{13}N^{+\cdot}$), m/z 98 ($C_6H_{12}N^{+}$).

The 2-[3-(cyclohex-2-enyloxy)-1H-pyrazol-4-yl]pyr
can be prepared in the following way:

5.4 g of potassium carbonate and 4.6 cm^3
3-bromocyclohexene are added to a suspension of
of 1-(3-hydroxy-4-pyridin-2-ylpyrazol-1-yl)ethanon
70 cm^3 of methyl ethyl ketone with stirring.
mixture is heated at the reflux of the solvent for
cooled to a temperature in the region of 20°C,
evaporated under reduced pressure (2.7 kPa).
residue is taken up with 50 cm^3 of tetrahydrofura
50 cm^3 of methanol, and 7 cm^3 of 5N sodium hydroxide

In 70 cm of pyridine is heated to 10
acetic anhydride are then added dropwise. After he
at 100°C for 1.5 h, the reaction medium is cooled
temperature in the region of 20°C and is poured
150 cm^3 of ice-cold water. The precipitate form
filtered, washed three times with water and dried
vacuum (2.7 kPa) to give 7.1 g of 1-(3-hydr
pyridin-2-ylpyrazol-1-yl)ethanone in the form of a
yellow solid.
IR spectrum (KBr): 3157; 2396; 1719; 1608; 1391;
1223; 1000; 929; 790 and 618 cm^{-1}.

The 4-pyridin-2-yl-1H-pyrazol-3-ol hydrochloride
prepared in the following way:

A solution, with stirring, of 18 g of ethyl est
3-dimethylamino-2-pyridin-2-ylacrylic acid and
3.95 cm^3 of hydrazine monohydrate in 120 cm^3 of et
is heated at the reflux of the solvent for 3 h
reaction mixture is concentrated under reduced pre
(2.7 kPa), 3N hydrochloric ethanol is added, an

The resulting brown oil is purified by chromatography on silica under an argon pre (50 kPa) [eluent: cyclohexane/ethyl acetate (90/ volume)]. After concentration of the fractions reduced pressure, 18 g of ethyl ester 3-dimethylamino-2-pyridin-2-ylacrylic acid are obt in the form of an orange-colored oil.

IR spectrum (CCl_4): 2980; 2929; 1686; 1619; 1602; 1271; 1219; 1096 and 1085 cm^{-1}.

Example 36

1-(2-Piperidin-1-ylethyl)-4-pyridin-4-yl-1H-pyrazol ol dihydrochloride monohydrate

7 cm^3 of 12N hydrochloric acid are added to a st solution of 720 mg of 4-[3-benzyloxy-1-(2-piperid ylethyl)-1H-pyrazol-4-yl]pyridine in 7 cm^3 of eth After 7 h at the reflux of the solvent, and then at a temperature in the region of 20°C, the rea medium is evaporated under reduced pressure (2.7

7 Hz: 2H); 11.75 (unresolved peak: 1H).

The 4-[3-benzyloxy-1-(2-piperidin-1-ylethyl pyrazol-4-yl]pyridine can be prepared in the foll way:

A solution of 720 mg of 4-(3-benzyloxy-1H-pyraz yl)pyridine in 20 cm^3 of dimethylformamide is added suspension of 230 mg of sodium hydride (at 75 liquid petroleum jelly) in 10 cm^3 of dimethylform under an argon atmosphere and with stirring. heating at 50°C for 30 min, the mixture is stirre 30 min at a temperature in the region of 20°C, solution of 740 mg of 1-(2-chloroethyl)piper hydrochloride is then added. The reaction mediu stirred for 15 h at a temperature in the region of and is then poured into water. The aqueous pha extracted twice with ethyl acetate. The organic p are pooled, washed successively with water a saturated aqueous sodium chloride solution, dried

hydroxy-4-pyridin-4-ylpyrazol-1-yl)ethanone in 25
methyl ethyl ketone with stirring. The mixtur
heated at the reflux of the solvent for 3 h, cool
a temperature in the region of 20°C, and filtered
filtrate is evaporated under reduced pre
(2.7 kPa). The resulting brown oil is purified by
chromatography on silica under an argon pre
(50 kPa) [eluent: ethyl acetate/cyclohexane (80/
volume)]. After concentration of the fractions
reduced pressure, 720 mg of 4-(3-benzyloxy-1H-pyr
4-yl)pyridine are obtained in the form of a
solid.

^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
(s: 2H); 7.36 (tt, J = 7.5 and 1.5 Hz: 1H); 7.44 (
= 7.5 and 1.5 Hz: 2H); 7.52 (broad d, J = 7.5 Hz:
7.66 (dd, J = 5 and 2 Hz: 2H); 8.33 (s: 1H); 8.47
J = 5 and 2 Hz: 2H); from 12.25 to 12.50 (unres
peak: 1H).

The 1-(3-hydroxy-4-pyridin-4-ylpyrazol-1-yl)eth
can be prepared in the following way:

2.75 cm³ of hydrazine monohydrate in 30 cm³ of ethan
heated at the reflux of the solvent for 3 h.
reaction mixture is cooled in an ice bath, and
solid formed is filtered off and taken up with w
The suspension is adjusted to pH 6 with 1N hydroch
acid and is then filtered. The solid obtained is w
with water and is dried under vacuum (2.7 kPa) to
5.1 g of 4-pyridin-4-yl-1H-pyrazol-3-ol hydrochl
in the form of a yellow solid.
IR spectrum (KBr): 3355; 2464; 2059; 1965; 1637;
1527; 1207; 1193; 1075; 1022; 914; 838 and 519 cm^{-1}

The ethyl ester of 3-dimethylamino-2-pyridin-
acrylic acid can be prepared in the following way:

24 cm^3 of C-tert-butoxy-N,N,N',N'-tetramethylmet
diamine are added to a solution of 15 cm^3 of ethyl
of 2-pyridin-4-ylacrylic acid in 100 cm^3
tetrahydrofuran and heating is carried out at
reflux of the solvent for 15 h, and the rea
mixture is then evaporated to dryness under re

pyrazol-3-ol

0.5 g of 3-benzyloxy-4-(4-fluorophenyl)-1-(2-piper
1-ylethyl)-1H-pyrazole hydrochloride is introduced
an autoclave with 12.8 mg of palladium-on-charcoa
10%) and 25 cm^3 of ethanol. The device is placed un
hydrogen pressure of 500 kPa at a temperature of
for 5 hours. After cooling to a temperature in
region of 20°C, the reaction medium is filtered
supercel; the filtrate is washed with 3 times 100 c
ethanol, and concentrated to dryness under re
pressure (2 kPa). The residue obtained is purifie
chromatography, under a nitrogen pressure of 50 kP
a column of silica gel (particle size 20-45 µ; dia
1 cm; height 25 cm), eluting with a mixture
dichloromethane and of a 2N solution of ammon
methanol (93/7 by volume). Concentration is perf
under reduced pressure (2 kPa); 160 mg of 4-(4-fl
phenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol
obtained in the form of a white solid.

temperature of the reaction medium, for 14 hours. cooling, 30 cm^3 of a saturated sodium hydrogen carb solution are added to the mixture, which is extr with 30 cm^3 of ethyl acetate. The organic phase is over magnesium sulfate, filtered and concentrat dryness under reduced pressure (3 kPa). The resid purified by chromatography on silica gel, eluting a mixture of ethyl acetate and methanol (30, volume). After concentration of the fractions reduced pressure, 0.57 g of a yellowish oi obtained, which is used as it is in the following 0.57 g of 3-benzyloxy-4-(4-fluorophenyl)- piperidin-1-ylethyl)-1H-pyrazole is taken up with of diethyl ether and 0.5 cm^3 of a 4N soluti hydrochloric acid in diethyl ether. The precip formed is filtered over dried. 0.5 g of 3-benzylo (4-fluorophenyl)-1-(2-piperidin-1-ylethyl)-1H-pyra is obtained. 1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6 ppm): from 1.25 to 1.50 (mt: 1H); from 1.60 to (mt: 5H); 2.91 (mt: 2H); 3.44 (very broad d, J = Hz: 2H); 3.52 (mt: 2H); 4.47 (broad t, J = 6.5 Hz

stirring for 21 hours at ambient temperature, excess sodium hydride is destroyed by slowly a water, and the reaction medium is then run into 1 (water and extracted with 2 times 200 cm^3 of acetate. The pooled organic phases are dried magnesium sulfate, filtered and concentrated to dr under reduced pressure (3 kPa). The oily re obtained is taken up with 20 cm^3 of acetone and rur a solution of 3.6 g of oxalic acid in 30 cm^3 of ace The solid formed is triturated and then isolat filtration and dried at ambient temperature, to 11.3 g of 3-benzyloxy-4-bromo-1-(2-piperid ylethyl)-1H-pyrazole oxalate. 50 cm^3 of a satu sodium hydrogen carbonate solution are added to 5 this oxalate and the mixture is extracted 2 × 100 cm^3 of ethyl acetate. The pooled organic p are dried over magnesium sulfate, filtered concentrated to dryness under reduced pressure (3 3.84 g of 3-benzyloxy-4-bromo-1-(2-piperid ylethyl)-1H-pyrazole are thus obtained in the form light oil.

by settling out. The organic phase is extracted
with 50 cm^3 of water and the organic phases are p
and dried over magnesium sulfate, filtered
concentrated to dryness under reduced pressure (3
The oily residue obtained is taken up with 10 cm^3
hydrochloric dioxane and the solid formed is tritu
in ethyl ether and isolated by filtration. 12.5
3-benzyloxy-4-bromo-1H-pyrazole are thus obtaine
the form of a white solid which melts at around
(with decomposition).
Mass spectrum (EI): m/z 252 ($M^{+\cdot}$), m/z 91 (base peal
^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
(s: 2H); from 7.30 to 7.50 (mt: 5H); 7.81 (s: 1H);
11.80 to 12.70 (very broad unresolved peak: 1H).

The 3-benzyloxy-1H-pyrazole can be prepared in
following way:

50 cm^3 of a saturated sodium hydrogen carbonate sol
are added to 10.6 g of 3-benzyloxy-1H-pyr

to dryness under reduced pressure (3 kPa). The
residue obtained is dissolved in a mixture of 150 c
tetrahydrofuran and 100 cm^3 of methanol, and 4 cm^3
10M sodium hydroxide solution are then added the
After stirring for 0.65 hour at ambient tempera
the mixture is concentrated to dryness under re
pressure (3 kPa). The pasty residue obtained is
up with 250 cm^3 of ethyl acetate and washed with 2
10 cm^3 of brine. The organic phase is dried
magnesium sulfate, filtered and concentrated
reduced pressure (3 kPa). 100 cm^3 of 1N hydroch
ether are added to the residue and the solid form
triturated and then isolated by filtration. The
is solubilized in 250 cm^3 of isopropanol at around
and the mixture is then partially concentrated
the first crystals appear, 5 cm^3 isopropyl acetat
added, and the mixture is cooled to around 0°C.
filtration and drying, 10.6 g of 3-benzylox
pyrazole hydrochloride are obtained in the for
salmon-pink crystals which melt at 100°C.

215°C.

^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): (s: 3H); 6.02 (d, J = 3 Hz: 1H); 8.15 (d, J = 1H); from 10.80 to 11.20 (unresolved peak: 1H).

Example 38

4-(4-Trifluoromethoxyphenyl)-1-(2-piperidin-1-yleth 1H-pyrazol-3-ol dihydrochloride

600 mg of 3-benzyloxy-4-(4-trifluoromethoxypheny (2-piperidin-1-ylethyl)-1H-pyrazole in 4.5 cm^3 ethanol and 4.5 cm^3 of 12N hydrochloric acid are br to reflux at a temperature in the region of 100° 7 hours. After cooling to a temperature in the r of 20°C, the reaction medium is concentrated to dr under reduced pressure (2 kPa); the residu precipitated from a mixture of diisopropyl ethe acetone. 464 mg of 4-(4-trifluoromethoxyphenyl)-

hydride at 75% in liquid petroleum jelly are
portionwise to the reaction medium and the temper
is allowed to return to approximately 20°C. 431
1-(2-chloroethyl)piperidine hydrochloride are
added and the stirring is maintained at
temperature for 15 hours. The reaction medium is
up with 300 cm^3 of ice-cold water and 300 cm^3 of
acetate. The organic phase is separated by set
out, washed with 200 cm^3 of water and concentrat
dryness under reduced pressure (2 kPa). The resid
purified on an FC50SI-HP silica cartridge, eluting
a mixture of dichloromethane and methanol (95/
volume). The product obtained is again purified
FC50SI-HP silica cartridge, eluting with a mixtu
dichloromethane and methanol (98/2 by volume). 6
of 3-benzyloxy-4-(4-trifluoromethoxyphenyl)-
piperidin-1-ylethyl)-1H-pyrazole are obtained in
form of a colorless oil. Mass spectrum (CI): m/
($[M+H]^+$) (base peak).

m/z 91 (base peak).

The 3-benzyloxy-1-(toluene-4-sulfonyl)-4-(4-trifl
methoxyphenyl)-1H-pyrazole can be prepared in
following way:

2.04 g of 4-trifluoromethoxyphenylboronic acid, 4.9
of a 2N aqueous potassium carbonate solution and 4
of tetrakis(triphenylphosphine)palladium are added
solution of 1.5 g of 3-benzyloxy-4-iodo-1-(tolue
sulfonyl)-1H-pyrazole in a mixture of 40 cm^3 of to
and ethanol (4/1 by volume) in a three-necked f
The three-necked flask containing the reaction m
is placed in a bath preheated to a temperature i
region of 120°C; the stirring is continued fo
minutes at this temperature. The mixture is then c
to a temperature in the region of 20°C, and fil
over supercel. The filtrate is taken up with 300 c
ethyl acetate and 100 cm^3 of water. The organic pha
separated by settling out and concentrated to dr

are then added and the stirring is maintained at
temperature for 15 hours. The reaction medium is
up with 300 cm^3 of ice-cold water and 500 cm^3 of
acetate. The organic phase is separated by set
out, washed with 300 cm^3 of water and 300 cm^3
saturated aqueous sodium chloride solution, dried
anhydrous magnesium sulfate, filtered and concent
to dryness under reduced pressure (2 kPa). The re
is crystallized from diisopropyl ether. 7.24
3-benzyloxy-4-iodo-1-(toluene-4-sulfonyl)-1H-pyrazo
are obtained in the form of a powder. Mass spe
(EI): m/z 454 ($M^{+\cdot}$), m/z 299, m/z 91 (base peak).

The 3-benzyloxy-4-iodo-1H-pyrazole can be prepar
the following way:

A suspension of 0.32 g of 3-benzyloxy-1H-pyra
0.3 g of sodium acetate and 0.65 g of iodine in 5
of chloroform is stirred at ambient temperature
26 hours. 50 cm^3 of a 0.5N sodium thiosulfate sol

(s: 2H); from 7.30 to 7.50 (mt: 5H); 7.71 (s: 1H); 12.20 to 12.60 (broad unresolved peak: 1H).

Example 39

4-Phenyl-1-(2-piperidin-1-ylpropyl)-1H-pyrazol-3-ol dihydrochloride

2 cm^3 of a 4N solution of hydrochloric acid in di are added, at a temperature in the region of 20°C, mixture of 150 mg of 1-{2-[3-(cyclohex-2-enylox phenylpyrazol-1-yl]-1-methylethyl}piperidine in 5 c anhydrous methanol. The reaction medium is stirre this temperature for 20 hours, concentrated to dr under reduced pressure (2 kPa), and taken up with 2 of dichloromethane. The solution is concentrate dryness under reduced pressure (2 kPa). The residu precipitated with 20 cm^3 of diisopropyl ether. 110 4-phenyl-1-(2-piperidin-1-ylpropyl)-1H-pyrazol-3-ol dihydrochloride are obtained in the form of a y solid.

methylethyl ester, 0.4 cm³ of piperidine and 1.
potassium carbonate in 20 cm³ of dimethylformami
heated while stirring at a temperature in the regi
80°C for 6 hours and then for 15 hours at a temper
in the region of 20°C. The reaction medium is tak
with 100 cm³ of water and 100 cm³ of ethyl acetate
organic phase is separated by settling out, washed
2 times 100 cm³ of water and 100 cm³ of a satu
aqueous sodium chloride solution, dried over anhy
magnesium sulfate, filtered and concentrated to dr
under reduced pressure (2 kPa). The residue is pur
by chromatography, under a nitrogen pressure of 50
on a column of silica gel (particle size 20-4
diameter 2 cm; height 40 cm), eluting with a mixtu
cyclohexane and ethyl acetate (80/20 by volume).
concentration of the fractions under reduced pre
(2 kPa), 150 mg of 1-{2-[3-(cyclohex-2-enylox
phenylpyrazol-1-yl]-1-methylethyl}piperidine
obtained in the form of a yellow oil. Mass spe
(EI): m/z 365 ($M^{+\cdot}$), m/z 112 (base peak).

4 cm; height 60 cm), eluting with a mixtu
cyclohexane and ethyl acetate (80/20 by volume).
concentration of the fractions under reduced pre
(2 kPa), 300 mg of methanesulfonic acid 2-[3-(cycl
2-enyloxy)-4-phenylpyrazol-1-yl]-1-methylethyl
are obtained in the form of a colorless oil.
spectrum (EI): m/z 376 ($M^{+\cdot}$), m/z 296 (base peak).

The 1-[3-(cyclohex-2-enyloxy)-4-phenylpyrazol-1
propan-2-ol can be prepared in the following way:

2.4 g of 3-(cyclohex-2-enyloxy)-4-phenyl-1H-pyr
are dissolved in 25 cm^3 of anhydrous dimethylform
under an inert atmosphere and with stirring. 2.24
potassium tert-butoxide, followed by 0.7 cm
methyloxirane are added at a temperature in the r
of 20°C. The reaction medium is heated at a temper
in the region of 60°C for 1 hour. A further 0.7 c
methyloxirane is then added and the mixture is h
for 1 hour at a temperature in the region of 60°C
mixture is cooled to a temperature in the regi

Example 40

3-(4-Phenylpyrazol-1-ylmethyl)-1-aza-bicyclo[2.2.2]
octane dihydrochloride

A solution of 0.4 g of 3-(pyrazol-1-ylmethy
azabicyclo[2.2.2]octane in 5 cm^3 of dimethylformami
added to a mixture of 0.4 g of sodium hydride at 7
liquid petroleum jelly and of 10 cm^3 of dime
formamide. The reaction medium is heated
temperature in the region of 50°C for approxim
1 hour, and the solution is then cooled
temperature in the region of 20°C. 1.75 g of 3-ch
methylquinuclidine are added slowly, and the rea
medium is heated at a temperature in the region of
for 16 hours and then cooled to a temperature i
region of 20°C. The mixture is taken up with 100
water and 100 cm^3 of ethyl acetate. The organic pha
separated by settling out, washed with 2 times 10
of water and 100 cm^3 of a saturated aqueous s
chloride solution, and then concentrated to dr

solution of hydrochloric acid in isopropyl ether
cm^3 of ethanol. 230 mg of 3-(4-phenylpyrazol-
methyl)-1-azabicyclo[2.2.2]octane dihydrochloride
obtained.
^1H NMR spectrum (300 MHz, (CD3)2SO d6, δ in ppm):
1.65 to 1.95 (mt: 4H); from 2.00 to 2.15 (mt: 1H);
(mt: 1H); 2.97 (broad dd, J = 13 and 7 Hz: 1H);
3.10 to 3.40 (mt: 5H); 4.25 (dd, J = 13 and 8 Hz:
4.32 (dd, J = 13 and 8 Hz: 1H); 7.21 (broad t
7.5 Hz: 1H); 7.38 (t, J = 7.5 Hz: 2H); 7.59 (broad
= 7.5 Hz: 2H); 7.94 (s: 1H); 8.25 (s: 1H);
(unresolved peak: 1H). Mass spectrum (EI): m/z 267
(base peak), m/z 183, m/z 123.

The 4-phenyl-1H-pyrazole can be prepared in
following way:

1.044 g of 4-phenyl-1-(toluene-4-sulfonyl)-1H-pyra
7 cm^3 of a 1N solution of n-tetrabutylammonium flu
in tetrahydrofuran and 35 cm^3 of tetrahydrofura
heated at a temperature in the region of 70°C

The 4-phenyl-1-(toluene-4-sulfonyl) in pyrazole c
prepared in the following way:

11.72 g of phenylboronic acid are added to a st
solution of 8.7 g of 4-iodo-1-(toluene-4-sulfonyl
pyrazole in 200 cm^3 of 1,2-dimethoxyethane unde
inert atmosphere. The reaction medium is heate
110°C and then 20.63 g of finely ground tri
potassium phosphate and 2.18 g of bis(triph
phosphine)palladium chloride are added; the mixtu
heated at the reflux of the solvent for 3 hour
then cooled to a temperature in the region of 20°
then filtered over supercel. The filtrate is tak
with 250 cm^3 of ethyl acetate and washed with 8
100 cm^3 of water and 100 cm^3 of a saturated aq
sodium chloride solution. The organic phase
separated by settling out, dried over anhy
magnesium sulfate, filtered and concentrated to dr
under reduced pressure (2 kPa). The residue is pur
by chromatography, under a nitrogen pressure of 50
on a column of silica gel (particle size 20-4

toluenesulfonyl chloride are then added and
stirring is maintained for 3 hours at this tempera
The reaction medium is taken up with 100 g of ic
then 700 cm^3 of water and 700 cm^3 of ethyl acetate
organic phase is separated by settling out, washed
9 times 300 cm^3 of water and 2 times 100 cm^3
aqueous sodium chloride solution, dried over anhy
magnesium sulfate, filtered and then concentrated
reduced pressure (2 kPa). The residue is recrystal
from 1 000 cm^3 of diisopropyl ether. 10.9 g of 4-io
(toluene-4-sulfonyl)-1H-pyrazole are obtained in
form of white crystals. Mass spectrum (EI): m/z
($M^{+\cdot}$), m/z 284, m/z 91 (base peak).

Example 41

4-(5-Chlorothiophen-2-yl)-1-(2-piperidin-1-ylethyl)
pyrazol-3-ol hydrochloride

The product is prepared according to the proc
described for the preparation of 4-(4-trifl

The 3-benzyloxy-4-(5-chlorothiophen-2-yl)-1-(2-piperidin-1-ylethyl)-1H-pyrazole can be prepared i following way:

The product is prepared according to the proc described for the preparation of 3-benzyloxy- trifluoromethoxyphenyl)-1-(2-piperidin-1-ylethyl)-1 pyrazole, using 345 mg of 3-benzyloxy- chlorothiophen-2-yl)-1H-pyrazole, 100 mg of s hydride at 75% in liquid petroleum jelly, 305 m 1-(2-chloroethyl)piperidine and 10 cm^3 of anhy dimethylformamide. After purification on an FC50 silica cartridge, eluting with a mixture dichloromethane and methanol (95/5 by volume), 4 of the expected product are obtained in the form orange-colored oil. Mass spectrum (CI): m/z 402 ([M (base peak).

