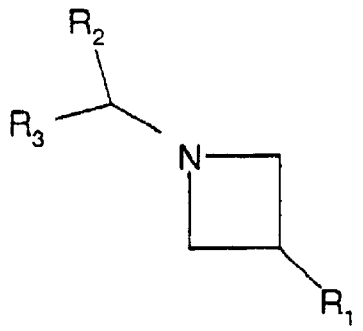
PHARMACEUTICAL COMPOSITIONS CONTAINING AZETIDINE DERIVATIVES, NOVEL AZETIDINE DERIVATIVES AND THEIR PREPARATION

The present invention relates to pharmaceutical compositions containing, as active ingredient, at least one compound of formula:



(I)

or one of its pharmaceutically acceptable salts, to the novel derivatives of formula (I), to their pharmaceutically acceptable salts and to their preparation.

The compound of formula (I) for which R_2 and R_3 represent phenyl radicals, R_1 represents a radical $-N(R_4)SO_2R_6$, R_4 represents a phenyl radical and R_6 represents a methyl radical is described as a synthesis intermediate in patent WO 99/01451. The other compounds and their pharmaceutically acceptable salts are novel and as such form part of the invention.

In formula (I)

R_1 represents a radical $-N(R_4)R_5$, $-N(R_4)-CO-R_5$, $-N(R_4)-SO_2R_6$,

R_2 and R_3, which are identical or different, represent either an aromatic chosen from phenyl, naphthyl and indenyl, these aromatics being unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, formyl, hydroxyl, trifluoromethyl, trifluoromethoxy, -CO-alk, cyano, -COOH, COOalk, $-CONR_7R_8$, $-CO-NH-NR_9R_{10}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkyl or $-alk-NR_7R_8$ radicals; or a heteroaromatic chosen from benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, 2,3-dihydrobenzofuryl, 2,3-dihydrobenzothienyl, furyl, imidazolyl, isochromanyl, isoquinolyl, pyrrolyl, pyridyl, pyrimidyl, quinolyl, 1,2,3,4-tetrahydroisoquinolyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with a halogen atom or an alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, -COOH, COOalk, $-CO-NH-NR_9R_{10}$, $-CONR_7R_8$, $-alk-NR_9R_{10}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl or hydroxyalkyl radical,

R_4 represents a radical $-C(R_{11})(R_{12})-Het$, -Het, $-(CR_{11})(R_{12})-Ar$, Ar, cycloalkyl or norbornyl,

R_5 represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, $-alk-CONR_7R_8$, $-alk-NR_7R_8$, alkoxy, Ar, Het,

$-CH_2Ar$, $-CH_2Het$ or alkyl radical optionally substituted with one or more halogen atoms,

R_6 represents a hydroxyalkyl, -alk-COOalk, $-alk-CONR_7R_8$, $-alk-NR_7R_8$, alkoxy, Ar, Het, $-CH_2Ar$, $-CH_2Het$ or alkyl radical optionally substituted with 1 or more halogen atoms,

R_7 and R_8, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_7 and R_8 together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_9 and R_{10}, which are identical or different, represent a hydrogen atom or an alkyl, -COOalk, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl radical or alternatively R_9 and R_{10} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl, -COalk, -COOalk, -CO-NHalk, -CS-NHalk, oxo, hydroxyalkyl, -alk-O-alk or $-CO-NH_2$ radicals,

R_{11} represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, $-alk-CONR_7R_8$, $-alk-NR_7R_8$, alkoxyalkyl, Ar,

Het, $-CH_2Ar$, $-CH_2Het$ or alkyl radical optionally substituted with one or more halogen atoms,

R_{12} represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, $-alk-CONR_7R_8$, $-alk-NR_7R_8$, alkoxyalkyl or alkyl radical optionally substituted with one or more halogen atoms,

or alternatively R_{11} and R_{12} together form with the carbon atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic ring, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

Ar represents a phenyl, naphthyl or indenyl radical, these different radicals being optionally substituted with one or more halogen atoms or alkyl, alkoxy, -CO-alk, cyano, -COOH, -COOalk, $-CONR_{13}R_{14}$, $-CO-NH-NR_{15}R_{16}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, $-alk-NR_{15}R_{16}$, $-NR_{15}R_{16}$, alkylthioalkyl, formyl, CF_3, OCF_3, Het, -O-alk-NH-cycloalkyl, SO_2NH_2, hydroxyl, hydroxyalkyl, -NHCOalk, NHCOOalk radicals or on 2 adjacent carbon atoms with dioxymethylene,

Het represents a 3- to 10-membered unsaturated or saturated mono- or bicyclic heterocycle containing one or more heteroatoms chosen from oxygen, sulfur and nitrogen optionally substituted with one or more halogen atoms or alkyl, alkoxy, alkoxycarbonyl, oxo or hydroxyl radicals, the nitrogen-containing heterocycles being optionally in their N-oxidized form,

R_{13} and R_{14}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{13} and R_{14} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_{15} and R_{16}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{15} and R_{16} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

alk represents an alkyl or alkylene radical.

In the preceding definitions and in those which follow, unless otherwise stated, the alkyl and alkylene radicals and portions and the alkoxy radicals and portions are in the form of a straight or branched chain and contain 1 to 6 carbon atoms and the cycloalkyl radicals contain 3 to 10 carbon atoms.

Among the alkyl radicals, there may be mentioned the methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl and hexyl radicals. Among the alkoxy radicals, there may be mentioned the methoxy, ethoxy, n-propoxy, iso-propoxy,

n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and pentyloxy radicals.

Among the cycloalkyl radicals, there may be mentioned the cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl radicals.

The term halogen comprises chlorine, fluorine, bromine and iodine.

Among the heterocycles represented by Het, the following heterocycles may be mentioned: benzimidazole, benzoxazole, benzothiazole, benzothiophene, cinnoline, thiophene, quinazoline, quinoxaline, quinoline, pyrazole, pyrrole, pyridine, imidazole, indole, isoquinoline, pyrimidine, thiazole, thiadiazole, piperidine, piperazine, triazole, furan, tetrahydroisoquinoline, tetrahydroquinoline, these heterocycles being optionally substituted with one or more halogen atoms or alkyl, alkoxy, alkoxycarbonyl, oxo, hydroxyl, OCF_3 or CF_3 radicals.

The compounds of formula (I) may be provided in the form of enantiomers and of diastereoisomers. These isomers and mixtures thereof also form part of the invention.

Preferably, the compounds of formula (I) are those for which

R_1 represents a radical $-N(R_4)R_5$