The 3-benzyloxy-4-(5-chlorothiophen-2-yl)-1H-pyr can be prepared in the following way:

389 mg of 2-bromo-5-chlorothiophene, 32.5 mg
tris(trifuryl)phosphine and 34.7 mg of tri
benzylideneacetone)dipalladium are added, with sti
and under an inert atmosphere, to a solution of
of 3-benzyloxy-1-(toluene-4-sulfonyl)-4-trib
stannanyl-1H-pyrazole in 20 cm^3 of dioxane. The rea
medium is heated at a temperature in the regio
100°C for 15 hours. The mixture is then cooled
temperature in the region of 20°C, and filtered
supercel. The filtrate is concentrated to dryness
reduced pressure (2 kPa), and taken up
cyclohexane; the insoluble material is filtered
over sintered glass, and the filtrate is concent
to dryness under reduced pressure (2 kPa); the re
obtained is purified on an FC50SI-HP silica cartr
eluting with a mixture of cyclohexane and ethyl ac
(90/10 by volume). 200 mg of 3-benzyloxy-
chlorothiophen-2-yl)-1-(toluene-4-sulfonyl)-1H-pyra
are obtained in the form of a yellow powder.
spectrum (EI): m/z 444 ($M^{+\cdot}$), m/z 289 and m/z 91
peak).

anhydrous magnesium sulfate, filtered and concent
to dryness under reduced pressure (2 kPa). The re
is purified by chromatography, under a nit
pressure of 50 kPa, on a column of silica gel (par
size 20-45 µ; diameter 2 cm; height 40 cm), el
with a mixture of cyclohexane and ethyl acetate
by volume). 4.5 g of 3-benzyloxy-1-(toluе
sulfonyl)-4-tributylstannanyl-1H-pyrazole are obt
in the form of a yellow oil. Mass spectrum (EI)
618 ($M^{+\cdot}$), m/z 561 (base peak).

Example 42

4-(3-Methoxyphenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol hydrochloride

The product is prepared according to the proc
described for the preparation of 4-(4-trifluoro
oxyphenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-o
using 760 mg of 3-benzyloxy-4-(3-methoxyphenyl)-
piperidin-1-ylethyl)-1H-pyrazole, 6.5 cm^3 of

The product is prepared according to the proc
described for the preparation of 3-benzyloxy-
trifluoromethoxyphenyl)-1-(2-piperidin-1-ylethyl)-
pyrazole, using 590 mg of 3-benzyloxy-
methoxyphenyl)-1H-pyrazole, 176 mg of sodium hydri
75% in liquid petroleum jelly, 542 mg of
chloroethyl)piperidine and 10 cm^3 of anhy
dimethylformamide. After purification on an FC5(
silica cartridge, eluting with a mixture
dichloromethane and methanol (98/2 by volume), 7
of the expected product are obtained in the form
colorless oil. Mass spectrum (EI): m/z 391 ($M^{+\cdot}$), m
(base peak).

The 3-benzyloxy-4-(3-methoxyphenyl)-1H-pyrazole c
prepared in the following way:

The product is prepared according to the proc
described for the preparation of 3-benzyloxy-
trifluoromethoxyphenyl)-1H-pyrazole, using 1.32

pyrazole, using 1.5 g of 3-benzyloxy-4-iodo-1-(tol
4-sulfonyl)-1H-pyrazole, 1.5 g of 3-methoxyph
boronic acid, 496 mg of tetrakis(triphenylphosph
palladium, and 496 cm^3 of a 2N aqueous solutic
potassium carbonate in a mixture of 30 cm^3 of to
and ethanol (4/1 by volume). After purification
FC50SI-HP silica cartridge, eluting with a mixtu
cyclohexane and ethyl acetate (90/10 by volume), 1
of the expected product are obtained in the fo
pale yellow crystals. Mass spectrum (EI): m/z 434
m/z 279 and m/z 91 (base peak).

Example 43

4-(2-Methoxyphenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol hydrochloride

The product is prepared according to the proc
described for the preparation of 4-(4-trifluorometh
phenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol,
using 450 mg of 3-benzyloxy-4-(2-methoxyphenyl)-

The 3-benzyloxy-1-(2-methoxyphenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazole can be prepared in the following way:

The product is prepared according to the procedure described for the preparation of 3-benzyloxy-4-(2-trifluoromethoxyphenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazole, using 382 mg of 3-benzyloxy-4-(2-methoxyphenyl)-1H-pyrazole, 114 mg of sodium hydride at 70% in liquid petroleum jelly, 351 mg of 1-(2-chloroethyl)-piperidine and 11 cm^3 of anhydrous dimethylformamide. After purification on an FC50SI-HP silica cartridge eluting with a mixture of dichloromethane and methanol (95/5 by volume), 450 mg of the expected product are obtained in the form of a pale yellow oil. Mass spectrum (EI): m/z 391 ($M^{+\cdot}$), m/z 98 (base peak).

The 3-benzyloxy-4-(2-methoxyphenyl)-1H-pyrazole can be prepared in the following way:

described for the preparation of 3-benzylo
(toluene-4-sulfonyl)-4-(4-trifluoromethoxyphenyl)-1
pyrazole, using 1 g of 3-benzyloxy-4-iodo-1-(tolue
sulfonyl)-1H-pyrazole, 1 g of 2-methoxyphenylbo
acid, 330 mg of tetrakis(triphenylphosphine)palla
and 3.3 cm^3 of a 2N aqueous solution of pota
carbonate in a mixture of 15 cm^3 of toluene and et
(4/1 by volume). After purification on an FC50
silica cartridge, eluting with a mixture of cycloh
and ethyl acetate (80/20 by volume), 720 mg of
expected product are obtained in the form of a
powder. Mass spectrum (CI): m/z 435 ([M+H]+) and
281 (base peak).

Example 44

4-(3-Hydroxyphenyl)-1-(2-piperidin-1-ylethyl)-1H-
pyrazol-3-ol hydrochloride

hydrochloric acid and 5 cm³ of dioxane. The mixtu
stirred for 10 minutes and is then concentrate
dryness under reduced pressure (2 kPa). 198 mg of
hydroxyphenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol
ol hydrochloride are obtained in the form of an
colored powder.

^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
1.25 to 1.50 (mt: 1H); from 1.60 to 1.90 (mt: 5H);
(mt: 2H); from 3.30 to 3.55 (mt: 4H); 4.40 (t,
6.5 Hz: 2H); 6.55 (ddd, J = 8-3 and 1.5 Hz: 1H);
7.00 to 7.15 (mt: 3H); 8.06 (s: 1H); from 9.10 to
(broad unresolved peak: 1H); from 9.90 to
(unresolved peak: 1H); from 10.30 to 10.45 (unres
peak: 1H). Mass spectrum (EI): m/z 287 (M+.), m/
(base peak).

Example 45

4-(4-Hydroxyphenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol hydrochloride

pressure (2 kPa). The white powder obtained is tak
with 300 µl of 12N hydrochloric acid and 5 c
dioxane. The mixture is stirred for 10 minutes and
concentrated to dryness under reduced pressure (2
101 mg of 4-(4-hydroxyphenyl)-1-(2-piperid
ylethyl)-1H-pyrazol-3-ol hydrochloride are obtain
the form of an ecru-colored powder.
^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
1.25 to 1.50 (mt: 1H); from 1.60 to 1.90 (mt: 5H);
(mt: 2H); from 3.30 to 3.50 (mt: 4H); 4.38 (t,
6.5 Hz: 2H); 6.75 (broad d, J = 8.5 Hz: 2H);
(broad d, J = 8.5 Hz: 2H); 7.85 (s: 1H); from 9.
9.35 (broad unresolved peak: 1H); from 10.00 to
(unresolved peak: 1H); from 10.15 to 10.30 (unres
peak: 1H).
Mass spectrum (EI): m/z 287 (M+.), m/z 98 (base pea

Example 46

reflux of the solvent and filtered under v
conditions. The resulting solid is dried under v
(2.7 kPa) to give 400 mg of 4-(4-methoxyphenyl)-
piperidin-1-ylethyl)-1H-pyrazol-3-ol dihydrochlori
the form of a white powder.
IR spectrum (KBr): 3052; 2933; 2655; 2559; 1578;
1518; 1501; 1453; 1248; 1170; 1020; 837; 810; 65
528 cm^{-1}.
^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
1.30 to 1.50 (mt: 1H); from 1.60 to 1.90 (mt: 5H);
2.80 to 3.05 (mt: 2H); 3.46 (mt: 4H); 3.76 (s:
4.37 (broad t, J = 6 Hz: 2H); 6.93 (d, J = 8.5 Hz:
7.57 (d, J = 8.5 Hz: 2H); 7.92 (broad s: 1H); from
to 9.95 (broad unresolved peak: 1H); 10.32 (broa
1H).

The 1-{2-[3-benzyloxy-4-(4-methoxyphenyl)pyraz
yl]ethyl}piperidine can be prepared in the foll
way:

(90/10 by volume)]. After concentration of fractions under reduced pressure (2.7 kPa), 700 1-{2-[3-benzyloxy-4-(4-methoxyphenyl)pyrazol-1-yl]ethyl}piperidine are obtained in the form yellow oil.

Mass spectrum (EI): m/z 391 ($M^{+\cdot}$), m/z 280 [$C_7H_{13}N)^{+\cdot}$], m/z 111 ($C_7H_{13}N^{+\cdot}$), m/z 98 ($C_6H_{12}N^{+}$), 91 ($C_7H_7^{+}$).

Example 47

4-(3-Fluorophenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol dihydrochloride

3.5 cm^3 of 12N hydrochloric acid are added to a st solution of 400 mg of 1-{2-[3-benzyloxy-fluorophenyl)pyrazol-1-yl]ethyl}piperidine in 3.5 ethanol. After 7 h at the reflux of the solvent, then 15 h at a temperature in the region of 20°C reaction medium is evaporated to dryness under re

ethyl]piperidine can be prepared in the following

1.15 g of 3-fluorophenylboronic acid, 4.1 cm^3 of aqueous potassium carbonate solution and 475 m tetrakis(triphenylphosphine)palladium are added stirred solution, under an argon atmosphere, of 1 1-[2-(3-benzyloxy-4-bromopyrazol-1-yl)ethyl]piperid in a mixture of 20 cm^3 of toluene and of 5 c ethanol. After heating at the reflux of the solven 3 h and at a temperature in the region of 20°C 15 h, ethyl acetate and water are added to the rea medium, which is filtered over supercel. The fil is separated by settling out, and the organic pha then washed successively with 2 times water a saturated aqueous sodium chloride solution; it is over magnesium sulfate, filtered and evaporated reduced pressure (2.7 kPa). The brown oil obt (2.1 g) is purifed by flash chromatography on s under an argon pressure (50 kPa) [eluent: acetate]. After concentration of the fractions reduced pressure, 400 mg of 1-{2-[3-benzyloxy-

(2.7 kPa) at 45°C for 1 h, and is then triturat
diisopropyl ether. The precipitate formed is fil
and dried under vacuum (2.7 kPa) to give 350 m
1-(2-piperidin-1-ylethyl)-4-(3-trifluoromethylpheny
1H-pyrazol-3-ol dihydrochloride in the form of a
yellow solid.
IR spectrum (KBr): 2955; 2629; 2533; 1619; 1533;
1188; 1170; 1117; 1076; 800; 696 and 688 cm^{-1}.
^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
(mt: 1H); from 1.60 to 1.90 (mt: 5H); 2.94 (mt:
from 3.30 to 3.55 (mt: 4H); 4.43 (t, J = 6.5 Hz:
7.50 (broad d, J = 7.5 Hz: 1H); 7.59 (t, J = 7.5
1H); 7.95 (broad d, J = 7.5 Hz: 1H); 8.01 (broa
1H); 8.22 (s: 1H); 10.24 (unresolved peak: 1H);
10.60 to 10.90 (broad unresolved peak: 1H).

The 1-{2-[3-benzyloxy-4-(3-trifluoromethylphe
pyrazol-1-yl]ethyl}piperidine can be prepared in
following way:

acetate/methanol (95/5 by volume)]. After concentration of the fractions under reduced pressure (2.7 kPa) residue is obtained which is taken up with acetate. The solution is treated with carbon b filtered and evaporated under reduced pre (2.7 kPa) to give 470 mg of 1-{2-[3-benzyloxy-trifluoromethylphenyl)pyrazol-1-yl]ethyl}piperidine the form of an orange-colored oil.

^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): 1.30 to 1.55 (mt: 6H); 2.40 (unresolved peak: 4H); (unresolved peak: 2H); 4.10 (unresolved peak: 2H); (s: 2H); from 7.30 to 7.55 (mt: 6H); 7.58 (t, 7.5 Hz: 1H); 7.92 (broad d, J = 7.5 Hz: 1H); (broad s: 1H); 8.25 (s: 1H).

Example 49

1-(2-Piperidin-1-ylethyl)-4-pyridin-3-yl-1H-pyrazol 3-ol dihydrochloride

(mt: 1H); from 1.60 to 1.90 (mt: 5H); 2.94 (mt:
from 3.25 to 3.65 (mt: 3H); 4.50 (t, J = 6.5 Hz:
7.88 (broad dd, J = 8 and 5 Hz: 1H); 8.39 (s: 1H);
(broad d, J = 8 Hz: 1H); 8.60 (broad d, J = 5 Hz:
9.02 (broad d, J = 1.5 Hz: 1H); 10.60 (unresolved
1H); 11.20 (unresolved peak: 1H).

The 3-[3-benzyloxy-1-(2-piperidin-1-ylethyl
pyrazol-4-yl]pyridine can be prepared in the foll
way:

580 mg of 3-diethylboranylpyridine, 690 mg of s
carbonate dissolved in 20 cm^3 of water, and 390 m
tetrakis(triphenylphosphine)palladium are added
stirred solution of 950 mg of 1-[2-(3-benzylo
bromopyrazol-1-yl)ethyl]piperidine in 100 cm^3 of di
and under an argon atmosphere. After heating at
reflux of the solvent for 3 h, the reaction mediu
cooled to a temperature in the region of 20°C,
acetate and water are added, and the mixture

1453; 1362; 1167; 1020; 708 and 702 cm^{-1}.

Example 50

4-(4-Chlorophenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol dihydrochloride

3.5 cm^3 of 12N hydrochloric acid are added to a st solution of 470 mg of 1-{2-[3-benzyloxy-chlorophenyl)pyrazol-1-yl]ethyl}piperidine in 3.5 ethanol. After 7 h at the reflux of the solvent then 15 h at a temperature in the region of 20°C reaction mixture is evaporated to dryness under re pressure (2.7 kPa). The residue is dried under v (2.7 kPa) at 45°C for 2 h, and is then triturate diisopropyl ether. The precipitate formed is fil and dried under vacuum (2.7 kPa) to give 430 m 4-(4-chlorophenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol dihydrochloride in the form of a solid.

30 min at a temperature in the region of 20°C
400 mg of 1-(2-chloroethyl)piperidine hydrochlorid
then added. The reaction medium is stirred for 15
a temperature in the region of 20°C, and is then p
into water. The aqueous phase is extracted twice
ethyl acetate. The organic phases are pooled, w
successively with water and a saturated aqueous s
chloride solution, dried over magnesium sul
filtered and evaporated under reduced pre
(2.7 kPa) to give a pale yellow oil, which is pur
by flash chromatography on alumina CTB1 under an
pressure (50 kPa) [eluent: cyclohexane/ethyl ac
(95/5, then 90/10 by volume)]. After concentrati
the fractions under reduced pressure, 470 mg of
[3-benzyloxy-4-(4-chlorophenyl)pyrazol-1-
yl]ethyl}piperidine are obtained in the form of a
yellow oil.
IR spectrum (CCl_4): 2938; 1574; 1509; 1482; 1452;
1171; 1094; 1037; 1014; 834; 695 and 511 cm^{-1}.

is washed successively with two times water a
saturated aqueous sodium chloride solution; it is
over magnesium sulfate, filtered and evaporated
reduced pressure (2.7 kPa). The resulting yellow
is purified by flash chromatography on silica und
argon pressure (50 kPa) [eluent: cyclohexane/
acetate (80/20 by volume), then ethyl acetate].
concentration of the fractions under reduced pre
(2.7 kPa), 440 mg of 3-benzyloxy-4-(4-chlorophenyl
pyrazole are obtained in the form of a white s
Mass spectrum (EI): m/z 284 ($M^{+\cdot}$), m/z 206 [
$C_6H_6)^{+\cdot}$], m/z 91 ($C_7H_7^+$).

The 3-benzyloxy-4-(4-chlorophenyl)-1-(toluе
sulfonyl)-1H-pyrazole can be prepared in the foll
way:

1.15 g of 4-chlorophenylboronic acid, 3.6 cm^3 of
aqueous potassium carbonate solution and 360 m
tetrakis(triphenylphosphine)palladium are added

(toluene-4-sulfonyl)-1H-pyrazole are obtained in
form of an orange-colored solid. Mass spe
(CI): m/z 456 (MNH_4^+), m/z 439 (MH^+).

Example 51

4-(3-Chlorophenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol dihydrochloride

5 cm^3 of 12N hydrochloric acid are added to a st
solution of 550 mg of 1-{2-[3-benzyloxy-
chlorophenyl)pyrazol-1-yl]ethyl}piperidine in 5 c
ethanol. After 7 h at the reflux of the solvent
then 15 h at a temperature in the region of 20°C
reaction medium is evaporated to dryness under re
pressure (2.7 kPa). The residue is dried under v
(2.7 kPa) at 45°C for 2 h, and is then triturat
diisopropyl ether. The precipitate formed is fil
and dried under vacuum (2.7 kPa) to give 460 m
4-(3-chlorophenyl)-1-(2-piperidin-1-ylethyl)-1H-

liquid petroleum jelly) in 15 cm^3 of dimethylform
under an argon atmosphere and with stirring.
heating at 50°C for 30 min, the mixture is stirre
30 min at a temperature in the region of 20°C,
solution of 500 mg of 1-(2-chloroethyl)piper
hydrochloride is then added. The reaction mediu
stirred at a temperature in the region of 20°C
15 h, and is then poured into water. The aqueous
is extracted twice with ethyl acetate. The or
phases are pooled, washed successively with water
saturated aqueous sodium chloride solution, dried
magnesium sulfate, filtered and evaporated
reduced pressure (2.7 kPa) to give a yellow oil
is purified by flash chromatography on alumina
under an argon pressure (50 kPa) [el
cyclohexane/ethyl acetate (95/5 by volume)].
concentration of the fractions under reduced pres
550 mg of 1-{2-[3-benzyloxy-4-(3-chlorophenyl)pyr
1-yl]ethyl}piperidine are obtained in the form
yellow oil.

is purified by flash chromatography on silica und
argon pressure (50 kPa) [eluent: cyclohexane/
acetate (70/30 by volume)]. After concentration c
fractions under reduced pressure (2.7 kPa), 500
3-benzyloxy-4-(3-chlorophenyl)-1H-pyrazole are obt
in the form of a white solid.
IR spectrum (KBr): 3148; 2957; 1601; 1505; 1446;
1355; 1237; 1229; 1046; 785; 729; 682 and 597 cm^{-1}.

The 3-benzyloxy-4-(3-chlorophenyl)-1-(toluе
sulfonyl)-1H-pyrazole can be prepared in the foll
way:

1.03 g of 3-chlorophenylboronic acid, 3.3 cm^3 of
aqueous potassium carbonate solution and 380 m
tetrakis(triphenylphosphine)palladium are added
stirred solution, under an argon atmosphere, of 1
3-benzyloxy-4-iodo-1-(toluene-4-sulfonyl)-1H-pyrazo
in 20 cm^3 of toluene to which 5 cm^3 of ethanol have
added. After heating at the reflux of the solven

Example 52

4-(2-Fluorophenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol dihydrochloride:

7 cm^3 of 12N hydrochloric acid are added to a st
solution of 800 mg of 1-{2-[3-benzyloxy-
fluorophenyl)pyrazol-1-yl]ethyl}piperidine in 10 c
ethanol. After 7 h at the reflux of the solvent
then 15 h at a temperature in the region of 20°C
reaction medium is evaporated to dryness under re
pressure (2.7 kPa). The crude is taken up with eth
and the mixture is then evaporated to dryness
reduced pressure (2.7 kPa); the operation is rep
twice. The residue is triturated in diisopropyl e
and the precipitate formed is filtered off, and is
dissolved under hot conditions in ethanol. The cry
which have appeared after cooling of the solution
ice bath are filtered and dried under vacuum (2.7
to give 470 mg of 4-(2-fluorophenyl)-1-(2-piperid

heating at 50°C for 30 min, the mixture is stirred
temperature in the region of 20°C for 30 min
625 mg of 1-(2-chloroethyl)piperidine hydrochloric
added. The reaction medium is stirred for 15 h
temperature in the region of 20°C, and is then p
into 100 cm^3 of water. The aqueous phase is extr
twice with ethyl acetate. The organic phases
pooled, washed successively with two times water
saturated aqueous sodium chloride solution, dried
magnesium sulfate, filtered and evaporated
reduced pressure (2.7 kPa) to give a yellow
(1.1 g), which is purified by flash chromatograp
alumina CTB1 under an argon pressure (50 kPa) [el
cyclohexane/ethyl acetate (95/5 by volume)].
concentration of the fractions under reduced pres
800 mg of 1-{2-[3-benzyloxy-4-(2-fluorophenyl)pyr
1-yl]ethyl}piperidine are obtained in the form
yellow oil.

IR spectrum (CCl_4): 2938; 2855; 2801; 1572; 1512;
1358; 1175; 1044; 1027 and 696 cm^{-1}.

acetate (70/30 by volume)]. After concentration c
fractions under reduced pressure (2.7 kPa), 650
3-benzyloxy-4-(2-fluorophenyl)-1H-pyrazole are obt
in the form of a white solid.
IR spectrum (KBr): 3161; 2954; 2691; 1572; 1474;
1353; 1264; 1045; 1036; 1027; 759; 729 and 654 cm^{-1}

The 3-benzyloxy-4-(2-fluorophenyl)-1-(toluе
sulfonyl)-1H-pyrazole can be prepared in the foll
way:

1.4 g of 2-fluorophenylboronic acid, 5 cm^3 of
aqueous potassium carbonate solution and 500 r
tetrakis(triphenylphosphine)palladium are added
stirred solution, under an argon atmosphere, of
of 3-benzyloxy-4-iodo-1-(toluene-4-sulfonyl
pyrazole in a mixture of 20 cm^3 of toluene and of
of ethanol. After heating at the reflux of the sc
for 3 h, the reaction medium is cooled to a temper
in the region of 20°C and evaporated under re

4-(2-Chlorophenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol hydrochloride

5 cm^3 of 12N hydrochloric acid are added to a st solution of 570 mg of 1-{2-[3-benzyloxy- chlorophenyl)pyrazol-1-yl]ethyl}piperidine in 7 ethanol. After 7 h at the reflux of the solvent then 15 h at a temperature in the region of 20°C reaction medium is evaporated to dryness under re pressure (2.7 kPa). The residue is taken up ethanol, and the mixture is then evaporated to dr under vacuum (2.7 kPa). The operation is rep twice, and the lacquer obtained is then dried vacuum (2.7 kPa) at 45°C for 30 min, and is dissolved under hot conditions in ethanol. The cry formed after cooling of the solution in an ice bat filtered and dried under vacuum (2.7 kPa) to 380 mg of 4-(2-chlorophenyl)-1-(2-piperidin-1-ylet

suspension of 140 mg of sodium hydride (at 7
liquid petroleum jelly) in 10 cm^3 of dimethylfor
under an argon atmosphere and with stirring.
heating at 50°C for 30 min, the mixture is stirre
temperature in the region of 20°C for 30 min
453 mg of 1-(2-chloroethyl)piperidine hydrochlori
then added. The reaction medium is stirred
temperature in the region of 20°C for 15 h, and i
poured into 100 cm^3 of water. The aqueous pha
extracted twice with ethyl acetate. The organic
are pooled, washed successively with two times
and a saturated aqueous sodium chloride solution,
over magnesium sulfate, filtered and evaporated
reduced pressure (2.7 kPa) to give a yello
(0.8 g), which is purified by flash chromatograp
alumina CTB1 under an argon pressure (50 kPa) [e
cyclohexane/ethyl acetate (95/5 by volume)].
concentration of the fractions under reduced pres
570 mg of 1-{2-[3-benzyloxy-4-(2-chlorophenyl)py

over magnesium sulfate, filtered and evaporated
reduced pressure (2.7 kPa). The resulting o
triturated in pentane. The precipitate forme
filtered off and dried under reduced pressure t
500 mg of 3-benzyloxy-4-(2-chlorophenyl)-1H-pyraz
the form of a yellow solid. Mass spectrum (EI): m
($M^{+\cdot}$), m/z 249 [$(M - Cl)^+$], m/z 91 ($C_7H_7^+$).

The 3-benzyloxy-4-(2-chlorophenyl)-1-(tolu
sulfonyl)-1H-pyrazole can be prepared in the fol
way:

1.55 g of 2-chlorophenylboronic acid, 5 cm^3 of
aqueous potassium carbonate solution and 500
tetrakis(triphenylphosphine)palladium are added
stirred solution, under an argon atmosphere, of
of 3-benzyloxy-4-iodo-1-(toluene-4-sulfonyl
pyrazole in 20 cm^3 of toluene to which 5 cm^3 of et
have been added. After heating at the reflux o
solvent for 5 h, the reaction medium is evapo

1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(4-chlorophenyl)
pyrazol-3-ol dihydrochloride

2.5 cm^3 of 12N hydrochloric acid are added to a st
solution of 220 mg of 3-[3-benzyloxy-
chlorophenyl)pyrazol-1-yl]-1-azabicyclo[2.2.2]octa
5 cm^3 of ethanol. After 7 h at the reflux o
solvent, and then 15 h at a temperature in the
of 20°C, the reaction medium is evaporated to d
under reduced pressure (2.7 kPa). The residue is
up with ethanol, and the mixture is then evaporat
dryness under vacuum (2.7 kPa). The operatic
repeated twice, and the foam obtained is
triturated in diisopropyl ether. The precipitate
is filtered off and dried under vacuum (2.7 kP
give 170 mg of 1-(1-azabicyclo[2.2.2]oct-3-yl)-
chlorophenyl)-1H-pyrazol-3-ol dihydrochloride in
form of a white solid.

argon atmosphere, of 500 mg of 3-benzyloxy-4-(4-ch
phenyl)-1H-pyrazole in 20 cm^3 of dimethylforma
After heating at 110°C for 15 h, the reaction medi
poured into 100 cm^3 of water and the mixtur
extracted twice with ethyl acetate. The organic p
are washed successively with two times water a
saturated aqueous sodium chloride solution, dried
magnesium sulfate, filtered and evaporated
reduced pressure (2.7 kPa). The orange-colored
(650 mg) obtained is purified by flash chromatog
on silica under an argon pressure (50 kPa) [el
ethyl acetate, then dichloromethane/methanol (80/
volume)]. After concentration of the fractions
reduced pressure (2.7 kPa), 220 mg of 3-[3-benzylo
(4-chlorophenyl)pyrazol-1-yl]-1-azabicyclo[2.2.2]oc
are obtained in the form of a pale yellow oil.
IR spectrum (CCl_4): 3035; 2941; 2873; 1605; 1574;
1481; 1454; 1165; 1095; 1014; 834; 695 and 513 cm^{-1}

Example 55

IR spectrum (KBr): 2931; 2801; 2660; 2557; 1599; 1517; 1459; 1425; 1165; 1095; 950; 891; 840; 788; 627 and 440 cm^{-1}.

^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): 1.65 to 2.05 (mt: 4H); 2.43 (mt: 1H); from 3.15 to (mt: 4H); from 3.70 to 3.85 (mt: 2H); 4.67 (mt: 7.20 (ddd, J = 8-2 and 1 Hz: 1H); 7.38 (t, J = 1H); 7.67 (broad d, J = 8 Hz: 1H); 7.75 (t, J = 1H); 8.31 (s: 1H); from 10.30 to 10.60 (unresolved peak: 1H); 10.68 (broad s: 1H).

The 3-[3-benzyloxy-4-(3-chlorophenyl)pyrazol-1-y azabicyclo[2.2.2]octane can be prepared in following way:

560 mg of potassium tert-butoxide, followed solution of 740 mg of toluene-4-sulfonic 1-azabicyclo[2.2.2]oct-3-yl ester in 20 cm^3 of dime formamide, are added to a stirred solution, unde argon atmosphere, of 570 mg of 3-benzyloxy-4-(3-ch

Example 56

1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(3-fluorophenyl)-
pyrazol-3-ol hydrochloride

2 cm^3 of 12N hydrochloric acid are added to a st
solution of 85 mg of 3-[3-benzyloxy-4-(3-fluorophe
pyrazol-1-yl]-1-azabicyclo[2.2.2]octane in 4 cm
ethanol. After 7 h at the reflux of the solvent
then 15 h at a temperature in the region of 20°C
reaction medium is evaporated to dryness under re
pressure (2.7 kPa). The residue is taken up
ethanol, and the mixture is then evaporated to dr
under vacuum (2.7 kPa). The operation is rep
twice, and the foam obtained is then triturate
diisopropyl ether. The precipitate formed is fil
off and dried under vacuum (2.7 kPa) to give 63
1-(1-azabicyclo[2.2.2]oct-3-yl)-4-(3-fluorophenyl)-

1-azabicyclo[2.2.2]oct-3-yl ester in 20 cm
dimethylformamide, are added to a stirred solu
under an argon atmosphere, of 250 mg of 3-benzylo
(3-fluorophenyl)-1H-pyrazole in 20 cm^3
dimethylformamide. After heating at 110°C for 15 h
reaction medium is poured into 100 cm^3 of water, ar
mixture is extracted twice with ethyl acetate
organic phases are washed successively with two
water and a saturated aqueous sodium chloride solu
dried over magnesium sulfate, filtered and evapo
under reduced pressure (2.7 kPa). The orange-co
oil (345 mg) obtained is purified by
chromatography on silica under an argon pressur
kPa) [eluent: cyclohexane/ethyl acetate (90/1
volume), then dichloromethane/methanol (80/20
volume)]. After concentration of the fractions
reduced pressure (2.7 kPa), 270 mg of 3-[3-benzy
4-(3-fluorophenyl)pyrazol-1-yl]-1-
azabicyclo[2.2.2]octane are obtained in the form
pale yellow oil.

acid in ethyl acetate. The reaction medium is st
for 5 min at 0°C, left to return to a temperatu
the region of 20°C, and then stirred again at
temperature for 20 min before being concentrated
reduced pressure (2.7 kPa). The crude product is
on a vane pump (10^{-3} kPa) to give 160 mg of 1-(1-me
pyrrolidin-3-yl)-4-phenyl-1H-pyrazol-3-ol hydrochl
in the form of a very hygroscopic solid.
(electrospray): m/z 244 (MH^+).
^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6 at 80°C,
ppm): from 2.30 to 2.65 (m: 2H); 2.91 (s: 3H);
3.10 to 4.00 (m: 4H); 5.03 (m: 1H); 7.14 (t, J
Hz: 1H); 7.32 (t, J = 7.5 Hz: 2H); 7.65 (t, J = 7.
2H); 8.00 (s: 1H).

The 1-(1-methylpyrrolidin-3-yl)-4-phenyl-1H-pyraz
ol can be prepared in the following way:

7.55 cm^3 of a 4M aqueous hydrochloric acid solutic
added to a solution of 505 mg of 3-benzyloxy-

m/z 334 (MH^+).

The 3-benzyloxy-1-(1-methylpyrrolidin-3-yl)-4-pl
1H-pyrazole can be obtained in the following way:

123 mg of sodium hydride (at 50% in oil) are added
solution of 428 mg of 3-benzyloxy-4-phenyl-1H-py
in 8.5 cm^3 of dimethylformamide, stirred und
nitrogen atmosphere and at 0°C. After stirring
temperature in the region of 20°C for 30 m
solution of 398 mg of methanesulfonic acid (1-me
pyrrolidin-3-yl) ester in 5.6 cm^3 of dimethylforn
is added. The reaction medium is stirred for 1
80°C and then poured into a water/ethyl ac
mixture. After stirring for 5 min, the mediu
separated by settling out and the aqueous pha
extracted three times with ethyl acetate. The or
phases are pooled, washed with a saturated ac
sodium chloride solution, dried over magnesium sul
filtered through an Iena filter and evaporated

at -10°C. The reaction medium is stirred at -10°
5 min and then at a temperature in the region of
for 2 h, before being concentrated to dryness
reduced pressure (2.7 kPa). The residue obtain
taken up with water and ethyl acetate. The soluti
stirred for 5 min and is then separated by set
out. The aqueous phase is extracted three times
ethyl acetate. The organic phases are pooled, w
successively with a 5% aqueous sodium bicarb
solution and a saturated aqueous sodium chl
solution, dried over magnesium sulfate, filtered
evaporated under reduced pressure (2.7 kPa) to
399 mg of methanesulfonic acid (1-methylpyrrolid
yl) ester in the form of a colorless oil.
(electrospray): m/z 180 (MH^+), m/z 84 [MH^+ - (SO_2CH_3

Example 58

1-[2-(1-Methylpyrrolidin-2-yl)ethyl]-4-phenyl-1H-pyrazol-3-ol dihydrochloride

ethyl]-4-phenyl-1H-pyrazol-3-ol in 5 cm^3 of methan
acidified (pH 1) with a solution of hydrochloric
in methanol. The reaction medium is stirred for
at a temperature in the region of 20°C, and is
concentrated under reduced pressure (2.7 kPa)
placed in a freezer overnight. The residue is tak
with acetonitrile, spin-filtered, and then washed
acetonitrile before being dried under vacuum to
160 mg of 1-[2-(1-methylpyrrolidin-2-yl)ethy
phenyl-1H-pyrazol-3-ol dihydrochloride in the form
hygroscopic amorphous white powder.
(electrospray): m/z 272 (MH^+).
^1H NMR spectrum (400 MHz, $(CD_3)_2SO$ d6, δ in ppm):
(m: 1H); 1.92 (m: 2H); 2.09 (m: 1H); 2.21 (m: 1H)
(m: 1H); 2.77 (d, J = 5.0 Hz: 3H); 3.01 (m: 1H);
(m: 1H); 3.52 (m: 1H); 4.04 (dt, J = 14.0 and 6.
1H); 4.07 (dt, J = 14.0 and 6.5 Hz: 1H); 7.11 (t
7.5 Hz: 1H); 7.31 (t, J = 7.5 Hz: 2H); 7.63 (t
7.5 Hz: 2H); 7.98 (s: 1H); 10.70 (s: 1H).

evaporated under reduced pressure (2.7 kPa) to
580 mg of a crude product which is purifie
chromatography on 25 g of silica gel [e
dichloromethane then dichloromethane/methanol (90/
volume)]. After concentration of the fractions
reduced pressure, 200 mg of 3-benzyloxy-1-
methylpyrrolidin-2-yl)ethyl]-4-phenyl-1H-pyrazole
obtained in the form of an amorphous white p
along with 240 mg of a mixture consistin
3-benzyloxy-1-[2-(1-methylpyrrolidin-2-yl)ethyl]-4
phenyl-1H-pyrazole and of 3-benzyloxy-4-pheny
pyrazole. The mixture is again purified
chromatography on 10 g of silica gel [e
dichloromethane/methanol (50/50 then 90/10 by vo
to give 90 mg of 3-benzyloxy-4-phenyl-1H-pyrazol
140 mg of 3-benzyloxy-1-[2-(1-methylpyrrolidin-
ethyl]-4-phenyl-1H-pyrazole, having the same appea
as the previous batch. LCMS (electrospray): m/
(MH^+).

dihydrochloride

A suspension of 608 mg of 3-benzyloxy-4-p
1-(pyrrolidin-3-yl)-1H-pyrazole dihydrochloride
60 mg of palladium-on-charcoal at 10% in 18 c
ethanol is hydrogenated at a temperature in the
of 20°C under an atmosphere of 1300 mbar for 3 h
reaction medium is diluted with methanol, filtered
hyflosupercel and rinsed with methanol. The filtra
evaporated under reduced pressure (2.7 kPa) to
365 mg of a white powder. This reaction cru
recrystallized from 20 cm^3 of ethanol at reflux
solution obtained is allowed to return to a tempe
in the region of 20°C, and is then immersed in a
bath. The crystals obtained are filtered under
conditions through an Iena filter, rinsed success
with ethanol and then ethyl ether and dried
vacuum (13 kPa) to give 185 mg of 1-(pyrrolidin-
4-phenyl-1H-pyrazol-3-ol dihydrochloride in the fo
a white powder. LCMS (electrospray): m/z 230 (MH^+)

phenyl-1-(pyrrolidin-3-yl)-1H-pyrazole dihydrochlo
in the form of a white powder, which are
immediately.

The 3-benzyloxy-1-(1-tert-butoxycarbonylpyrrolid
yl)-4-phenyl-1H-pyrazole can be prepared in
following way:

129 mg of sodium hydride (at 50% in oil) are added
solution of 450 mg of 3-benzyloxy-4-phenyl-1H-pyr
in 9 cm^3 of dimethylformamide, stirred under a nit
atmosphere at 0°C. After stirring at a temperatu
the region of 20°C for 30 min, 621 mg
methanesulfonic acid (1-tert-butoxycarbonylpyrrol
3-yl) ester are added. The reaction medium is st
for 1 h at 80°C and then poured into a water/
acetate mixture. After stirring for 5 min, the m
is separated by settling out and the aqueous pha
extracted three times with ethyl acetate. The or
phases are pooled, washed with a saturated aq

The methanesulfonic acid (1-tert-butoxycarb pyrrolidin-3-yl) ester can be prepared in the foll way:

A solution of 0.33 cm^3 of methanesulfonyl chlori 3.2 cm^3 of dichloromethane is added dropwise solution of 710 mg of 1-tert-butoxycarbon hydroxypyrrolidine and 0.62 cm^3 of triethylamin 14.2 cm^3 of dichloromethane, stirred under a nit atmosphere at -10°C. The reaction medium is stirr -10°C for 5 min, and then at a temperature in region of 20°C for 2 h, before being concentrat dryness under reduced pressure (2.7 kPa). The re obtained is taken up with water and ethyl acetate solution is stirred for 5 min and is then separat settling out. The aqueous phase is extracted times with ethyl acetate. The organic phases pooled, washed successively with an aqueous soluti sodium bicarbonate at 5% and of sodium chloride,

out. The aqueous phase is extracted three times
ethyl acetate. The organic phases are pooled,
over magnesium sulfate, filtered through an Iena
and then concentrated to dryness under reduced pr
(2.7 kPa) to give 1.823 g of 1-tert-butoxycarbo
hydroxypyrrolidine in the form of colorless cry
m/z 188 (MH^+), m/z 132 [MH^+ - tBu].

Example 60

1-[(1-Methylpyrrolidin-2-(S)-yl)methyl]-4-phenyl-1
pyrazol-3-ol

3.75 cm^3 of a 4M hydrochloric acid solution are ad
a solution of 263 mg of 3-benzyloxy-
methylpyrrolidin-2-(S)-yl)methyl]-4-phenyl-1H-pyra
in 2 cm^3 of ethanol. The reaction medium is stir
reflux for 7 h and is then concentrated under r
pressure. The violet oil obtained is taken up
times with 10 cm^3 of isopropanol and then evaporat

^{1}H NMR spectrum (400 MHz, DMSO d6, δ in ppm): 1.6
1H); 1.76 (m: 2H); 1.95 (m: 1H); 2.30 (partially
m: 1H); 2.34 (s: 3H); 2.82 (m: 1H); 3.14 (m: 1H);
(dd, J = 7-14 Hz: 1H); 4.11 (dd, J = 6-14 Hz: 1H),
(bt, J = 8 Hz: 1H); 7.35 (bt, J = 8 Hz: 2H); 7.5
1H); 7.70 (bd, J = 8 Hz: 2H).

The 3-benzyloxy-1-[(1-methylpyrrolidin-2-(S)
methyl]-4-phenyl-1H-pyrazole can be prepared in
following way:

136 mg of sodium hydride (at 50% in oil) are added
solution of 283 mg of 3-benzyloxy-4-phenyl-1H-pyr
in 6 cm^3 of dimethylformamide, stirred under a nit
atmosphere at ambient temperature. After stirri
ambient temperature for 30 min, a solution of 250
1-methyl-2-(S)-chloromethylpyrrolidine hydrochlori
6 cm^3 of dimethylformamide is added. The reaction
is stirred at 80°C for 1 h, and is then cool
ambient temperature and hydrolyzed. After extra

methanol in 2 cm^3 of dichloromethane cooled in a b
ice-cold water. The solution obtained is heat
reflux for 3 hours and then stirred at a
temperature for 18 hours. After evaporation
reduced pressure at 35°C, the brown residue obtai
dissolved in ethanol and then concentrated to d
under reduced pressure. The dry extract obtain
dissolved in 1 cm^3 of ethanol and then precipitat
gradually adding 6 cm^3 of ethyl ether. The susp
obtained is cooled using a bath of ice-cold wat
the solid is filtered off and then washed with
ether. After drying under vacuum, 258 mg of 1-met
(S)chloromethylpyrrolidine hydrochloride are ob
in the form of a very hygroscopic ochre solid.
spectrum (EI): m/z 133 ($M^{+\cdot}$).

Example 61

4-Phenyl-1-pyrrolidin-3-ylmethyl-1H-pyrazol-3-ol hydrochloride

and then lyophilized overnight. The various batch
20 combined, to give 80 mg of 4-phenyl-1-pyrroli
ylmethyl-1H-pyrazol-3-ol hydrochloride in the for
white powder. ^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$
in ppm): 1.66 (m, 1H); 1.99 (m, 1H); 2.73 (m, 1H)
(m, 1H); from 3.02 to 3.25 (m, 2H); 4.01 (d, J
25 Hz, 2H); 7.12 (broad t, J = 7.5 Hz, 1H); 7.32 (br
J = 7.5 Hz, 2H); 7.65 (broad d, J = 7.5 Hz, 2H)
(s, 1H); 8.36 (broad s, 1H); from 6.70 to 8.70
very broad m, 1H). Mass spectrum (EI): m/z 244$^+$ (M

30 The 1-(1-benzylpyrrolidin-3-ylmethyl)-4-phen
pyrazol-3-ol hydrochloride can be prepared i
following way:

phenyl-1H-pyrazole hydrochloride can be prepared following way:

129 mg of sodium hydride (at 50% in oil) are adde a single step, to a solution of 450 mg of 3-benz 4-phenyl-1H-pyrazole in 9 cm^3 of anh dimethylformamide stirred under an argon atmosphe 0°C. After stirring for 30 min at a temperature region of 20°C, a solution of 630 mg of methanesu acid (1-benzylpyrrolidin-3-ylmethyl) ester in 9 anhydrous dimethylformamide is added. The re medium is stirred for 4 h at 80°C and then plunge a water/ethyl acetate mixture. After stirrin 5 min, the medium is separated by settling out a aqueous phase is extracted three times with acetate. The organic phases are combined, washed with water and then once with a saturated a sodium chloride solution, dried over magnesium su and filtered through an iena funnel. The magn sulfate is rinsed with ethyl acetate. The co organic phases are evaporated under reduced pr and the residue obtained is dried overnight on a

benzylpyrrolidin-3-ylmethyl)-4-phenyl-1H-pyrazole
the form of a free base. The product is taken up
5 cm^3 of ethyl acetate. The medium is cooled to
before the addition of 5 cm^3 of a 3M hydrochloric
solution in ethyl acetate. The solution is concen
to dryness under reduced pressure, to give a brow
Attempts to crystallize the crude residue obtained
carried out in vain (ethyl acetate, ethanol, meth
diethyl ether or hexane). 940 mg of 3-benzyl
(1-benzylpyrrolidin-3-ylmethyl]-4-phenyl-1H-pyrazo
hydrochloride are thus recovered. Mass spectrum
m/z 424$^+$ $(M+H)^+$.

The methanesulfonic acid (1-benzylpyrrolid
ylmethyl) ester can be prepared in the following w

A solution of 0.455 cm^3 of methanesulfonic chlori
9.7 cm^3 of anhydrous dichloromethane is added dr
to a solution of 1 g of (1-benzylpyrrolid
yl)methanol and 0.844 cm^3 of triethylamine in 20
dichloromethane, stirred under an argon atmosphe
0°C. The reaction medium is stirred for 5 min a

17.1 cm^3 of a 1M lithium aluminium hydride solut
tetrahydrofuran are added to a solution of 2
1-benzyl-5-oxopyrrolidine-3-carboxylic acid
ester in 40 cm^3 of tetrahydrofuran, stirred at 0°C
a nitrogen atmosphere. After stirring for 15 m
0°C, the reaction medium is allowed to return
temperature in the region of 20°C and is stirre
4 h. A mixture consisting of 0.65 cm^3 of water
6.5 cm^3 of tetrahydrofuran is added dropwise t
reaction medium. 0.65 cm^3 of a 15% aqueous
hydroxide solution and 1.95 cm^3 of water are
successively added. The medium is stirred
temperature in the region of 20°C until the for
of a filterable solid, to which two spatul
magnesium sulfate are added. After filtration t
an iena funnel, rinsing and concentrating to d
under reduced pressure, 1.72 g of (1-benzylpyrro
3-yl)methanol are obtained in the form of a col
oil. Mass spectrum (EI): m/z 192$^+$ $(M+H)^+$.

sodium carbonate. The aqueous phase is again ext
three times with dichloromethane. The organic
are combined, dried over magnesium sulfate, fi
and concentrated to dryness under reduced pressu
give 100 mg of a product which is recrystallized
minimum amount of ethanol. After leaving the p
overnight in a refrigerator, filtering and d
58 mg of 1-((2R)-1-methylpyrrolidin-2-ylmeth
phenyl-1H-pyrazol-3-ol are obtained in the form
white solid. ^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$ d
a drop of AcOH d4, δ in ppm): from 1.62 to 2.0
4H); 2.42 (s, 3H); 3.02 (m, 1H); 3.21 (m, 2H);
(dd, J = 7.0 and 14.0 Hz, 1H); 4.13 (dd, J = 5.
14.0 Hz, 1H); 7.13 (broad t, J = 7.5 Hz, 1H);
(broad t, J = 7.5 Hz, 2H); 7.65 (broad d, J = 7.
2H); 7.97 (s, 1H). Mass spectrum (EI): 258(+)=(M+
The 3-benzyloxy-1-((2R)-1-methylpyrrolidin-2-ylme
4-phenyl-1H-pyrazole can be prepared in the fol
way:

A solution of 400 mg of 3-benzyloxy-4-phenyl-
pyrrolidin-2-ylmethyl)-1H-pyrazole hydrochl

3.17 cm^3 of a 4N hydrochloric acid solution in d
are added to a solution of 500 mg of 3-benzyl
((2R)-1-tert-butoxycarbonylpyrrolidin-2-ylmethyl)-
phenyl-1H-pyrazole in 5 cm^3 of dioxane. The re
medium is stirred overnight at a temperature i
region of 20°C and is then concentrated to d
under reduced pressure, to give 400 mg of 3-benz
4-phenyl-1-((2R)-pyrrolidin-2-ylmethyl)-1H-pyrazol
hydrochloride in the form of a white solid.
spectrum (EI): m/z 334$^+$
$(M+H)^+$, m/z 667$^+$ $(2M+H)^+$.

The 3-benzyloxy-4-phenyl-1-((2R)-1-tert-butoxycarb
pyrrolidin-2-ylmethyl)-1H-pyrazole can be prepar
the following way:

A solution of 251 mg of 3-benzyloxy-4-phen
pyrazole and 72 mg of sodium hydride (50% in oi
5 cm^3 of dimethylformamide is stirred for 1 h
adding a solution of 364 mg of methanesulfonic
((2R)-1-tert-butoxycarbonylpyrrolidin-2-ylmethyl)
in 5 cm^3 of dimethylformamide. The reaction medi

A solution of 1.2 cm^3 of methanesulfonyl chlori
20 cm^3 of dichloromethane is added dropwise
solution of 3 g of (2R)-1-tert-butoxycarbo
hydroxymethylpyrrolidine and 2.27 cm^3 of triethy
in 65 cm^3 of dichloromethane, stirred under a ni
atmosphere at -10°C. The reaction medium is allo
return to 20°C, before concentrating to dryness
reduced pressure. The residue obtained is taken u
water, and extracted twice with 20 cm^3 of ethyl ac
The combined organic phases are washed three time
20 cm^3 of a 5% aqueous sodium bicarbonate sol
dried over magnesium sulfate, filtered,
concentrated to dryness under reduced pressure, t
3.75 g of a mixture of methanesulfonic acid ((
tert-butoxycarbonylpyrrolidin-2-ylmethyl) ester a
(2R)-1-tert-butoxycarbonyl-2-hydroxymethylpyrrolid
The mixture is again reacted under the same cond
as above, but with 0.3 eq of triethylamine and
of methanesulfonyl chloride. After a similar treat
3.63 g of methanesulfonic acid ((2R)-1-
butoxycarbonylpyrrolidin-2-ylmethyl) ester are ob

concentration to dryness, the crystalline produ
taken up with 5 cm^3 of ethyl acetate, spin-filtere
taken up twice with 0.5 cm^3 of ethyl acetate, t
70 mg of 4-phenyl-1-(piperidin-3-yl)-1H-pyrazo
hydrochloride in the form of a crystalline product
^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm):
1.72 to 2.22 (m, 4H); 2.86 (m, 1H); from 3.10 t
(partially masked m, 3H); 4.36 (m, 1H); 7.14 (br
J = 7.5 Hz, 1H); 7.33 (broad t, J = 7.5 Hz, 2H);
(broad d, J = 7.5 H, 2H); 8.07 (s, 1H); 9.18 (br
2H); 10.4 (broad s, 1H). Mass spectrum (EI): m/
$(M+H)^+$.

The 3-benzyloxy-4-phenyl-1-(piperidin-3-yl)-1H-py
hydrochloride can be prepared in the following way

2 cm^3 of a 4N hydrochloric acid solution in
acetate are added to a solution of 230 m
3-benzyloxy-1-(1-tert-butoxycarbonylpiperidin-3-yl
phenyl-1H-pyrazole in 2 cm^3 of ethyl acetate, cool
means of an ice bath. The reaction medium is allo
return to a temperature in the region of 20°C a

acid (1-tert-butoxycarbonylpiperidin-3-yl) este
4.5 cm^3 of anhydrous dimethylformamide is added
reaction medium is stirred for 3 h at 80°C and is
after cooling, poured into water. The aqueous ph
extracted four times with 50 cm^3 of ethyl acetat
combined organic phases are washed with a sat
aqueous sodium chloride solution, dried over mag
sulfate, filtered, and then concentrated to d
under reduced pressure. The product obtained is
up with dichloromethane, which, after spin-filt
gives 380 mg of 3-benzyloxy-4-phenyl-1H-pyrazole
form of a beige solid. The filtrate,
concentration to dryness, is purified by chromato
on a column of 70 g of silica (Merck, eluent: 9
volume dichloromethane/ethyl acetate).
concentration of the fractions under reduced pre
280 mg of 3-benzyloxy-1-(1-tert-butoxycar
piperidin-3-yl)-4-phenyl-1H-pyrazole are obtained
a purity of 70%. These 280 mg are again purifi
chromatography on a column of 30 g of silica (
eluent: 70/30 by volume dichloromethane/heptane).
concentration of the fractions under reduced pre

triethylamine in 7 cm³ of dichloromethane, stirred
a nitrogen atmosphere at -10°C. The reaction medi
allowed to return to a temperature in the regi
20°C and is stirred for 3 h, before concentrati
dryness under reduced pressure. The residue obtai
taken up with ethyl acetate. The organic pha
successively washed with a 5% aqueous
bicarbonate solution and then a saturated a
sodium chloride solution, dried over magnesium su
filtered, and concentrated to dryness under re
pressure, to give 0.9 g of methanesulfonic
(1-tert-butoxycarbonylpiperidin-3-yl) ester in the
of a colorless oil. Mass spectrum (EI): m/z 280$^+$ (
m/z 224$^+$ [(M+H)$^+$-tBu+H].

Example 64

1-(1-Methylpiperidin-2-ylmethyl)-4-phenyl-1H-pyraz
ol hydrochloride

A solution of 610 mg of 3-benzyloxy-
methylpiperidin-2-ylmethyl)-4-phenyl-1H-pyrazole

spectrum (300 MHz, $(CD_3)_2SO$ d6 at 353K, δ in ppm): 1.37 to 1.87 (m, 6H); 2.86 (broad m, 4H); from 3.
3.60 (very broad m, 2H); 4.24 (broad m, 1H);
(broad m, 1H); 7.16 (broad t, J = 7.5 Hz, 1H);
(broad t, J = 7.5 Hz, 2H); 7.67 (broad d, J = 7.
2H); 7.97 (s, 1H); from 10.0 to 10.6 (very bro
2H). Mass spectrum (EI): m/z 272$^+$ $(M+H)^+$, m/z 3
HCl^+.

Example 65

1-(1-methylazepan-3-yl)-4-phenyl-1H-pyrazol-3-ol hydrochloride

The 1-(1-methylazepan-3-yl)-4-phenyl-1H-pyrazol hydrochloride can be prepared according to the method used for preparing the 1-(1-methylpiperid ylmethyl)-4-phenyl-1H-pyrazol-3-ol hydrochloride, using 470 mg of 3-benzyloxy-1-(1-methylazepan-3-y phenyl-1H-pyrazole, 10 cm^3 of ethyl acetate, 5 cm^3 4M hydrochloric acid solution in ethyl acetate, then 51 mg of palladium-on-charcoal at 10% and 15 c

426 mg of sodium hydride (at 50% in oil) are adde
three portions, to a solution of 2 g of 3-benzylo
phenyl-1H-pyrazole in 20 cm^3 of anhydrous dime
formamide, stirred under a nitrogen atmosphere.
stirring for 30 min at a temperature in the regi
20°C, 1.3 g of a 75/25 mixture of 1-meth
chloromethylpiperidine and of methanesulfonic
(1-methylpiperidin-2-ylmethyl) ester are
dropwise. The reaction medium is stirred for 3
80°C and then, after cooling, is poured in
water/ice mixture. The aqueous phase is extracted
ethyl acetate. The organic phase is washed wi
saturated aqueous sodium chloride solution, dried
magnesium sulfate, filtered, and then concentrat
dryness under reduced pressure. The product is pur
by two successive chromatographies on a column of
of silica (Merck, eluent: 97/3 by v
dichloromethane/methanol). After concentration o
fractions under reduced pressure, 460 mg
3-benzyloxy-1-(1-methylazepan-3-yl)-4-phenyl-1H-
pyrazole and 650 mg of 3-benzyloxy-

7.5 Hz, 1H); from 7.28 to 7.45 (m, 5H); 7.51 (bi
J = 7.5 Hz, 2H); 7.65 (broad d, J = 7.5 Hz, 2H);
(s, 1H).

The mixture of 2-chloromethyl-1-methylpiperidin a
methanesulfonic acid (1-methylpiperidin-2-ylme
ester can be prepared in the following way:

A solution of 0.815 cm^3 of methanesulfonyl chlori
added dropwise to a solution of 1.31 cm^3 of (1-me
piperidin-2-yl)methanol and 1.53 cm^3 of triethylam
26 cm^3 of dichloromethane, stirred under a nit
atmosphere at -10°C. The reaction medium is allow
return to a temperature in the region of 20°C a
stirred for 3 h before concentration to dryness
reduced pressure. The residue obtained is taken up
ethyl acetate. The organic phase is successively w
with a 5% aqueous sodium bicarbonate solution and
a saturated aqueous sodium chloride solution,
over magnesium sulfate, filtered, and concentrat
dryness under reduced pressure, to give 1.3 g
75/25 mixture of 2-chloromethyl-1-methylpiperidi

precipitated from a mixture of diisopropyl ethe
ethanol. 0.357 g of 4-phenyl-1-(2-piperidin-1-yle
1H-pyrazol-3-ol hydrochloride is obtained in the
of a white solid. ^{1}H NMR spectrum (300 MHz) - δ
in DMSO-d6: 1,40 (m, 1H); from 1.63 to 1.87 (m,
2.92 (m, 2H); from 3.36 to 3.52 (m, 4H); 4.43 (t
6.5 Hz, 2H); 7.14 (tt, J = 1.5 and 7.5 Hz, 1H),
(broad t, J = 7.5 Hz, 2H); 7.64 (broad d, J = 7
2H); 8.05 (s, 1H); from 10.35 to 10.72 (broad m,
IR spectrum (KBr): 2939; 1606; 1581; 1520; 1454;
1170; 771; 700; 673 and 427 cm^{-1}.

The 3-benzyloxy-4-phenyl-1-(2-piperidin-1-ylethy
pyrazole oxalate can be obtained in the following

The procedure is carried out as in example 15, but
0.166 g of sodium hydride (at 75% by mass in
petroleum jelly), 0.515 g of 1-(2-chloroe
piperidine hydrochloride and 0.5 g of 3-benzyl
phenylpyrazole. 0.754 g of 3-benzyloxy-4-phenyl
piperidin-1-ylethyl)-1H-pyrazole oxalate is
obtained in the form of a white powder. IR spe

(broad d, J = 7.5 Hz, 2H); 8.06 (s, 1H); 8.33 (s
IR spectrum (KBr): 2949; 1679; 1713; 1606; 1460;
955; 763; 703 and 476 cm^{-1}.

Example 67

4-(Thiophen-2-yl)-1-(2-piperidin-1-ylethyl)-1H-pyr
3-ol hydrochloride

A suspension of 0.15 g of 4-(5-chlorothiophen-2-
(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol hydroch
and 5 mg of palladium-on-charcoal (at 10%) in 15
methanol is stirred in an autoclave under a hy
pressure of 3000 kPa, at a temperature of 60°
20 hours. The reaction medium is then filtered t
Celite®, rinsed with methanol and concentrate
dryness under reduced pressure (3 kPa). The resi
triturated with diisopropyl ether; after filtrati
the solid which has appeared and drying under
(70 Pa) at a temperature of 60°C, 0.1 g of 4-(thi
2-yl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol
chloride is obtained in the form of a gray powder

hydrochloric acid and 10 cm^3 of ethanol. The mixt
heated for 24 hours at a temperature close to
After cooling to a temperature close to 20°C
reaction medium is taken up with three times 30
toluene and then three times 30 cm^3 of aceton
ethanol, concentrated to dryness under reduced pre
(2kPa); the residue is precipitated from 30 c
acetone. 0.26 g of 4-(3,4-dichlorophenyl)
piperidin-1-ylethyl)-1H-pyrazol-3-ol hydrochlorid
obtained in the form of a whitish powder. ^{1}
spectrum (300 MHz) - δ in ppm - in DMSO-d6: from
to 1.92 (m, 6H); from 2.85 to 3.60 (m, 6H); 4.36
m, 2H); from 7.55 to 7.68 (m, 2H); 7.90 (d, J = 2.
1H); 8.15 (broad s, 1H); from 9.35 to 9.48 (bro
1H); 10.8 (broad s, 1H). IR spectrum, KBr: 2945;
1604; 1525; 1448; 1180; 1028 and 806 cm^{-1}.

3-Benzyloxy-4-(3,4-dichlorophenyl)-1-(2-piperidin-
ylethyl)-1H-pyrazole

The procedure is carried out as in example 15, but
0.135 g of sodium hydride (75% by mass in

Hz, 2H); 7.51 (d, J = 7.5 Hz, 2H); from 7.57 to
(m, 2H); 7.88 (d, J = 2.5 Hz, 1H); 8.21 (m, 1H).
spectrum (CI): m/z=430 (MH^+) base peak.

3-Benzyloxy-4-(3,4-dichlorophenyl)-1H-pyrazole

The procedure is carried out as in example 38, but
0.3 g of 1-(toluene-4-sulfonyl)-3-benzyloxy-4-
dichlorophenyl)-1H-pyrazole and 1.6 cm^3 of a 1N sol
of tetrabutylammonium fluoride in tetrahydrofura
15 cm^3 of tetrahydrofuran. 0.2 g of 3-benzyloxy-4-
dichlorophenyl)-1H-pyrazole is thus obtained in
form of an oil which crystallizes. ^1H NMR spe
(300 MHz) - δ in ppm - in DMSO-d6: 5.35 (s, 2H);
7.32 to 7.46 (m, 3H); 7.50 (broad d, J = 7.5 Hz,
7.59 (d, J = 9.0 Hz, 1H); 7.70 (dd, J = 2.5 and 9.
1H); 7.95 (d, J = 2.5 Hz, 1H); 8.23 (s, 1H);
(broad m, 1H). Mass spectrum (EI): m/z=318 ($M^{+\cdot}$), r
($C_7H_7^+$) base peak.

3-Benzyloxy-1-(toluene-4-sulfonyl)-4-(3,4-dichloro
phenyl)-1H-pyrazole

Example 69

4-(4-Bromophenyl)-1-(2-piperidin-1-ylethyl)-1H-pyr
3-ol

The procedure is carried out as in example 38, but
0.32 g of 3-benzyloxy-4-(4-bromophenyl)-1-(2-pipe
1-ylethyl)-1H-pyrazole, 3 cm^3 of 12N hydrochloric
and 10 cm^3 of ethanol. The mixture is heated
20 minutes at a temperature close to 100°C.
cooling to a temperature close to 20°C, the rea
medium is taken up with 5 times 30 cm^3 of acetone.
concentration to dryness under reduced pre
(3 kPa), the residue is triturated with 30 c
diisopropyl ether and then purified by chromatogr
under a nitrogen pressure of 50 kPa, on a colu
silica gel (particle size: 20-45 μ; diameter
height 20 cm), eluting with ethyl acetate th
mixture of ethyl acetate and methanol (95/5 then
then 80/20 by volume). Fractions 10 to 28 are comb
and concentrated to dryness under reduced pre

3-benzyloxy-4-(4-bromophenyl)pyrazole. After h
the reaction medium for 1 hour at 50°C, the medi
cooled to a temperature close to 20°C, and tak
with 300 cm^3 of ethyl acetate and 300 cm^3 of wate
organic phase is separated by settling out, drie
magnesium sulfate, filtered, and concentrate
dryness under reduced pressure (3 kPa). The resi
purified by chromatography, under a nitrogen pr
of 50 kPa, on a column of silica gel (particle
20-45 μ; diameter 3 cm; height 40 cm), eluting
mixture of ethyl acetate and of cyclohexane (5/9
10/95 by volume). Fractions 19 to 35 are combine
concentrated to dryness under reduced pressure (3
0.32 g of 3-benzyloxy-4-(4-bromophenyl)-1-(2-pipe
1-ylethyl)-1H-pyrazole is thus obtained in the f
a colorless oil. ^1H NMR spectrum (300 MHz) - δ in
in DMSO-d6:

From 1.34 to 1.53 (m, 6H); 2.38 (m, 4H); 2.68 (t
6.5 Hz, 2H); 4.07 (t, J = 6.5 Hz, 2H); 5.32 (s
from 7.32 to 7.55 (m, 7H); 7.60 (broad d, J = 8

3-Benzyloxy-1-(toluene-4-sulfonyl)-4-(4-bromopheny
1H-pyrazole

The procedure is carried out as in example 38, but
1.817 g of 1-(toluene-4-sulfonyl)-3-benzyloxy-4-
1H-pyrazole, 2.41 g of 4-bromophenylboronic
2.54 g of tripotassium phosphate, and 0.421
dichlorobis(triphenylphosphine)palladium in 40 c
dimethoxyethane. After purification by chromatogr
under a nitrogen pressure of 50 kPa, on a colu
silica gel (particle size 20-45 μ; diameter
height 60 cm), eluting with a mixture of ethyl ac
and of cyclohexane (5/95 by volume), fractions 15
are combined, and concentrated to dryness under re
pressure (3 kPa). 1.5 g of 3-benzyloxy-1-(tolue
sulfonyl)-4-(4-bromophenyl)-1H-pyrazole are
obtained in the form of a yellow oil
crystallizes. ^{1}H NMR spectrum (300 MHz) - δ in ppm
DMSO-d6 for 77% of the mixture: 2.42 (s, 3H); 5.3
2H); from 7.33 to 7.50 (m, 7H); 7.59 (broad d, J
Hz, 2H); 7.72 (broad d, J = 8.5 Hz, 2H); 7.84 (m,

silica (particle size 20-40 μm), eluting with a m
of dichloromethane and of a 2N solution of ammo
methanol (90/10 by volume). 0.258 g of 4-(1H-in
yl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-ol
obtained in the form of a flaky white solid.
spectrum (300 MHz) - δ in ppm - in DMSO-d6: fro
to 1.55 (m, 6H); 2.40 (m, 4H); 2.66 (t, J = 6.
2H); 4.00 (t, J = 6.5 Hz, 2H); 6.39 (broad t, J
Hz, 1H); from 7.27 to 7.40 (m, 3H); 7.81 (m, 2H);
(broad s, 1H); 10.95 (broad m, 1H). IR spectrum,
3265; 2944; 1593; 1524; 1242; 1184; 1044; 891;
762; 725 and 437 cm^{-1}. Mass spectrum (EI): m/z=310
m/z=98 ($C_6H_{12}N^+$) base peak.

3-Benzyloxy-4-(1H-indol-5-yl)-1-(2-piperidin-1-ylethyl)-1-H-pyrazole

The procedure is carried out as in example 37, but
3.39 g of 3-benzyloxy-4-bromo-1-(2-piperi
ylethyl)-1H-pyrazole, 3.14 g of 5-indolylboronic
3.87 g of potassium carbonate, 1.2 g of tet
(triphenyl)phosphine palladium in 70 cm^3 of toluen

The procedure is carried out as in example 38, but
0.592 g of 3-benzyloxy-4-(5-bromothiophen-2-yl)-
piperidin-1-ylethyl)-1H-pyrazole, 3.65 cm^3 of
hydrochloric acid and 4 cm^3 of ethanol. The mixtu
heated for 2 hours at a temperature close to
After cooling to a temperature close to 20°C
reaction medium is taken up with ethanol,
concentrated to dryness under reduced pressure (2
the residue is precipitated from diisopropyl ethe
then purified on a cartridge of silica (particle
20-40 μm), eluting with a mixture of dichlorome
and of a 2N ammoniacal methanol solution (90/
volume). 0.068 g of 4-(5-bromothiophen-2-yl)-
piperidin-1-ylethyl)-1H-pyrazole-3-ol is obtaine
the form of a yellow powder. ^1H NMR spectrum (300 M
δ in ppm - in DMSO-d6: from 1.33 to 1.53 (m, 6H);
(m, 4H); 2.62 (t, J = 6.5 Hz, 2H); 3.99 (t, J = 6.
2H); 6.93 (d, J = 3.5 Hz, 1H); 7.10 (d, J = 3.
1H); 7.85 (s, 1H); from 10.45 to 10.75 (very bro
1H). IR spectrum, KBr: 2938; 1593; 1536; 1471;

dryness under reduced pressure (3 kPa). The resi
taken up with 10 cm^3 of acetone and 170 mg of
acid in solution in 2 cm^3 of acetone. The precipit
filtered through sintered glass, washed with ac
dried, and then purified on a cartridge of
(particle size 20-40 μm), eluting with a mixtu
dichloromethane and of methanol (95/5 then 90/
volume). 0.716 g of 3-benzyloxy-4-(5-bromothiop
yl)-1-(2-piperidin-1-ylethyl)-1H-pyrazole oxalat
thus obtained in the form of a yellow powder.
spectrum (300 MHz) - δ in ppm - in DMSO-d6: 1.4
2H); 1.65 (m, 4H); from 2.86 to 3.00 (broad m,
3.25 (broad partially masked m, 2H); 4.30 (broad
6.5 Hz, 2H); 5.32 (s, 2H); 7.01 (d, J = 3.5 Hz,
7.15 (d, J = 3.5 Hz, 1H); from 7.32 to 7.54 (m,
8.09 (s, 1H). IR spectrum, KBr: 2948; 2536; 1724;
1595; 1532; 1498; 1451; 1363; 1173; 1008; 79
702 cm^{-1}. Mass spectrum (EI): m/z=445 ($M^{+\cdot}$),
($C_6H_{12}N^+$) base peak.

3-Benzyloxy-4-(5-bromothiophen-2-yl)pyrazole

The procedure is carried out as in example 38, bu
1 g of 1-(toluene-4-sulfonyl)-3-benzyloxy-4-io
pyrazole, 1.32 g of 5-bromothiophen-2-ylboronic
1.22 g of potassium carbonate and 309 m
dichlorobis(triphenylphosphine)palladium in 20 c
toluene and 5 cm^3 of ethanol. After purification
cartridge of silica (particle size 20-40 μm), e
with a mixture of ethyl acetate and of cyclo
(10/90 by volume), 0.85 g of 1-(toluene-4-sulfon
benzyloxy-4-(5-bromothiophen-2-yl)-1H-pyrazole is
obtained in the form of an orange gum. IR spe
CCl_4: 1597; 1527; 1494; 1391; 1190; 1179; 1096;
695; 671; 595 and 540 cm^{-1}. Mass spectrum
m/z=489(M^+), m/z=263 ($HPPh_3$) base peak.

Example 72

2-[1-(2-Piperidin-1-ylethyl)-1H-pyrazol-4-yl]benza

0.373 g of 4-(4-cyanophenyl)-1-(2-piperidin-1-ylet
1H-pyrazole oxalate and 11 cm^3 of 0.1N sodium hyd
in 20 cm^3 of dichloromethane are stirred

obtained in the form of a white solid which me
168°C.

^{1}H NMR spectrum (300 MHz) - δ in ppm - in DMSO-d6
1.33 to 1.55 (m, 6H); 2.40 (m, 4H); 2.68 (t, J
Hz, 2H); 4.22 (t, J = 6.5 Hz, 2H); from 7.23 to
(m, 4H); 7.50 (broad d, J = 8.5 Hz, 1H); 7.70 (d
1.0 Hz, 1H); 7.75 (broad m, 1H); 7.98 (d, J = 1.
1H). IR spectrum, KBr: 3380; 3162; 2921; 1646;
954; 858; 754 and 633 cm^{-1}. Mass spectrum (CI): m/
(MH^+) base peak.

4-(4-Cyanophenyl)-1-(2-piperidin-1-ylethyl)-1H-pyr
oxalate

The procedure is carried out as in example 15, but
0.098 g of sodium hydride (at 75% by mass in
petroleum jelly), 0.305 g of 1-(2-chloroet
piperidine hydrochloride and 0.2 g of
cyanophenyl)-1H-pyrazole. 0.373 g of 4-(4-c
phenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazole ox

tetrahydrofuran. After purification on a cartric
silica (particle size 20-40 μm), eluting with a m
of dichloromethane and of acetone (90/10 by vo
0.202 g of 4-(4-cyanophenyl)-1H-pyrazole is
obtained in the form of a white solid. ^{1}H NMR spe
(300 MHz) - δ in ppm - in DMSO-d6: 7.43 (m, 1H);
7.69 to 7.80 (m, 2H); 7.88 (m, 1H); from 8.00 to
(broad m, 2H); 13.3 (broad m, 1H). IR spectrum,
3153; 2966; 2218; 1601; 1516; 1347; 1044; 949; 763
and 501 cm^{-1}. Mass spectrum (EI): m/z=169 ($M^{+\cdot}$)
peak, m/z=142 [$(M-CHN)^+$], m/z=115 [$(m/z=142-CHN)^+$].

1-(Toluene-4-sulfonyl)-4-(4-cyanophenyl)-1H-pyrazo

The procedure is carried out as in example 41 fo
preparation of 3-benzyloxy-4-(5-chlorothiophen-1-y
(toluene-4-sulfonyl)-1H-pyrazole, but using 0.943
1-(toluene-4-sulfonyl)-4-tributylstannanyl-1H-pyra
0.43 g of 2-cyano-1-iodobenzene, 84 mg
tris(dibenzylideneacetone)palladium and 77 mg
tris(trifuryl)phosphine in 11 cm^3 of dioxane.

preparation of 3-benzyloxy-1-(toluene-4-sulfonyl)-4-
tributylstannanyl-1H-pyrazole, but using 1.5
1-(toluene-4-sulfonyl)-4-iodo-1H-pyrazole, 2.65 c
1,1,1,2,2,2-hexabutyldistannane, 58 mg of pal
diacetate and 136 mg of triphenylphosphine in 20
DMF. After 2 purifications on a cartridge of
(particle size 20-40 μm), eluting with cyclohexar
then a mixture of cyclohexane and of ethyl a
(95/5 by volume), 0.743 g of 1-(toluene-4-sulfon
tributylstannanyl-1H-pyrazole is thus obtained i
form of a colorless oil. IR spectrum, CH_2Cl_2:
2925; 2873; 2854; 1378; 1175; 1064; 957; 673; 5
543 cm^{-1}. Mass spectrum (EI): m/z=511 ($M^{+\cdot}$), m/z=4
- $C_4H_8)^{+\cdot}$] base peak, m/z=399 [(m/z=455 - C_4
m/z=343 [(m/z=399 - $C_4H_8)^{+\cdot}$], m/z=91 ($C_7H_7^+$).

Example 73

4-(2-Hydroxyphenyl)-1-(2-piperidin-1-ylethyl)-1H-
pyrazole hydrochloride

dichloromethane and of methanol (90/10 by volume)
gum obtained is taken up with a 1N hydrochloric di
ether solution. 0.172 g of 4-(2-hydroxyphenyl)-
piperidin-1-ylethyl)-1H-pyrazole hydrochloride
obtained in the form of a pink powder. ^{1}H NMR spe
(300 MHz) - δ in ppm - in DMSO-d6: from 1.30 to
(broad m, 6H); from 2.38 to 3.62 (very broad m,
from 4.22 to 4.60 (broad m, 2H); 6.82 (dt, J = 1.
8.0 Hz, 1H); 6.92 (broad d, J = 8.0 Hz, 1H); 7.03
J = 1.5 and 8.0 Hz, 1H); 7.54 (dd, J = 1.5 and 8.
1H); 7.98 (broad s, 1H); 8.23 (broad s, 1H); from
to 9.45 (very broad m, 1H); 9.76 (broad s, 1H
spectrum, KBr: 3144; 2938; 2539; 1560; 1461;
1282; 1238; 1111; 954; 856; 747 and 478 cm^{-1}.
spectrum (EI): m/z=271 ($M^{+\cdot}$), m/z=98 [$C_6H_{12}N^+$] base

4-(2-Methoxyphenyl)-1-(2-piperidin-1-ylethyl)-1H-
pyrazole oxalate

The procedure is carried out as in example 15, but
0.22 mg of sodium hydride (at 75% by mass in
petroleum jelly), 0.681 g of 1-(2-chloroet

The procedure is carried out as in example 38, bu
1.08 g of 1-(toluene-4-sulfonyl)-4-(2-methoxyph
1H-pyrazole and 7.3 cm^3 of a 1N solutio
tetrabutylammonium fluoride in tetrahydrofuran
58 cm^3 of tetrahydrofuran. After purification
cartridge of silica (particle size 20-40 μm), e
with a mixture of dichloromethane and of me
(90/10 by volume), 0.463 g of 4-(2-methoxypheny
pyrazole is thus obtained in the form of an off
solid. ^1H NMR spectrum (300 MHz) - δ in ppm - in
d6: 3.89 (s, 3H); 6.97 (dt, J = 1.5 and 8.5 Hz,
7.06 (broad d, J = 8.5 Hz, 1H); 7.21 (m, 1H); 7.6
J = 1.5 and 8.5 Hz, 1H); from 7.85 to 8.20 (very
m, 2H); 12.9 (broad m, 1H). IR spectrum, KBr:
2936; 2832; 1569; 1488; 1466; 1263; 1247; 1148;
950; 753; 661 and 628 cm^{-1}. Mass spectrum (EI): m/
($M^{+\cdot}$) base peak, m/z=159 [$(M - CH_3)^+$], m/z=131 [(m/
- CO)$^+$].

1-(Toluene-4-sulfonyl)-4-(2-methoxyphenyl)-1H-pyra

550 cm^{-1}. Mass spectrum (EI): m/z=328 ($M^{+\cdot}$) base
m/z=264 [$(M - SO_2)^{+\cdot}$], m/z=173 [$(M - C_7H_7SO_2)^+$],
($C_7H_7^+$).

Example 74

4-(1H-Indol-5-yl)-1-(2-piperidin-1-ylethyl)-1H-pyr

The procedure is carried out as in example 38, but
1.22 g of 4-iodo-1-(2-piperidin-1-ylethyl)-1H-pyra
1.93 g of 1H-indol-5-ylboronic acid, 2.547
tripotassium phosphate, 0.421 g of dichlo
(triphenylphosphine)palladium in 50 cm^3 of dimet
ethane. After purification by chromatography, un
nitrogen pressure of 50 kPa, on a column of silic
(particle size 20-45 μ; diameter 3 cm; height 6
eluting with a mixture of ethyl acetate and of met
(95/5 then 90/10 by volume), fractions 18 to 3
combined, and concentrated to dryness under re
pressure (3 kPa). 0.23 g of 4-(1H-indol-5-yl)-
piperidin-1-ylethyl)-1H-pyrazole is thus obtaine
the form of a whitish powder. ^1H NMR spectrum (300

the reaction medium is taken up with 1000 cm^3 of
acetate and 1000 cm^3 of water; the organic pha
separated by settling out, washed with 3 times 10
of water and 500 cm^3 of a saturated aqueous
chloride solution, dried over magnesium su
filtered, and concentrated to dryness under re
pressure (3 kPa). The residue is purifie
chromatography, under a nitrogen pressure of 50 k
a column of silica gel (particle size 20-45 μ; di
6 cm; height 60 cm), eluting with a mixture of
acetate and of cyclohexane (30/70 by volume) and
ethyl acetate. Fractions 16 to 20 are combined
concentrated to dryness under reduced pressure (3
8.2 g of 4-iodo-1-(2-piperidin-1-ylethyl)-1H-pyr
are thus obtained in the form of a light yellow o
NMR spectrum (300 MHz) - δ in ppm - in DMSO-d6:
1.34 to 1.52 (m, 6H); 2.36 (m, 4H); 2.64 (t, J
Hz, 2H); 4.22 (t, J = 6.5 Hz, 2H); 7.51 (broad s,
7.92 (broad s, 1H). Mass spectrum (CI): m/z=306
base peak.

in ppm - in DMSO-d6: 1.40 (m, 1H); from 1.63 to
(m, 5H); 2.30 (s, 3H); from 2.82 to 3.02 (broad m
from 3.27 to 3.53 (m, 4H); 4.38 (broad t, J = 6.
2H); 7.15 (broad d, J = 8.5 Hz, 2H); 7.54 (broad
8.5 Hz, 2H); 7.98 (s, 1H); 10.05 (very broad m,
10.4 (broad m, 1H). IR spectrum, KBr: 2941; 2646;
1534; 1447; 1179; 1010; 818; 627 and 515 cm^{-1}.
spectrum (EI): m/z=285 ($M^{+\cdot}$), m/z=98 ($C_6H_{12}N^+$) base

3-Benzyloxy-4-(4-methylphenyl)-1-(2-piperidin-1-yl
ethyl)-1H-pyrazole oxalate

The procedure is carried out as in example 15, but
0.123 g of sodium hydride (at 75% by mass in
petroleum jelly), 0.38 g of 1-(2-chloroethyl)piper
hydrochloride and 0.39 g of 3-benzyloxy-4-(4-me
phenyl)pyrazole. 0.632 g of 3-benzyloxy-
methylphenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazol
oxalate is thus obtained in the form of a white po
IR spectrum, KBr: 2931; 2639; 2543; 1719; 1618;
1519; 1452; 1279; 1180; 818; 721 and 500 cm^{-1}.
spectrum (CI): m/z=376 (MH^+) base peak.

The procedure is carried out as in example 38, bu
1 g of 1-(toluene-4-sulfonyl)-3-benzyloxy-4-io
pyrazole, 0.898 g of 4-methylphenylboronic
0.913 g of potassium carbonate and 0.331
tetrakis(triphenylphosphine)palladium in 13 cm
toluene, 3 cm^3 of ethanol and 3.3 cm^3 of water. 0
of 3-benzyloxy-1-(toluene-4-sulfonyl)-4-(4-m
phenyl)-1H-pyrazole is thus obtained in the form
pinkist-beige cottonwool-like solid. IR spectrum,
1589; 1485; 1377; 1191; 1179; 1098; 813; 702; 67
and 538 cm^{-1}. Mass spectrum (EI): m/z=418 ($M^{+\cdot}$), m
[(M - $C_7H_7SO_2$)$^+$], m/z=91 ($C_7H_7^+$) base peak.

Example 76

1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(1H-indol-5-yl)-
pyrazole

The procedure is carried out as in example 38, but
1 g of 1-(1-azabicyclo[2.2.2]oct-3-yl)-4-io
pyrazole, 0.797 g of 1H-indol-5-ylboronic acid, 1.
of potassium carbonate, 0.463 g of dichlor

1H); 11.0 (broad m, 1H). IR spectrum, KBr: 3113; 1587; 1454; 1362; 1165; 1058; 976; 881; 792; 729 and 435 cm^{-1}. Mass spectrum (ES): m/z=293 (MH^+) peak.

The enantiomers are separated by HPLC on chi AD 20 μm with, as eluent, a mixture of heptan ethanol and of butylamine (40/60/0.2 by volume) enantiomers, A and B, are obtained, which are pu according to the following protocol: enantiomer purified by extraction with ethyl acetate and solubilized in 100 ml of water. The pH of the so is adjusted to 10 with 0.1N sodium hydroxide organic phase is extracted with 100 ml of acetate. The aqueous phase is separated by settli with 2 x 50 ml of dichloromethane. The organic pha dried with anhydrous sodium sulfate, filtered, concentrated to dryness under reduced pressure organic phase is controlled by reverse-phase pol HPLC on a Thermo hypersil Hypurity C18 250*4.6 column; eluent: 95/5 gradient: acetate buffer/a nitrile for 50 minutes. 42.6 mg of (-)-1-(1-azabic

pyrazole, enantiomer B are obtained ($[\alpha]_D$ -
(solvent: dimethyl sulfoxide, concentration: 0.42)

1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-iodo-1H-pyrazole

The procedure is carried out as in example 5, but
0.48 g of sodium hydride (at 75% by mass in
petroleum jelly), 3.079 g of toluene-4-sulfonic
1-azabicyclo[2.2.2]oct-3-yl ester and 1.94 g of 4-
pyrazole in 30 cm^3 of dimethylformamide. The resid
purified by chromatography, under a nitrogen pre
of 50 kPa, on an alumina CBT1 column, eluting
ethyl acetate and then a mixture of ethyl acetat
of methanol (95/5 then 90/10 by volume). Fractio
to 39 are combined, and concentrated to dryness
reduced pressure (3 kPa). The oil obtained is
purified on an alumina CBT1 column, eluting with
acetate. Fractions 11 to 15 are combined,
concentrated to dryness under reduced pressure (3
0.33 g of 1-(1-azabicyclo[2.2.2]oct-3-yl)-4-iod
pyrazole is obtained in the form of an oil
crystallizes. ^1H NMR spectrum (400 MHz) - δ in ppm

to 100°C, and then cooled to a temperature clo
20°C; the reaction medium is concentrated to d
under reduced pressure (3 kPa), then taken up
twice 20 cm^3 of ethanol and concentrated to d
under reduced pressure (2 kPa); the residu
precipitated from 20 cm^3 of diisopropyl ether. 80
1-(1-azabicyclo[2.2.2]oct-3-yl)-4-(5-chlorothiophe
yl)-1H-pyrazol-3-ol hydrochloride, isomer A,
obtained in the form of a grayish powder. ^{1}
spectrum (300 MHz) - δ in ppm - in DMSO-d6: from
to 1.98 (m, 4H); 2.36 (m, 1H); from 3.07 to
(partially masked m, 4H); 3.71 (m, 2H); 4.62 (m,
7.03 (m, 2H); 8.10 (broad s, 1H); 10.75 (broad m,
IR spectrum, KBr: 1602; 1536; 1459; 1164; 1005; 7
502 cm^{-1}.

Mass spectrum (ES): m/z=310 (MH^+) base peak. $[\alpha]_D$ =
(solvent: MeOH, concentration 0.1266).

obtained is precipitated from 20 cm³ of diisop
ether. 100 mg of 1-(1-azabicyclo[2.2.2]oct-3-yl)-
chlorothiophen-2-yl)-1H-pyrazole-3-ol hydrochlo
isomer B, are obtained in the form of a grayish po
^{1}H NMR spectrum (300 MHz) - δ in ppm - in DMSO-d6:
1.62 to 2.00 (m, 4H); 2.38 (m, 1H); from 3.05 to
(m, 4H); 3.73 (m, 2H); 4.63 (m, 1H); 7.03 (m, 2H);
(broad s, 1H); 10.75 (broad m, 1H). IR spectrum,
1601; 1536; 1457; 1163; 1004; 794 and 502 cm^{-1}.
spectrum (CI): m/z=310 (MH^+) base peak. $[\alpha]_D$ =
(solvent: MeOH, concentration: 0.2168).

1-(1-Azabicyclo[2.2.2]oct-3-yl)-3-benzyloxy-4-(5-
chlorothiophen-2-yl)-1H-pyrazole, isomers A and B

The procedure is carried out as in example 5, but
0.495 g of sodium hydride (at 75% by mass in l
petroleum jelly), 3.178 g of toluene-4-sulfonic
1-azabicyclo[2.2.2]oct-3-yl ester and 1.94 g
3-benzyloxy-4-(5-chlorothiophen-2-yl)pyrazole in
of dimethylformamide. The residue is purifie
chromatography, under a nitrogen pressure of 50 kP

Using 0.45 g of 1-(1-aza-bicyclo[2.2.2]oct-3-y
benzyloxy-4-(5-chlorothiophen-2-yl)-1H-pyrazole,
enantiomers are separated by HPLC on chi
AD 20 μm, eluting with a mixture of 70% hepta
ethanol/15% methanol/0.1% triethylamine. 138 m
1-(1-azabicyclo[2.2.2]oct-3-yl)-3-benzyloxy-4-(5-
chlorothiophen-2-yl)-1H-pyrazole, isomer A ([
+28.2° (solvent: MeOH, concentration: 0.5)) and 1
of 1-(1-azabicyclo[2.2.2]oct-3-yl)-3-benzyloxy
chlorothiopen-2-yl)-1H-pyrazole, isomer B ($[\alpha]_D$ =
(solvent: MeOH, concentration: 0.5)) are obtained.
spectrum (IE): m/z=399 ($M^{+\cdot}$), m/z=308 [(M - C_7
m/z=110 ($C_7H_{12}N^+$), m/z=91 ($C_7H_7^+$) base peak.

Example 79

1-(1-Azabicyclo[2.2.2]oct-2-ylmethyl)-4-phenyl-1H-
pyrazol-3-ol hydrochloride

1.8 cm^3 of 6N hydrochloric acid is added to a sol
of 0.8 g of 2-(3-benzyloxy-4-phenylpyrazol-1-ylmet
1-azabicyclo[2.2.2]octane in 20 cm^3 of ethanol an

at 2.50 ppm): 1.55 (m, 1H); from 1.71 to 1.95 (m
2.08 (m, 1H); from 3.12 to 3.35 (partially mask
3H); 3.50 (m, 1H); 3.88 (m, 1H); 4.27 (dd, J = 7.
14.0 Hz, 1H); 4.42 (dd, J = 7.5 and 14.0 Hz, 1H);
(broad t, J = 7.5 Hz, 1H); 7.32 (broad t, J = 7.
2H); 7.63 (broad d, J = 7.5 Hz, 2H); 8.01 (s, 1H);
(broad m, 1H); 10.45 (broad m, 1H). Mass spe
(EI): m/z=283 ($M^{+\cdot}$), m/z=201 [(M - $C_5H_8N)^{+\cdot}$], m/
[(M - $C_7H_{12}N)^{+\cdot}$], m/z=124 ($C_8H_{14}N^+$) base peak, r
($C_5H_8N^+$), m/z=36 ($HCl^{+\cdot}$).

The 2-(3-benzyloxy-4-phenylpyrazol-1-ylmethyl)-1
bicyclo[2.2.2]octane can be obtained in the foll
way:

182 mg of sodium hydride (at 75% by mass in l
petroleum jelly) are added gradually, under an
atmosphere and at ambient temperature, to a soluti
0.95 g of 3-benzyloxy-4-phenylpyrazole in 20 c
anhydrous dimethylformamide. After stirring for t
quarters of an hour at a temperature in the regi
50°C, a solution of 1.25 g of 1-azabicyclo[2.2.2]c

oil which solidifies slowly as an amorphous solid
spectrum (EI): m/z=373 ($M^{+\cdot}$), m/z=282 [(M - C
m/z=124 ($C_8H_{14}N^+$), m/z=91 ($C_7H_7^+$) base peak,
($C_5H_8N^+$).

The 1-azabicyclo[2.2.2]oct-2-ylmethyl methanesul
can be obtained in the following way:

0.69 cm^3 of pyridine followed, dropwise, by 0.66
methanesulfonyl chloride are added, at a temperatu
the region of 0°C and under an argon atmosphere,
solution of 1 g of (1-azabicyclo[2.2.2]oct-
methanol in 40 cm^3 of dichloromethane. The suspens
stirred for 20 minutes at around 0°C and the
18 hours at ambient temperature. 15 cm^3 of a satu
potassium carbonate solution are then added t
mixture, which is extracted with 3 times 50 cm^3 of
acetate. The combined organic phases are dried
anhydrous magnesium sulfate, filtered, and concent
to dryness under reduced pressure (3 kPa). The re
obtained is purified by chromatography on alu
eluting with ethyl acetate. After concentratin

atmosphere and at ambient temperature, to a solut
0.65 g of 4-(3,5-difluorophenyl)-1H-pyrazole in
of anhydrous dimethylformamide. After stirring
three-quarters of an hour at a temperature i
region of 50°C, a solution of 1.17 g
3-[(methanesulfonyl)oxy]-1-azabicyclo[2.2.2]octane
10 cm^3 of anhydrous dimethylformamide is added drop
and the mixture is then heated for 20 hours
temperature in the region of 110°C. The mixtu
cooled to ambient temperature, 5 cm^3 of water are
added, and the mixture is concentrated under re
pressure (3 kPa). The residue is taken up with 20
water and extracted with 250 cm^3 of ethyl acetate
organic phase is washed with 4 times 20 cm^3 of w
then dried, filtered and concentrated to dryness
reduced pressure (3 kPa). The residue obtaine
purified by chromatography on alumina, eluting w
mixture of dichloromethane and of ethyl acetate
by volume). After concentrating the fractions
reduced pressure, an oil is obtained, whic
dissolved in 35 cm^3 of acetone and 20 cm^3 o
hydrochloric ether are added. After stirring for 1

15.7 cm^3 of a solution of tetrabutylammonium fluor
tetrahydrofuran at 1M are added, at a
temperature, to a solution of 2.1 g of 4-(3,5-dif
phenyl)-1-(toluene-4-sulfonyl)-1H-pyrazole in 70
tetrahydrofuran. The mixture is refluxed for 4.5
and then cooled to ambient temperature and concent
to dryness under reduced pressure (3 kPa). 50
water are added to the residue, which is extracte
200 cm^3 of ethyl acetate. The organic phase is
with 50 cm^3 of water and then with 25 cm^3 of brine
is finally dried over anhydrous magnesium su
filtered, and concentrated to dryness under re
pressure (3 kPa). The residue is triturated in 40
dichloromethane, and then isolated by filtration
vacuum. 0.65 g of 4-(3,5-difluorophenyl)-1H-pyrazo
thus obtained in the form of white crystals which
at around 185°C. Mass spectrum (EI): m/z=180 ($M^{+\cdot}$)
peak, m/z=153 [$(M - HCN)^+$], m/z=126 [(m/z=153 - HCN

The 4-(3,5-difluorophenyl)-1-(toluene-4-sulfonyl
pyrazole can be prepared in the following way:

under reduced pressure, 2.2 g of 4-(3,5-dif
phenyl)-1-(toluene-4-sulfonyl)-1H-pyrazole are ob
in the form of a white powder. Mass spectrum
m/z=334 ($M^{+\cdot}$), m/z=270 [$(M - SO_2)^{+\cdot}$], m/z=155 (C_7H
m/z=91 ($C_7H_7^+$) base peak.

Example 81

4-Benzo[b]thiophen-2-yl-1-(2-piperidin-1-ylethyl)-
pyrazol-3-ol hydrochloride

8 cm^3 of 12N hydrochloric acid are added to a st
solution of 930 mg of 1-[2-(4-benzo[b]thiophen-2-
benzyloxypyrazol-1-yl)ethyl]piperidine in 15 cm
ethanol. After 7 h at the reflux of the solvent
then 15 h at a temperature in the region of 20°C
reaction medium is evaporated to dryness under re
pressure (2.7 kPa). The residue is, three t
successively dissolved in ethanol and evaporate
dryness under reduced pressure (2.7 kPa) and is
triturated in 20 cm^3 of diisopropyl ether.
precipitate formed is filtered off and dried

pyrazole are added, portionwise, to a suspensi
225 mg of sodium hydride (at 75% in liquid pet
jelly) in 30 cm^3 of dimethylformamide under an
atmosphere and with stirring. After heating at 50
30 min, the mixture is stirred for 1 h at a tempe
in the region of 20°C, and then 725 mg of 1-(2-cl
ethyl)piperidine are added, portionwise, thereto
reaction medium is stirred for 15 h at a temperatu
the region of 20°C, and is then poured into 100
water. The aqueous phase is extracted twice with
acetate. The organic phases are combined,
successively with two times water and a satu
aqueous sodium chloride solution, dried over magn
sulfate, filtered, and evaporated under re
pressure (2.7 kPa), to give a yellow oil whi
purified by flash chromatography on alumina CBT1
an argon pressure (50 kPa) [eluent: cyclohexane/
acetate (95/5 by volume)]. After concentrating
fractions under reduced pressure, 930 mg of 1-
benzo[b]thiophen-2-yl-3-benzyloxypyrazol-1-yl)ethyl
piperidine are obtained in the form of a pale y
oil. ^1H NMR spectrum (300 MHz) - δ in ppm - in DMS

residue. The organic phase is washed successively
two times water and a saturated aqueous sodium chl
solution; it is dried over magnesium sulfate
evaporated under reduced pressure (2.7 kPa). The
yellow oil obtained (0.98 g) is purified by
chromatography on silica under an argon pre
(50 kPa) [eluent: cyclohexane/ethyl acetate (70/
volume)]. After concentrating the fractions
reduced pressure (2.7 kPa), 860 mg
4-benzo[b]thiophen-2-yl-3-benzyloxy-1H-pyrazole
obtained in the form of a white solid. IR spe
(KBr): 3173; 2950; 1586; 1530; 1501; 1445; 1363;
1215; 1166; 1022; 818; 745; 736; 727; 693 and 564

The 4-benzo[b]thiophen-2-yl-3-benzyloxy-1-(tolue
sulfonyl)-1H-pyrazole can be prepared in the foll
way:

2.4 g of 2-benzothienylboronic acid, 6.6 cm^3 of
aqueous potassium carbonate solution and 660 m
tetrakis(triphenylphosphine)palladium are added
solution, under an argon atmosphere with stirrin

solid is triturated in diisopropyl ether. filtration, 1.4 g of 4-benzo[b]thiophen-2- benzyloxy-1-(toluene-4-sulfonyl)-1H-pyrazole obtained in the form of a white solid. Mass spe (EI): 460(+)=M(+); 305(+)=M(+)-Ts.

Exemple 82

1-(2-Piperidin-1-ylethyl)-4-thiophen-3-yl-1H-pyraz ol hydrochloride

6 cm^3 of 12N hydrochloric acid are added to a st solution of 640 mg of 1-[2-(3-benzyloxy-4-thiop ylpyrazol-1-yl)ethyl]piperidine in 10 cm^3 of eth After 7 h at the reflux of the solvent, and then at a temperature in the region of 20°C, the rea medium is evaporated to dryness under reduced pre (2.7 kPa). The residue is, three times, success dissolved in ethanol and evaporated to dryness reduced pressure (2.7 kPa), and it is then tritu in diisopropyl ether. The precipitate forme filtered off and dried under vacuum (2.7 kPa), to

dimethylformamide under an argon atmosphere and
stirring. After heating for 30 min at 50°C, the mi
is stirred for 30 min at a temperature in the regi
20°C, and 654 mg of 1-(2-chloroethyl)piper
hydrochloride are then added portionwise thereto
reaction medium is stirred for 15 h at a temperatu
the region of 20°C and is then poured into 100 c
water. The aqueous phase is extracted twice with
acetate. The organic phases are combined, w
successively with two times water and a satu
aqueous sodium chloride solution, dried over magn
sulfate, filtered, and evaporated under re
pressure (2.7 kPa), to give an orangey oil whi
purified by flash chromatography on alumina CTB1
an argon pressure (50 kPa) [eluent: cyclohexane/
acetate (95/5 by volume)]. After concentrating
fractions under reduced pressure, 640 mg of 1-[
benzyloxy-4-thiophen-3-yl-pyrazol-1-yl)ethyl]piperi
are obtained in the form of a yellow oil. ^{1}H
spectrum (300 MHz) - δ in ppm - in DMSO-d6: from
to 1.54 (m, 6H); 2.38 (m, 4H); 2.67 (t, J = 6.

reduced pressure (2.7 kPa). The residue obt
(0.96 g) is purified by flash chromatography on s
under an argon pressure (50 kPa) [el
cyclohexane/ethyl acetate (70/30 by volume)].
concentrating the fractions under reduced pre
(2.7 kPa), 650 mg of 3-benzyloxy-4-thiophen-3-y
pyrazole are obtained in the form of a cream s
Mass spectrum (EI): 256(+)=M(+); 91(+)=C_7H_7(+).

The 3-benzyloxy-4-thiophen-3-yl-1-(toluene-4-sulfo
1H-pyrazole can be prepared in the following way:

1.7 g of 3-thienylboronic acid, 6.6 cm^3 of a 2N ac
potassium carbonate solution and 660 mg
tetrakis(triphenylphosphine)palladium are added
solution, under an argon atmosphere and with stir
of 2 g of 3-benzyloxy-4-iodo-1-(toluene-4-sulfonyl
pyrazole in 40 cm^3 of toluene to which 10 cm^3 of et
have been added. After heating for 5 h at the refl
the solvent and for 16 h at a temperature in the r
of 20°C, the reaction medium is evaporated
reduced pressure (2.7 kPa). Ethyl acetate, wate

4 cm^3 of 3N hydrochloric diethyl ether are added
solution of 442 mg of 4-[3-benzyloxy-1-(2-piperi
ylethyl)-1H-pyrazol-4-yl]benzamide in 20 cm^3 of et
After stirring for 1 h at a temperature in the
of 20°C, the solution is evaporated to dryness
reduced pressure (2.7 kPa). The residue is tak
with 25 cm^3 of ethanol. The solution obtain
introduced into an autoclave, and 52 mg of palla
on-charcoal at 10% are added thereto, and it is
placed under hydrogen (10 bar). After stirring fo
at 22°C, the reaction medium is filtered th
supercel, the filtrate is evaporated and the resi
triturated in diisopropyl ether. The resulting sol
filtered off, and dried under vacuum (2.7 kPa), to
118 mg of 4-[3-hydroxy-1-(2-piperidin-1-ylethyl
pyrazol-4-yl]benzamide hydrochloride in the form
cream solid. Mass spectrum (CI): 315(+)=(M+H)(+).
spectrum (300 MHz) - δ in ppm - in DMSO-d6: 1.4
1H); from 1.64 to 1.89 (m, 5H); 2.94 (m, 2H); from
to 3.53 (m, 4H); 4.41 (t, J = 6.5 Hz, 2H); 7.23
m, 1H); 7.73 (broad d, J = 8.5 Hz, 2H); from 7.

water. The aqueous phase is extracted twice with
acetate. The organic phases are combined, w
successively with two times water and a satu
aqueous sodium chloride solution, dried over magn
sulfate, filtered and evaporated under reduced pre
(2.7 kPa). The resulting solid is triturate
diisopropyl ether, filtered and crystallized
acetone. 445 mg of 4-[3-benzyloxy-1-(2-piperidin-
ethyl)-1H-pyrazol-4-yl]benzamide are thus obtain
the form of a white solid. ^{1}H NMR spectrum (300 MHz
in ppm - DMSO-d6: from 1.32 to 1.54 (m, 6H); 2.3
4H); 2.69 (t, J = 6.5 Hz, 2H); 4.09 (t, J = 6.
2H); 5.33 (s, 2H); 7.24 (broad m, 1H); from 7.
7.46 (m, 3H); 7.52 (broad d, J = 8.5 Hz, 2H);
(broad d, J = 7.5 Hz, 2H); from 7.81 to 7.88 (m,
8.17 (s, 1H).

The 4-(3-benzyloxy-1H-pyrazol-4-yl)benzamide can
prepared in the following way:

6.5 cm^3 of a 1N solution of tetrabutylammonium flu
in tetrahydrofuran are added to a solution, unde

tetrakis(triphenylphosphine)palladium are added
solution, under an argon atmosphere and with stir
of 2.5 g of 3-benzyloxy-4-iodo-1-(toluene-4-sulfo
1H-pyrazole in 40 cm^3 of toluene to which 10 c
ethanol have been added. After heating for 15 h a
reflux of the solvent, the reaction medium is cool
a temperature in the region of 20°C and evapo
under reduced pressure (2.7 kPa). Ethyl acetate,
and carbon black are added to the residue, whi
filtered through supercel. The filtrate is separat
settling out, and the organic phase is then w
successively with two times water and a satu
aqueous sodium chloride solution; it is dried
magnesium sulfate and evaporated under reduced pre
(2.7 kPa). The yellow oil obtained (3.7 g) is pur
by flash chromatography on silica under an
pressure (50 kPa) [eluent: cyclohexane/ethyl ac
(50/50 then 20/80 by volume)]. After concentratin
fractions under reduced pressure (2.7 kPa), 1.1
4-[3-benzyloxy-1-(toluene-4-sulfonyl)-1H-pyrazol-4-
benzamide are obtained in the form of a white s
Mass spectrum (EI): 447(+)=M(+); 91(+)=C_7H_7(+).

supercel, the filtrate is evaporated and the resi
triturated in diisopropyl ether. The resulting sol
filtered off, and dried under vacuum (2.7 kPa), to
528 mg of 3-[3-hydroxy-1-(2-piperidin-1-ylethyl
pyrazol-4-yl]benzamide hydrochloride in the form
pale yellow solid. Mass spectrum (CI): 315(+)=(M+H
^{1}H NMR spectrum (300 MHz) - δ in ppm - in DMSO-d6:
(m, 1H); from 1.65 to 1.88 (m, 5H); 2.94 (m, 2H);
3.41 to 3.54 (m, 4H); 4.42 (t, J = 6.5 Hz, 2H);
(broad m, 1H); 7.42 (t, J = 8.0 Hz, 1H); 7.64 (bro
J = 8.0 Hz, 1H); 7.82 (broad d, J = 8.0 Hz, 1H);
(broad m, 1H); 8.10 (s, 1H); 8.14 (broad s, 1H);
9.90 to 10.05 (very broad m, 1H); 10.55 (broad s,

The 3-[3-benzyloxy-1-(2-piperidin-1-ylethyl
pyrazol-4-yl]benzamide can be prepared in the foll
way:

1.16 g of 3-(3-benzyloxy-1H-pyrazol-4-yl)benzamide
added, portionwise, to a suspension of 315 mg of s
hydride (75% in liquid petroleum jelly) in 30 c
dimethylformamide under an argon atmosphere and

piperidin-1-ylethyl)-1H-pyrazol-4-yl]benzamide
obtained in the form of a pale yellow oil. [1]
spectrum (300 MHz) - δ in ppm - in DMSO-d6: from
to 1.54 (m, 6H); 2.40 (m, 4H); 2.70 (t, J = 6.
2H); 4.10 (t, J = 6.5 Hz, 2H); 5.33 (s, 2H); from
to 7.44 (m, 5H); 7.53 (broad d, J = 8.5 Hz, 2H);
(broad d, J = 8.0 Hz, 1H); 7.80 (broad d, J = 8.
1H); 7.92 (broad m, 1H); 8.11 (s, 1H); 8.15 (bro
1H).

The 3-(3-benzyloxy-1H-pyrazol-4-yl)benzamide ca
prepared in the following way:

11.8 cm^3 of a 1N solution of tetrabutylamm
fluoride in tetrahydrofuran is added to a solu
under an argon atmosphere and with stirring, of
of 3-[3-benzyloxy-1-(toluene-4-sulfonyl)-1H-pyraz
yl]benzamide in 40 cm^3 of tetrahydrofuran.
heating for 15 h at the reflux of the solvent,
reaction medium is evaporated under reduced pre
(2.7 kPa) and ethyl acetate is added to the res
The organic phase is washed successively with two

of 2.5 g of 3-benzyloxy-4-iodo-1-(toluene-4-sulf
1H-pyrazole in 40 cm^3 of toluene to which 10 c
ethanol have been added. After heating for 15 h a
reflux of the solvent, the reaction medium is cool
an ice bath. After filtration and then drying c
resulting crystals under vacuum (2.7 kPa), 2.1
3-[3-benzyloxy-1-(toluene-4-sulfonyl)-1H-pyrazol-4
benzamide are obtained in the form of a white s
Mass spectrum (EI): 447(+)=M(+); 91(+)=C_7H_7(+).

Example 85

(-)-1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-phenyl-1H-pyrazol-3-ol hydrochloride

15 cm^3 of 12N hydrochloric acid are added to a st
solution of 1.44 g of (+)-3-(3-benzylo
phenylpyrazol-1-yl)-1-azabicyclo[2.2.2]octane in 2
of ethanol. After 7 h at the reflux of the solvent
then 15 h at a temperature in the region of 20°C
reaction medium is evaporated to dryness under re
pressure (2.7 kPa). The residue is, three t

bicyclo[2.2.2]octane and the (-)-3-(3-benzyl
phenylpyrazol-1-yl)-1-azabicyclo[2.2.2]octane ca
prepared in the following way: an ethanolic sol
containing 1.5 g of 3-(3-benzyloxy-4-phenylpyraz
yl)-1-azabicyclo[2.2.2]octane is introduced on
column, 6 cm in diameter, containing 800 g of Chi
AD™ chiral stationary phase. The elution is carrie
by means of a mixture of 10% ethanol, 10% meth
0.1% triethylamine and 80% heptane. The flow o
mobile phase is 90 ml/min. The dextroro
enantiomer is eluted in the first position,
solution is evaporated to dryness under re
pressure (2.7 kPa), to give 0.66 g of oil.

^{1}H NMR spectrum (300 MHz) - δ in ppm - in DMSO-d6:
(m, 1H); from 1.50 to 1.71 (m, 3H); 2.08 (m, 1H);
2.65 to 2.79 (m, 3H); 2.99 (m, 1H); from 3.15 to
(m, 2H); 4.27 (m, 1H); 5.33 (s, 2H); 7.15 (tt, J
and 7.5 Hz, 1H); from 7.30 to 7.44 (m, 5H); 7.51 (
d, J = 7.5 Hz, 2H); 7.69 (broad d, J = 7.5 Hz,
8.20 (s, 1H). $[\alpha]^{20}_D$ = +27.0 +/- 0.8° (*c* 0.5, MeOH)
solution containing the levorotatory enantiomer e

solution of 1.44 g of (-)-3-(3-benzyl
phenylpyrazol-1-yl)-1-azabicyclo[2.2.2]octane in 2
of ethanol. After 7 h at the reflux of the solvent
then 15 h at a temperature in the region of 20°C
reaction medium is evaporated to dryness under re
pressure (2.7 kPa). The residue is, three t
successively dissolved in ethanol and evaporate
dryness under reduced pressure (2.7 kPa), and is
triturated in 20 cm^3 of diisopropyl ether.
precipitate formed is filtered off and dried
vacuum (2.7 kPa), to give 1.2 g of (+)-1-(1
bicyclo[2.2.2]oct-3-yl)-4-phenyl-1H-pyrazol-3-ol
hydrochloride in the form of a beige solid.
spectrum (EI): 269(+)=M(+); presence
38(+)=HCl(+). ^1H NMR spectrum (300 MHz) - δ in ppm
DMSO-d6: from 1.70 to 2.03 (m, 4H); 2.43 (m, 1H);
3.22 to 3.47 (m, 4H); from 3.72 to 3.86 (m, 2H);
(m, 1H); 7.15 (tt, J = 1.5 and 7.5 Hz, 1H); 7.34
t, J = 7.5 Hz, 2H); 7.67 (broad d, J = 7.5 Hz,
8.19 (s, 1H); 10.2 (broad m, 1H); from 10.3 to
(very broad m, 1H). $[\alpha]^{20}_D$ = +13.7 +/- 0.6° (*c* 0.5, M

bicyclo[2.2.2]oct-3-ylmethyl)-4-phenyl-1H-pyrazol-
hydrochloride in the form of a white solid.
spectrum (EI): 283(+)=M(+). ^{1}H NMR spectrum (300 M
δ in ppm - in DMSO-d6: from 1.66 to 1.93 (m, 4H);
(m, 1H); 2.52 (masked m, 1H); 2.94 (m, 1H); from
to 3.40 (m, 5H); from 3.98 to 4.12 (m, 2H); 7.13
= 1.5 and 7.5 Hz, 1H); 7.33 (broad t, J = 7.5 Hz,
7.64 (broad d, J = 7.5 Hz, 2H); 7.99 (s, 1H);
(broad m, 1H). $[\alpha]^{20}_D$ = -36.8 +/- 0.8° (*c* 0.5, MeOH)

The (-)-3-(3-benzyloxy-4-phenylpyrazol-1-ylmethy
azabicyclo[2.2.2]octane and the (+)-3-(3-benzylo
phenylpyrazol-1-ylmethyl)-1-azabicyclo[2.2.2]octane
be prepared in the following way:

A solution of 5 g of 3-benzyloxy-4-phenylpyrazol
30 cm^3 of dimethylformamide is added gradually, und
argon atmosphere and at a temperature in the regi
20°C, to a suspension of 1.9 g of sodium hydride
by mass in liquid petroleum jelly) in 50 cm
dimethylformamide. After stirring for 1 h
temperature in the region of 50°C, 5.8 g

introduced onto a column, 8 cm in diameter, conta
1180 g of Chiracel OD™ chiral stationary phase
elution is carried out by means of a mixture o
ethanol, 0.1% triethylamine and 50% heptane. The
rate of the mobile phase is 120 ml/min.
levorotatory enantiomer is eluted in the
position, the solution is evaporated to dryness
reduced pressure (2.7 kPa), to give 0.82 g of oil.

^{1}H NMR spectrum (300 MHz) - δ in ppm - in DMSO-d6:
1.24 to 1.59 (m, 4H); 1.78 (m, 1H); 2.14 (m, 1H);
(m, 1H); from 2.59 to 2.90 (m, 5H); 3.89 (d, J
Hz, 2H); 5.31 (s, 2H); 7.14 (tt, J = 1.5 and 7.
1H); from 7.30 to 7.44 (m, 5H); 7.50 (broad d, J
Hz, 2H); 7.64 (broad d, J = 8.5 Hz, 2H); 8.09 (s,
$[\alpha]^{20}_D$ = -37.8 +/- 0.8° (*c* 0.5, MeOH). The sol
containing the dextrorotatory enantiomer eluted i
second position is evaporated to dryness under re
pressure (2.7 kPa), to give 0.74 g of oil.

^{1}H NMR spectrum (300 MHz) - δ in ppm - in DMSO-d6:
1.24 to 1.60 (m, 4H); 1.78 (m, 1H); 2.14 (m, 1H);

dryness under reduced pressure (2.7 kPa), and
then triturated in diisopropyl ether. The precip
formed is filtered off and dried under
(2.7 kPa), to give 600 mg of (+)-1-(
bicyclo[2.2.2]oct-3-ylmethyl)-4-phenyl-1H-pyrazol-
hydrochloride in the form of a white solid.
spectrum (EI): 283(+)=M(+). ^{1}H NMR spectrum (300 M
δ in ppm - in DMSO-d6: from 1.67 to 1.94 (m, 4H);
(m, 1H); 2.52 (masked m, 1H); 2.94 (m, 1H); from
to 3.40 (m, 5H); from 3.99 to 4.12 (m, 2H); 7.13
= 1.5 and 7.5 Hz, 1H); 7.33 (broad t, J = 7.5 Hz,
7.64 (broad d, J = 7.5 Hz, 2H); 7.99 (s, 1H);
(broad m, 1H). $[\alpha]^{20}_D$ = +36.5 +/- 0.8° (*c* 0.5, MeOH

Example 89

1-(1-Azabicyclo[2.2.2]oct-3-ylmethyl)-4-(4-chlorophe
1H-pyrazol-3-ol hydrochloride

10 cm^3 of 12N hydrochloric acid are added to a st
solution of 430 mg of 3-[3-benzyloxy-4-(4-chlorophe
pyrazol-1-ylmethyl]-1-azabicyclo[2.2.2]octanebo

(m, 1H); from 2.66 to 2.81 (m, 4H); 2.88 (m, 1H);
(d, J = 8.0 Hz, 2H); 7.37 (broad d, J = 8.5 Hz,
7.67 (broad d, J. = 8.5 Hz, 2H); 8.00 (s, 1H);
10.35 to 10.5 (very broad m, 1H).

The 3-[3-benzyloxy-4-(4-chlorophenyl)pyrazol-1-ylmet
1-azabicyclo[2.2.2]octaneborane can be prepared i
following way:

A solution of 3 g of 3-benzyloxy-4-(4-chlorophenyl
pyrazole and of 3 g of potassium tert-butoxide in
of dimethylformamide, under an inert atmosphere and
stirring, is heated for 30 min at 50°C, and 3.1
3-chloromethyl-1-azabicyclo[2.2.2]octane hydrochl
are then added thereto. After refluxing for 15 h
reaction medium is poured into water, and the mi
is extracted with two times ethyl acetate. The or
phases are washed successively with two times wate
a saturated aqueous sodium chloride solution,
over magnesium sulfate, and evaporated under re
pressure (2.7 kPa). The beige oil (5.3 g) obtain
purified by flash chromatography on alumina CTB1

CTB1 under an argon pressure (50 kPa) [eluent: acetate, ethyl acetate/methanol (90/10 by volume) dichloromethane/methanol (80/20 by volume)]. concentrating the fractions under reduced pr (2.7 kPa), 430 mg of 3-[3-benzyloxy-4-(4-chloroph pyrazol-1-ylmethyl]-1-azabicyclo[2.2.2]octaneboran obtained in the form of an oil which is used w any other purification for the remainder o synthesis.

Example 90

(-)-1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(4-chlorophe 1H-pyrazol-3-ol hydrochloride

7 cm^3 of 12N hydrochloric acid are added to a s solution of 690 mg of (+)-3-[3-benzyloxy-4-(4-c phenyl)pyrazol-1-yl]-1-azabicyclo[2.2.2]octane in of ethanol. After 7 h at the reflux of the solvent reaction medium is cooled to a temperature i region of 20°C and evaporated to dryness under re pressure (2.7 kPa). The residue is triturated in

An ethanolic solution containing 0.29 g of (+/-)
benzyloxy-4-(4-chlorophenyl)pyrazol-1-yl]-1-azabic
[2.2.2]octane is introduced onto a column, 8
diameter, containing 1180 g of Chiralpak AD™
stationary phase. The elution is carried out by
of a mixture of heptane, of ethanol, of methanol
triethylamine (80/10/10/0.1 by volume), the flow
of the mobile phase being 120 ml/min. The de
rotatory enantiomer is eluted in the first posi
the solution is evaporated to dryness under re
pressure (2.7 kPa), so as to obtain 0.69 g of (+)
benzyloxy-4-(4-chlorophenyl)pyrazol-1-yl]-1-azabic
[2.2.2]octane in the form of an oil.

Mass spectrum (EI): 393(+)/...=M(+)/... (1 Cl); 9
C_7H_7. $[\alpha]^{20}_D$ = +25.4 +/- 0.8° (*c* 0.5, MeOH). The sol
containing the levorotatory enantiomer eluted i
second position is evaporated to dryness under re
pressure (2.7 kPa) so as to obtain 0.69 g of (-)
benzyloxy-4-(4-chlorophenyl)pyrazol-1-yl]-1-azabic
[2.2.2]octane in the form of an oil.

pressure (2.7 kPa), to give 580 mg of (+)-1-(
bicyclo[2.2.2]oct-3-yl)-4-(4-chlorophenyl)-1H-pyra
3-ol hydrochloride in the form of a beige solid.
spectrum (EI): 303(+)/...=M(+)/... (1 Cl). ^{1}H
spectrum (300 MHz) - δ in ppm - in DMSO-d6: from
to 2.02 (m, 4H); 2.42 (m, 1H); from 3.22 to 3.5
4H); 3.79 (m, 2H); 4.66 (m, 1H); 7.41 (broad d
8.5 Hz, 2H); 7.71 (broad d, J = 8.5 Hz, 2H); 8.2
1H); from 10.2 to 10.3 (very broad m, 1H); 10.65
m, 1H). $[\alpha]^{20}_D$ = +17.7 +/- 0.6° (*c* 0.5, MeOH).

Example 92

(-)-1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(4-fluorophe
1H-pyrazol-3-ol hydrochloride

5 cm^3 of 12N hydrochloric acid are added to a st
solution of 135 mg of (+)-3-[3-benzyloxy-4-(4-fl
phenyl)pyrazol-1-yl]-1-azabicyclo[2.2.2]octane in
of ethanol. After 7 h at the reflux of the solvent
reaction medium is cooled to a temperature in
region of 20°C and evaporated to dryness under re

A solution of 2 g of 3-benzyloxy-4-(4-fluorophenyl
pyrazole and of 1 g of potassium tert-butoxide in
of dimethylformamide, under an inert atmospher
stirred for 1 h 30 min at a temperature in the
of 20°C, and then a solution of 2.3 g of to
4-sulfonic acid 1-azabicyclo[2.2.2]oct-3-yl est
25 cm^3 of dimethylformamide is added thereto.
heating for 15 h at 100°C, the reaction medi
poured into water, and the mixture is extracted
two times ethyl acetate. The combined organic
are washed successively with two times water
saturated aqueous sodium chloride solution, dried
magnesium sulfate and evaporated under reduced pre
(2.7 kPa). The orangey oil obtained (2.3 g) is pur
by flash chromatography on alumina CTB1 under an
pressure (50 kPa) [eluent: ethyl acetate then
acetate/methanol (98/2 by volume)]. After concentr
the fractions under reduced pressure (2.7 kPa)
orangey oil is obtained (1.5 g), which is purifi
flash chromatography on silica under an argon pre
(50 kPa) [eluent: ethyl acetate/methanol (95/

An ethanolic solution containing 0.29 g of (+/-)-
benzyloxy-4-(4-fluorophenyl)pyrazol-1-yl]-1-azabic
[2.2.2]octane is introduced onto a column, 8
diameter, containing 1180 g of Chiralpak AD™
stationary phase. The elution is carried out by
of a mixture of heptane, of ethanol, of methanol a
triethylamine (80/10/10/0.1 by volume), the flow
of the mobile phase being 120 ml/min. The de
rotatory enantiomer is eluted in the first posi
the solution is evaporated to dryness under re
pressure (2.7 kPa) to give 0.135 g of (+)-3-[3-be
oxy-4-(4-fluorophenyl)pyrazol-1-yl]-1-azabicyclo[2.
octane in the form of an oil.

^{1}H NMR spectrum (300 MHz) - δ in ppm - in DMSO-d6:
(m, 1H); from 1.50 to 1.71 (m, 3H); 2.08 (m, 1H);
2.64 to 2.80 (m, 3H); 2.99 (m, 1H); from 3.16 to
(m, 2H); 4.26 (m, 1H); 5.33 (m, 2H); 7.17 (broad t
9.0 Hz, 2H); from 7.30 to 7.44 (m, 3H); 7.50 (bro
J = 7.5 Hz, 2H); 7.71 (broad dd, J = 6.0 and 9.
2H); 8.20 (s, 1H). $[\alpha]^{20}_D$ = +21.5 +/- 0.5° (c

20 cm^3 of a 1N solution of tetrabutylammonium flu
in tetrahydrofuran are added to a solution, und
argon atmosphere and with stirring, of 3.5
3-benzyloxy-4-(4-fluorophenyl)-1-(toluene-4-sulfon
1H-pyrazole in 50 cm^3 of tetrahydrofuran. After he
for 15 h at the reflux of the solvent, the rea
medium is evaporated under reduced pressure (2.7
and ethyl acetate is added to the residue. The or
phase is washed successively with two times water
saturated aqueous sodium chloride solution; it is
over magnesium sulfate and evaporated under re
pressure (2.7 kPa). The yellow solid obtained (2
is purified by flash chromatography on silica und
argon pressure (50 kPa) [eluent: cyclohexane/
acetate (70/30 by volume)]. After concentrating
fractions under reduced pressure (2.7 kPa), 2
3-benzyloxy-4-(4-fluorophenyl)-1H-pyrazole are obt
in the form of a white solid. Mass spectrum
268(+)=M(+).

with three times water and a saturated aqueous s
chloride solution; it is dried over magnesium su
and evaporated under reduced pressure (2.7 kPa)
yellow solid obtained (9 g) is purified by
chromatography on silica under an argon pre
(50 kPa) [eluent: cyclohexane/ethyl acetate (95/
volume)]. After concentrating the fractions
reduced pressure (2.7 kPa), 3.5 g of 3-benzylo
(4-fluorophenyl)-1-(toluene-4-sulfonyl)-1H-pyrazole
obtained in the form of a yellow solid. Mass spe
(EI): 422(+)=M(+); 267(+)=422(+)-Ts; 91(+)=C_7H_7(+).

Example 93

(+)-1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(4-fluopher
1H-pyrazol-3-ol hydrochloride

5 cm^3 of 12N hydrochloric acid are added to a st
solution of 137 mg of (-)-3-[3-benzyloxy-4-(4-fl
phenyl)pyrazol-1-yl]-1-azabicyclo[2.2.2]octane in
of ethanol. After 7 h at the reflux of the solvent
reaction medium is cooled to a temperature in

octane hydrochloride

A solution of 600 mg of 4-(4-chlorophenyl)-1H-pyr
and of 420 mg of potassium tert-butoxide in 20 c
dimethylformamide, in an inert atmosphere, is st
for 2 h at a temperature in the region of 20°C
then a solution of 1.1 g of toluene-4-sulfonic
1-azabicyclo[2.2.2]oct-3-yl ester in 20 cm^3 of dime
formamide is added thereto. After heating for 15
100°C, reaction medium is poured into water, an
mixture is extracted with two times ethyl acetate
combined organic phases are washed successively
two times water and a saturated aqueous sodium chl
solution, dried over magnesium sulfate, and evapo
under reduced pressure (2.7 kPa). The orangey
obtained (1 g) is purified by flash chromatograp
alumina CTB1 under an argon pressure (50 kPa) [el
ethyl acetate then ethyl acetate/methanol (95/
volume)]. After concentrating the fractions
reduced pressure (2.7 kPa), an orangey oil is obt
(840 mg) which is purified by flash chromatograp
silica under an argon pressure (50 kPa) [eluent:

7.64 (broad d, J = 8.5 Hz, 2H); 8.05 (s, 1H); 8.4
1H); from 10.05 to 10.35 (very broad m, 1H).

The 4-(4-chlorophenyl)-1H-pyrazole can be prepar
the following way:

21 cm^3 of a 1N solution of tetrabutylammonium flu
in tetrahydrofuran are added to a solution, und
argon atmosphere and with stirring, of 2.8
4-(4-chlorophenyl)-1-(toluene-4-sulfonyl)-1H-pyrazo
30 cm^3 of tetrahydrofuran. After heating for 8 h a
reflux of the solvent, the reaction mediu
evaporated under reduced pressure (2.7 kPa) and
acetate is added to the residue. The organic pha
washed successively with two times water a
saturated aqueous sodium chloride solution; it is
over magnesium sulfate and evaporated under re
pressure (2.7 kPa). The yellow solid obtained (2
is purified by flash chromatography on silica und
argon pressure (50 kPa) [eluent: cyclohexane/
acetate (50/50 by volume)]. After concentrating
fractions under reduced pressure (2.7 kPa), 1.2

acetate, water and carbon black are added t
residue, which is filtered through supercel.
filtrate is separated by settling out, and the or
phase is then washed successively with two times
and a saturated aqueous sodium chloride solution;
dried over magnesium sulfate and evaporated
reduced pressure (2.7 kPa). The oil obtained (10
is purified by flash chromatography on silica und
argon pressure (50 kPa) [eluent: cyclohexane/
acetate (90/10 by volume)]. After concentrating
fractions under reduced pressure (2.7 kPa),
resulting solid is triturated in diisopropyl e
After filtration and drying under reduced pre
(2.7 kPa), 2.8 g of 4-(4-chlorophenyl)-1-(tolue
sulfonyl)-1H-pyrazole are obtained in the form
orangey solid. ^{1}H NMR spectrum (300 MHz) - δ in ppm
DMSO-d6: 2.41 (s, 3H); from 7.44 to 7.53 (m, 4H);
(broad d, J = 9.0 Hz, 2H); 7.92 (broad d, J = 9.
2H); 8.42 (s, 1H); 9.04 (s, 1H).

aqueous phase is extracted with two times
acetate. The combined organic phases are washed
two times water and brine, and are then dried
magnesium sulfate, filtered, and concentrate
dryness under reduced pressure (2.7 kPa). The or
oil obtained (1.3 g) is purified by
chromatography on alumina CTB1 under an argon pre
(50 kPa) [eluent: ethyl acetate then
acetate/methanol (99/1 then 97/3 by volume)].
concentrating the fractions under reduced pre
(2.7 kPa), an oil is obtained (520 mg) whic
purified by flash chromatography on silica unde
argon pressure (50 kPa) [eluent: dichlorometha
ammoniacal methanol (97/3 by volume)]. Concentr
the appropriate fractions under reduced pre
(2.7 kPa) gives a pale yellow oil (330 mg) whic
dissolved in ethyl acetate. 0.985 cm^3 of 1N hydroch
ether is added to the solution, which is
evaporated to dryness under reduced pressure (2.7
The residue is triturated in diisopropyl ether an
resulting solid is filtered and then dried
reduced pressure (2.7 kPa), to give 353 mg of

gradually, under an argon atmosphere and
temperature in the region of 20°C, to a suspensi
530 mg of sodium hydride (at 75% by mass in
petroleum jelly) in 15 cm^3 of dimethylformamide.
stirring for 1 h at a temperature in the regi
50°C, 2.07 g of 3-chloromethyl-1-azabicyclo[2.2.2]
hydrochloride are added in small portions, an
mixture is then heated for 15 hours at a temperatu
the region of 100°C. The mixture is cooled
temperature in the region of 20°C and is then p
into water. The aqueous phase is extracted wit
times ethyl acetate. The combined organic phase
washed with two times water and brine, and then
over magnesium sulfate, filtered, and concentrat
dryness under reduced pressure (2.7 kPa). The or
oil obtained (1.8 g) is purified by flash chromatog
on alumina CTB1 under an argon pressure (50
[eluent: ethyl acetate then ethyl acetate/met
(98/2 then 95/5 by volume)]. After concentratin
fractions under reduced pressure (2.7 kPa), an o
obtained (550 mg) which is purified by flash chro
graphy on silica under an argon pressure (50

7.50 (dd, J = 2.0 and 8.0 Hz, 1H); 7.64 (d, J = 2
1H); 7.85 (s, 1H); 8.08 (s, 1H).

The 4-(3-chloro-4-methoxyphenyl)-1H-pyrazole ca
prepared in the following way:

35 cm^3 of a 1N solution of tetrabutylammonium flu
in tetrahydrofuran are added to a solution, und
argon atmosphere and with stirring, of 5.2
4-(3-chloro-4-methoxyphenyl)-1-(toluene-4-sulfonyl
pyrazole in 50 cm^3 of tetrahydrofuran. After heatir
6 h at the reflux of the solvent, the reaction m
is evaporated under reduced pressure (2.7 kPa)
ethyl acetate is added to the residue. The or
phase is washed successively with two times wate
the saturated aqueous sodium chloride solution;
dried over magnesium sulfate and evaporated
reduced pressure (2.7 kPa). The orangey solid obt
(5.1 g) is purified by flash chromatography on s
under an argon pressure (50 kPa) [eluent: cyclohe
ethyl acetate (50/50 by volume)]. After concentr
the fractions under reduced pressure (2.7 kPa), 1

residue, which is filtered through supercel
filtrate is separated by settling out, and the o
phase is then washed successively with two times
and a saturated aqueous sodium chloride solution;
dried over magnesium sulfate and evaporated
reduced pressure (2.7 kPa). The solid obtain
triturated in ethyl acetate, filtered and dried
reduced pressure (2.7 kPa), to give 5.2
4-(3-chloro-4-methoxyphenyl)-1-(toluene-4-sulfonyl
pyrazole in the form of a beige solid that is
without any other purification in the subsequent
^{1}H NMR spectrum (300 MHz) - δ in ppm - in DMSO-d
70% of the mixture: 2.40 (m, 3H); 3.88 (broad s,
7.19 (d, J = 8.5 Hz, 1H); 7.50 (broad d, J = 8
2H); 7.71 (dd, J = 2.0 and 8.5 Hz, 1H); from 7.
7.93 (m, 3H); 8.41 (s, 1H); 8.99 (s, 1H) (
evaluated at 70% by ^{1}H NMR + starting boronic acid)

filtered off, and taken up in ethanol under conditions. After filtration of the suspension hot conditions, water and carbon black are added t filtrate, which is filtered through Wattman® pape evaporated to dryness under reduced pressure (2.7 The resulting beige solid (330 mg) is dissolv 10 cm^3 of ethanol and 10 cm^3 of 12N hydrochloric After heating for 12 h at the reflux of the sol the mixture is cooled to a temperature in the regi 20°C, and evaporated to dryness under reduced pre (2.7 kPa). The solid obtained is, three t successively dissolved in ethanol and evaporate dryness under reduced pressure (2.7 kPa), and is triturated in diisopropyl ether, filtered and under vacuum (2.7 kPa), to give 370 mg 4-[1-(1-azabicyclo[2.2.2]oct-3-ylmethyl)-1H-pyrazol yl]-2-chlorophenol dihydrochloride in the form cream solid. Mass spectrum (ESP): 318(+)/...=(M+H ^1H NMR spectrum (300 MHz) - δ in ppm - in DMSO-d6: 1.66 to 1.92 (m, 4H); 2.07 (m, 1H); 2.60 (m, 1H); (m, 1H); from 3.10 to 3.39 (m, 5H); from 4.15 to (m, 2H); 7.00 (d, J = 8.5 Hz, 1H); 7.34 (dd, J

20°C, the reaction mixture is poured into wat
which dichloromethane has been added. The res
suspension is filtered and the solid is taken
water. The mixture is adjusted to pH 8 and
extracted with ethyl acetate. The organic pha
washed successively with two times water a
saturated aqueous sodium chloride solution, dried
magnesium sulfate, and evaporated under r
pressure (2.7 kPa). The beige solid obtained (8
is purified by flash chromatography on silica und
argon pressure (50 kPa) [eluent: dichlorome
methanol (80/20 by volume)]. Concentrating the
priate fractions under reduced pressure (2.7 kPa)
a residue which is triturated in diisopropyl
filtered and dried under reduced pressure (2.7 kPa
give 240 mg of 4-[1-(1-azabicyclo[2.2.2]oct-3-yl
pyrazol-4-yl]-2-chlorophenol in the form of a
solid. Mass spectrum (EI): 303(+)/...=M(+)/...(1 C
NMR spectrum (400 MHz) - δ in ppm - in DMSO-d6:
(m, 1H); 1.54 (m, 1H); 1.70 (m, 2H); 2.02 (m, 1H);
(m, 3H); 2.98 (m, 1H); from 3.20 to 3.50 (m, 2H);
(m, 1H); 6.98 (d, J = 9.0 Hz, 1H); 7.40 (dd, J

with two times water and a saturated aqueous
chloride solution, dried over magnesium sulfate
evaporated under reduced pressure (2.7 kPa).
orangey oil obtained (2 g) is purified by
chromatography on silica under an argon pre
(50 kPa) [eluent: ethyl acetate, ethyl acetate/met
(80/20 by volume) then dichloromethane/methanol
by volume)]. After concentrating the fractions
reduced pressure (2.7 kPa), 480 mg of 3-[4-(3-chlo
methoxyphenyl)pyrazol-1-yl]-1-azabicyclo[2.2.2]octa
are obtained in the form of an orangey oil.
spectrum (EI): m/z=317 ($M^{+\cdot}$), m/z=234 [(M - C_5H_9
m/z=109 [$C_7H_{11}N^{+\cdot}$], m/z=97 [$C_6H_{11}N^{+\cdot}$] base peak.

Examples 99 and 100

(-)-4-[1-(1-Azabicyclo[2.2.2]oct-3-yl)-1H-pyrazol-4
2-chlorophenol and (+)-4-[1-(1-azabicyclo[2.2.2]o
yl)-1H-pyrazol-4-yl]-2-chlorophenol

An ethanolic solution containing 0.173 g of 4-[1-(1
bicyclo[2.2.2]oct-3-yl)-1H-pyrazol-4-yl]-2-chloroph

(dd, J = 2.5 and 8.5 Hz, 1H); 7.60 (d, J = 2.5 Hz
7.85 (s, 1H); 8.23 (s, 1H); from 9.98 to 10.15
broad m, 1H). $[\alpha]^{20}_D$ = -4.1 +/- 0.6° (*c* 0.5, MeOH).

The solution containing the dextrorotatory enant
eluted in the second position is evaporated to d
under reduced pressure (2.7 kPa), to give 0.102
(+)-4-[1-(1-azabicyclo[2.2.2]oct-3-yl)-1H-pyrazol-4
2-chlorophenol in the form of an oil.

Mass spectrum (EI): 303(+)/...=M(+)/...(1 Cl). ^{1}
spectrum (400 MHz) - δ in ppm - in DMSO-d6: 1.3
1H); 1.54 (m, 1H); 1.70 (m, 2H); 2.12 (m, 1H);
2.70 to 2.83 (m, 3H); 3.00 (m, 1H); from 3.21 to
(m, 2H); 4.43 (m, 1H); 6.95 (d, J = 8.5 Hz, 1H);
(dd, J = 2.5 and 8.5 Hz, 1H); 7.61 (d, J = 2.5 Hz,
7.87 (s, 1H); 8.27 (s, 1H); 10.05 (broad m, 1H).
= +5.3 +/- 0.4° (*c* 0.5, MeOH).

Examples 101 and 102

Mass spectrum (EI): m/z=270 ($M^{+\cdot}$), m/z=187 [(M - C_5
base peak. ^{1}H NMR spectrum (400 MHz) - δ in ppm
DMSO-d6 (referenced at 2.50 ppm): 1.31 (m, 1H);
1.55 to 1.70 (m, 3H); 2.07 (m, 1H); from 2.65 to
(m, 2H); 2.90 (m, 1H); from 3.14 to 3.39 (part
masked m, 3H); 4.21 (m, 1H); 7.14 (m, 1H); 7.72
d, J = 7.5 Hz, 1H); 7.78 (m, 1H); 8.26 (s, 1H);
(broad d, J = 5.0 Hz, 1H); from 10.9 to 11.1 (bro
1H). $[\alpha]^{20}_D$ = -40.7 +/- 0.8° (*c* 0.5, dimethylformam

The solution containing the dextrorotatory enant
eluted in the second position is evaporated to dr
under reduced pressure (2.7 kPa), to give 0.113
(+)-1-(1-azabicyclo[2.2.2]oct-3-yl)-4-pyridin-2-yl-
pyrazol-3-ol in the form of an oil.

Mass spectrum (EI): m/z=270 ($M^{+\cdot}$), m/z=187 [(M - C_5
base peak. ^{1}H NMR spectrum (400 MHz) - δ in ppm
DMSO-d6 (referenced at 2.50 ppm): 1.32 (m, 1H);
1.56 to 1.68 (m, 3H); 2.08 (m, 1H); from 2.66 to
(m, 2H); 2.92 (m, 1H); from 3.14 to 3.42 (part

1H-pyrazol-3-ol hydrochloride in the form of a solid. Mass spectrum (EI): m/z=270 ($M^{+\cdot}$), m/z=187 ($C_5H_9N)^+$] base peak, m/z=36 ($HCl^{+\cdot}$).

The 3-[3-(cyclohex-2-enyloxy)-4-pyridin-2-ylpyraz yl]-1-azabicyclo[2.2.2]octane can be prepared i following way:

A solution of 2.5 g of 2-[3-(cyclohex-2-enyloxy pyrazol-4-yl]pyridine and of 1.4 g of potassium butoxide in 20 cm^3 of dimethylformamide, under an atmosphere, is stirred for 1 h at 50°C and a sol of 4 g of toluene-4-sulfonic acid 1-azabicyclo[2. oct-3-yl ester in 20 cm^3 of dimethylformamide is added thereto. After heating for 15 h at 100°C reaction medium is poured into water, and the mi is extracted with two times ethyl acetate. The com organic phases are washed successively with two water and a saturated aqueous sodium chloride solu dried over magnesium sulfate, and evaporated reduced pressure (2.7 kPa). The orangey oil obt (5.3 g) is purified by flash chromatography on al

1H); 7.74 (m, 2H); 8.18 (s, 1H); 8.47 (broad d
5.0 Hz, 1H).

Examples 103 and 104

(+)-1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-phenyl-1H-pyr
3-ylamine and (-)-1-(1-azabicyclo[2.2.2]oct-3-y
phenyl-1H-pyrazol-3-ylamine

An ethanolic solution containing 0.13 g of (+/-)
azabicyclo[2.2.2]oct-3-yl)-4-phenyl-1H-pyrazol-3-yl
is introduced onto a column, 8 cm in dia
containing 1180 g of 20 µM Chiralpak AD™
stationary phase. The elution is carried out by
of a mixture of heptane, of ethanol and of trie
amine (50/50/0.1 by volume), the flow rate o
mobile phase being 120 ml/min. The levoro
enantiomer is eluted in the first position,
solution is evaporated to dryness under re
pressure (2.7 kPa), to give 0.035 g of (-)-1-(
bicyclo[2.2.2]oct-3-yl)-4-phenyl-1H-pyrazol-3-ylam
in the form of an oil.

Mass spectrum (EI): m/z=268 ($M^{+\cdot}$), m/z=185 [(M - C_5H
m/z=109 ($C_7H_{11}N^{+\cdot}$) base peak. ^1H NMR spectrum (300 M
δ in ppm - in DMSO-d6 (referenced at 2.50 ppm):
(m, 1H); from 1.60 to 1.73 (m, 3H); 2.09 (m, 1H);
2.68 to 2.82 (m, 3H); from 2.90 to 3.53 (part
masked m, 3H); 4.19 (m, 1H); 4.63 (broad m, 2H);
(broad t, J = 7.5 Hz, 1H); 7.32 (broad t, J = 7.
2H); 7.51 (broad d, J = 7.5 Hz, 2H); 7.89 (s,
$[\alpha]^{20}_D$ = + (dimethylformamide).

The (+/-)-1-(1-azabicyclo[2.2.2]oct-3-yl)-4-pheny
pyrazol-3-ylamine can be prepared in the following

1.1 g of 1,3-dimethylbarbituric acid and 50 m
tetrakis(triphenylphosphine)palladium are added
solution of 280 mg of diallyl-[1-(1-azabicyclo[2.
oct-3-yl)-4-phenyl-1H-pyrazol-3-yl]amine in 10 cr
dichloromethane, under argon and with stirring.
heating for 15 h at the reflux of the reaction me
the mixture is evaporated to dryness under re
pressure (2.7 kPa). The residue is taken up wit

1H); 7.32 (broad t, J = 7.5 Hz, 2H); 7.52 (broad
7.5 Hz, 2H); 7.89 (s, 1H).

The diallyl-[1-(1-azabicyclo[2.2.2]oct-3-yl)-4-p
1H-pyrazol-3-yl]amine can be prepared in the fol
way:

A solution of 1.3 g of diallyl-(4-phenyl-1H-pyra
yl)amine and of 730 mg of potassium tert-butoxi
20 cm^3 of dimethylformamide, under an argon atmos
is stirred for 45 min at 45°C and then a soluti
2.3 g of toluene-4-sulfonic acid 1-azabicyclo[2
oct-3-yl ester in 15 cm^3 of dimethylformamide is
thereto. After heating for 15 h at 100°C, the re
medium is poured into water, and the mixtu
extracted with two times ethyl acetate. The co
organic phases are washed successively with two
water and a saturated aqueous sodium chloride sol
dried over magnesium sulfate, and evaporated
reduced pressure (2.7 kPa). The orangey oil ob
(1.8 g) is purified by flash chromatography on a
CTB1 under an argon pressure (50 kPa) [eluent:

7.61 (broad d, J = 7.5 Hz, 2H); 7.93 (s, 1H).

The diallyl-(4-phenyl-1H-pyrazol-3-yl)amine ca
prepared in the following way:

22 cm^3 of a 1N solution of tetrabutylammonium flu
in tetrahydrofuran are added to a solution, und
argon atmosphere and with stirring, of 2.9
diallyl-[4-phenyl-1-(2-trimethylsilanylethoxymethyl
pyrazol-3-yl]amine in 25 cm^3 of tetrahydrofuran.
heating to 18 h at the reflux of the solvent, 6.3
1N tetrabutylammonium fluoride solution are adde
the heating is continued for 4 h. After evaporati
the reaction medium to dryness under reduced pre
(2.7 kPa), ethyl acetate is added to the residu
the organic phase is washed successively with two
water and a saturated aqueous sodium chloride solu
it is dried over magnesium sulfate and evaporated
reduced pressure (2.7 kPa). The brown oil obt
(1.8 g) is purified by flash chromatography on s
under an argon pressure (50 kPa) [eluent: cyclohe
ethyl acetate (70/30 by volume)]. After concentr

residue is taken up with ethyl acetate. The o
solution is washed successively with two times
and a saturated aqueous sodium chloride solution;
dried over magnesium sulfate and evaporated
reduced pressure (2.7 kPa). The orangey oil obt
(4 g) is purified by flash chromatography on
under an argon pressure (50 kPa) [eluent: cyclohe
ethyl acetate (93/7 by volume)]. After concentr
the fractions under reduced pressure (2.7 kPa),
of diallyl-[4-phenyl-1-(2-trimethylsilanylethoxymet
1H-pyrazol-3-yl]amine are obtained in the form
orange oil. ^{1}H NMR spectrum (300 MHz) - δ in ppm
DMSO-d6 (referenced at 2.50 ppm): -0.03 (s, 9H);
(m, 2H); from 3.52 to 3.63 (m, 6H); from 5.04 to
(m, 4H); 5.24 (s, 2H); from 5.74 to 5.90 (m, 2H);
(tt, J = 1.5 and 7.5 Hz, 1H); 7.36 (broad t,
7.5 Hz, 2H); 7.58 (broad d, J = 7.5 Hz, 2H); 7.9
1H).

The 4-phenyl-1-(2-trimethylsilanylethoxymethyl)-1H-
zol-3-ylamine can be prepared in the following way

(s, 9H); 0.86 (m, 2H); 3.56 (m, 2H); 4.75 (bro
2H); 5.17 (s, 2H); 7.18 (broad t, J = 7.5 Hz, 1H)
(broad t, J = 7.5 Hz, 2H); 7.50 (broad d, J = 7
2H); 7.88 (s, 1H).

The 3-nitro-4-phenyl-1-(2-trimethylsilanylethoxyme
1H-pyrazole can be prepared in the following way:

8.8 g of phenylboronic acid, 36 cm^3 of a 2N a
potassium carbonate solution and 3.6 g of tetraki
phenylphosphine)palladium are added to a sol
under an argon atmosphere and with stirring, of
of 4-iodo-3-nitro-1-(2-trimethylsilanylethoxymethy
pyrazole in 120 cm^3 of toluene to which 30 c
ethanol have been added. After heating for 15
100°C, the reaction medium is cooled to a tempe
in the region of 20°C and is then evaporated
reduced pressure (2.7 kPa). The residue is tak
with ethyl acetate and the organic solution is
successively with two times water and a satu
aqueous sodium chloride solution; it is dried
magnesium sulfate and evaporated under reduced pre

stirring. The mixture is stirred for 45 min
temperature in the region of 20°C and 14 c
2-trimethylsilanylethoxymethyl chloride are then
added thereto. After stirring for 15 h at a tempe
in the region of 20°C, the reaction medium is
into 500 cm^2 of water and the mixture is extracte
three times 500 cm^3 of ethyl acetate. The organic
are combined, washed successively with two times
and a saturated aqueous sodium chloride solution,
over magnesium sulfate, filtered and evaporated
reduced pressure (2.7 kPa), to give an orang
(22 g) which is purified by flash chromatograp
silica under an argon pressure (50 kPa) [e
cyclohexane/ethyl acetate (85/15 by volume)].
concentrating the fractions under reduced pres
7.8 g of 4-iodo-3-nitro-1-(2-trimethylsilanylet
methyl)-1H-pyrazole are obtained in the form of a
yellow oil. ^1H NMR spectrum (300 MHz) - δ in ppm
DMSO-d6 (referenced at 2.50 ppm): -0.03 (s, 9H);
(m, 2H); 3.61 (m, 2H); 5.51 (s, 2H); 8.52 (s, 1H).

reduced pressure (3 kPa). Fractions 192 to 20
combined, washed with 5 cm^3 and concentrated to d
under reduced pressure (3 kPa). The 2 batches, i
form of an orange powder, are combined (266 mg
purified by HPLC in order to separate the enanti
on a 20 µm Chiralcel OD column with, as elue
mixture of heptane, of methanol, of ethanol a
triethylamine (60/10/30/0.2 by volume); each enant
is then taken up with 10 cm^3 of dichloromethan
5 cm^3 of water. The organic phase is washed w
saturated aqueous sodium chloride solution, dried
magnesium sulfate, filtered, and concentrate
dryness under reduced pressure (3 kPa). Each
powder thus obtained is then taken up with 20 c
absolute ethanol and then brought to the reflux c
solvent for 20 minutes. Each solution is filtere
washed with 5 cm^3 of absolute ethanol, and 1 cm^3 of
solution of hydrochloric diethyl ether is
thereto. The solutions are concentrated to dr
under reduced pressure, taken up with 5 cm^3 of et
and again concentrated to dryness under re
pressure; the residues are precipitated from 5 c

according to the invention can be used o
parenterally, rectally or topically.

As solid compositions for oral administration, us
be made of tablets, pills, powders (gelatin caps
wafer capsules) or granules. In these compositions
active principle according to the invention is
with one or more inert diluents such as st
cellulose, sucrose, lactose or silica, under a s
of argon. These compositions may also co
substances other than diluents, for example one or
lubricants such as magnesium stearate or talc, a c
coating (sugar-coated tablets) or a varnish.

As liquid compositions for oral administration, us
be made of pharmaceutically acceptable solut
suspensions, emulsions, syrups and elixirs, conta
inert diluents such as water, ethanol, glycerol,
oils or liquid paraffin. These compositions
comprise substances other than diluents, for ex
wetting, sweetening, thickening, flavoring
stabilizing products.

medium.

The compositions for rectal administration suppositories or rectal capsules which contain, be the active product, excipients such as cocoa bu semisynthetic glycerides or polyethylene glycols.

The compositions for topical administration may example, be creams, lotions, eye washes, throat sp nasal drops or aerosols.

The doses depend on the desired effect, on the dur of the treatment and on the route of administr used; they are generally between 5 mg and 1 000 m day orally for an adult, with single doses ranging 1 mg to 250 mg of active substance.

In general, the physician will determine appropriate dosage in accordance with the age, weight and all the other factors specific to individual to be treated.

cognitive impairments related to bacterial or
infections, attention deficit hyperactivity diso
schizophrenia, the treatment of inflammatory syndr
ulcerative colitis, Crohn's disease, irritable
syndrome, arthritis, the treatment of acute or ch
pain, fibromyalgia, the treatment of acute ne
degeneration subsequent to a trauma, to stroke
ischemia or to brain hypoxia, the treatment of ch
neural degeneration observed during Parkin
disease, Huntington's chorea, multisystem atr
progressive supranuclear paralysis or amyotr
lateral sclerosis, the treatment of epilepsy,
treatment of depression, of anxiety, of
depressive psychoses, of obsessive/compu
disorders, of phobias, of post-traumatic s
syndromes, of panic attacks, of Tourette's syndrom
anorexia and of bulimia, and sleep disorders.

The compounds of formula (I) can also be used
establishing a decrease in the consumption of addi
substances, for helping to maintain an abstinence

- Lactose..... 55
- Colloidal silica..... 1
- Sodium carboxymethylstarch..... 10
- Talc..... 10
- Magnesium stearate..... 1

EXAMPLE B

Tablets containing a dose of 50 mg of active pro
having the following composition, are pre
according to the conventional technique:

- Compound of formula (I)..... 50 mg
- Lactose..... 104 m
- Cellulose..... 40 m
- Polyvidone..... 10 m
- Sodium carboxymethylstarch..... 22 m
- Talc..... 10 m
- Magnesium stearate. ..... 2 m
- Colloidal silica..... 2 m

1-[(Toluene-4-sulfonyl)oxy]-2-(3-benzyloxy-4-phenylpyrazol-1-yl)ethyl

2-(3-Benzyloxy-4-phenylpyrazol-1-yl)ethanol

3-Benzyloxy-4-phenyl-1-[2-(tetrahydropyran-2-ylox
ethyl]-1H-pyrazole

2-[2-(3-Benzyloxy-4-phenylpyrazol-1-yl)ethyl]-2-az
bicyclo[2.2.1]heptane

[2-(3-Benzyloxy-4-phenylpyrazol-1-yl)ethyl]dimethyl
dihydrochloride

[3-(3-Benzyloxy-4-phenylpyrazol-1-yl)propyl]dimeth
amine dihydrochloride

[3-(3-Benzyloxy-4-phenylpyrazol-1-yl)propyl]dimeth
amine oxalate

(2S,6R)-1-[2-(3-Benzyloxy-4-phenylpyrazol-1-yl)eth
2,6-dimethylpiperidine dihydrochloride

(2S,6R)-1-[2-(3-Benzyloxy-4-phenylpyrazol-1-yl)eth
2,6-dimethylpiperidine

[2-(3-Benzyloxy-4-phenylpyrazol-1-yl)ethyl]diethyl
dihydrochloride

4-Phenyl-1-(2-piperidin-1-ylethyl)-1H-pyrazol-3-yl

N-[4-Phenyl-1-(2-piperidin-1-ylethyl)-1H-pyrazol-
formamide

{2-[3-(Cyclohex-2-enyloxy)-4-phenylpyrazol-1-yl]-
1-methylethyl}dimethylamine

3-(Cyclohex-2-enyloxy)-4-phenyl-1H-pyrazole

3-(3-Benzyloxy-4-phenylpyrazol-1-ylmethyl)-1-methy
piperidine

1-{2-[3-(Cyclohex-2-enyloxy)-5-methyl-4-phenylpyra
1-yl]ethyl}piperidine

3-(Cyclohex-2-enyloxy)-5-methyl-4-phenyl-1H-pyrazo

1-[3-(Cyclohex-2-enyloxy)-5-methyl-4-phenylpyrazol
yl]ethanone

3-[3-Benzyloxy-1-(2-dimethylaminoethyl)-1H-pyrazol-
yl]phenylamine

{2-[3-Benzyloxy-4-(4-nitrophenyl)pyrazol-1-yl]ethyl}-
dimethylamine

3-Benzyloxy-4-(4-nitrophenyl)-1H-pyrazole

1-[3-Hydroxy-4-(4-nitrophenyl)pyrazol-1-yl]ethanone

Dimethylammonium 4-(4-nitrophenyl)-1H-pyrazol-3-olate

3-Dimethylamino-2-(4-nitrophenyl)acrylic acid
ester

{2-[3-Benzyloxy-4-(4'-fluorobiphenyl-3-yl)pyrazol-1-
ethyl}dimethylamine

{2-[3-Benzyloxy-4-(3-bromophenyl)pyrazol-1-yl]ethyl}-
dimethylamine

dimethylamine

3-Benzyloxy-4-(4-bromophenyl)-1H-pyrazole

1-[4-(4-Bromophenyl)-3-hydroxypyrazol-1-yl]ethanor

4-(4-Bromophenyl)-1H-pyrazol-3-ol

2-(4-Bromophenyl)-3-dimethylaminoacrylic acid ethy
ester

2-[3-(Cyclohex-2-enyloxy)-1-(2-piperidin-1-ylethyl
pyrazol-4-yl]pyridine

2-[3-(Cyclohex-2-enyloxy)-1H-pyrazol-4-yl]pyridine

1-(3-Hydroxy-4-pyridin-2-ylpyrazol-1-yl)ethanone

4-Pyridin-2-yl-1H-pyrazol-3-ol hydrochloride

3-Dimethylamino-2-pyridin-2-ylacrylic acid ethyl e

3-Benzyloxy-4-bromo-1H-pyrazole hydrochloride

3-Benzyloxy-1H-pyrazole

3-Benzyloxy-1H-pyrazole hydrochloride

1-(3-Hydroxy-pyrazol-1-yl)ethanone

3-Benzyloxy-4-(4-trifluoromethoxyphenyl)-1-(2-pipe
1-ylethyl)-1H-pyrazole

3-Benzyloxy-4-(4-trifluoromethoxyphenyl)-1H-pyrazo

3-Benzyloxy-1-(toluene-4-sulfonyl)-4-(4-trifluoro-
methoxyphenyl)-1H-pyrazole

3-Benzyloxy-4-iodo-1-(toluene-4-sulfonyl)-1H-pyraz

3-Benzyloxy-4-iodo-1H-pyrazole

3-Benzyloxy-4-(5-chlorothiophen-2-yl)-1H-pyrazole

3-Benzyloxy-4-(5-chlorothiophen-2-yl)-1-(toluene-4-sulfonyl)-1H-pyrazole

3-Benzyloxy-1-(toluene-4-sulfonyl)-4-tributylstannyl-1H-pyrazole

3-Benzyloxy-4-(3-methoxyphenyl)-1-(2-piperidin-1-yl-ethyl)-1H-pyrazole

3-Benzyloxy-4-(3-methoxyphenyl)-1H-pyrazole

3-Benzyloxy-4-(3-methoxyphenyl)-1-(toluene-4-sulfonyl)-1H-pyrazole

3-Benzyloxy-4-(2-methoxyphenyl)-1-(2-piperidin-1-yl-ethyl)-1H-pyrazole

3-Benzyloxy-4-(2-methoxyphenyl)-1H-pyrazole

ethyl}piperidine

3-Benzyloxy-4-(4-chlorophenyl)-1H-pyrazole

3-Benzyloxy-4-(4-chlorophenyl)-1-(toluene-4-sulfor
1H-pyrazole

1-{2-[3-Benzyloxy-4-(3-chlorophenyl)pyrazol-1-yl]-
ethyl}piperidine

3-Benzyloxy-4-(3-chlorophenyl)-1H-pyrazole

3-Benzyloxy-4-(3-chlorophenyl)-1-(toluene-4-sulfor
1H-pyrazole

1-{2-[3-Benzyloxy-4-(2-fluorophenyl)pyrazol-1-yl]-
ethyl}piperidine

3-Benzyloxy-4-(2-fluorophenyl)-1H-pyrazole

3-[3-Benzyloxy-4-(3-fluorophenyl)pyrazol-1-yl]-1-
bicyclo[2.2.2]octane

1-(1-Methylpyrrolidin-3-yl)-4-phenyl-1H-pyrazol-3

3-Benzyloxy-1-(1-methylpyrrolidin-3-yl)-4-phenyl-
pyrazole

Methanesulfonic acid (1-methylpyrrolidin-3-yl) est

3-Benzyloxy-1-[2-(1-methylpyrrolidin-2-yl)ethyl]-
4-phenyl-1H-pyrazole

1-Methyl-2-(2-chloroethyl)pyrrolidine

3-Benzyloxy-4-phenyl-1-(pyrrolidin-3-yl)-1H-pyrazo
dihydrochloride

3-Benzyloxy-1-(1-tert-butoxycarbonylpyrrolidin-3-y
4-phenyl-1H-pyrazole

ester

(1-Benzylpyrrolidin-3-yl)methanol

3-Benzyloxy-1-((2R)-1-methylpyrrolidin-2-ylmethyl)
4-phenyl-1H-pyrazole

3-Benzyloxy-4-phenyl-1-((2R)-pyrrolidin-2-ylmethyl
pyrazole hydrochloride

3-Benzyloxy-4-phenyl-1-((2R)-1-tert-butoxycarbonyl
pyrrolidin-2-ylmethyl)-1H-pyrazole

Methanesulfonic acid ((2R)-1-tert-butoxycarbonyl-
pyrrolidin-2-ylmethyl) ester

3-Benzyloxy-4-phenyl-1-(piperidin-3-yl)-1H-pyrazol
hydrochloride

3-Benzyloxy-1-(1-tert-butoxycarbonylpiperidin-3-yl
4-phenyl-1H-pyrazole

4-Phenyl-1-(2-piperidin-1-ylethyl)-1H-pyrazole oxa

3-Benzyloxy-4-(3,4-dichlorophenyl)-1-(2-piperidin-
ethyl]-1H-pyrazole

3-Benzyloxy-4-(3,4-dichlorophenyl)-1H-pyrazole

3-Benzyloxy-1-(toluene-4-sulfonyl)-4-(3,4-dichloro
phenyl)-1H-pyrazole

3-Benzyloxy-4-(4-bromophenyl)-1-(2-piperidin-1-yle
1H-pyrazole

3-Benzyloxy-4-(4-bromophenyl)-1H-pyrazole

3-Benzyloxy-1-(toluene-4-sulfonyl)-4-(4-bromopheny
1H-pyrazole

3-Benzyloxy-4-(1H-indol-5-yl)-1-(2-piperidin-1-yle
1H-pyrazole

4-(2-Methoxyphenyl)-1-(2-piperidin-1-ylethyl)-1H-pyrazole oxalate

4-(2-Methoxyphenyl)-1H-pyrazole

1-(Toluene-4-sulfonyl)-4-(2-methoxyphenyl)-1H-pyra

4-Iodo-1-(2-piperidin-1-ylethyl)-1H-pyrazole

3-Benzyloxy-4-(4-methylphenyl)-1-(2-piperidin-1-yl ethyl]-1H-pyrazole oxalate

3-Benzyloxy-4-(4-methylphenyl)-1H-pyrazole

3-Benzyloxy-1-(toluene-4-sulfonyl)-4-(4-methylpher 1H-pyrazole

1-(1-Azabicyclo[2.2.2]oct-3-yl)-4-(5-chlorothiophe yl)-1H-pyrazol-3-ol hydrochloride

ethyl]piperidine

4-Benzo[b]thiophen-2-yl-3-benzyloxy-1H-pyrazole

4-Benzo[b]thiophen-2-yl-3-benzyloxy-1-(toluene-4-sulfonyl)-1H-pyrazole

1-[2-(3-Benzyloxy-4-thiophen-3-ylpyrazol-1-yl)ethy piperidine

3-Benzyloxy-4-thiophen-3-yl-1H-pyrazole

3-Benzyloxy-4-thiophen-3-yl-1-(toluene-4-sulfonyl) pyrazole

4-[3-Benzyloxy-1-(2-piperidin-1-ylethyl)-1H-pyrazo yl]benzamide

4-(3-Benzyloxy-1H-pyrazol-4-yl)benzamide

(-)-3-(3-Benzyloxy-4-phenylpyrazol-1-ylmethyl)-1-a
bicyclo[2.2.2]octane

(+)-3-(3-Benzyloxy-4-phenylpyrazol-1-ylmethyl)-1-a
bicyclo[2.2.2]octane

3-[3-Benzyloxy-4-(4-chlorophenyl)pyrazol-1-ylmethy
1-azabicyclo[2.2.2]octaneborane

(+)-3-[3-Benzyloxy-4-(4-chlorophenyl)pyrazol-1-yl]
1-azabicyclo[2.2.2]octane

(-)-3-[3-Benzyloxy-4-(4-chlorophenyl)pyrazol-1-yl]
1-azabicyclo[2.2.2]octane

(+)-3-[3-Benzyloxy-4-(4-fluorophenyl)pyrazol-1-yl]
1-azabicyclo[2.2.2]octane

(-)-3-[3-Benzyloxy-4-(4-fluorophenyl)pyrazol-1-yl]
1-azabicyclo[2.2.2]octane

3-[3-(Cyclohex-2-enyloxy)-4-pyridin-2-yl-pyrazol-
1-azabicyclo[2.2.2]octane

Diallyl-[1-(1-azabicyclo[2.2.2]oct-3-yl)-4-phenyl-
pyrazol-3-yl]amine

Diallyl-(4-phenyl-1H-pyrazol-3-yl)amine

Diallyl-[4-phenyl-1-(2-trimethylsilanylethoxymethy
1H-pyrazol-3-yl]amine

4-Phenyl-1-(2-trimethylsilanylethoxymethyl)-1H-pyr
3-ylamine

3-Nitro-4-phenyl-1-(2-trimethylsilanylethoxymethyl
pyrazole

4-Iodo-3-nitro-1-(2-trimethylsilanylethoxymethyl)-
pyrazole.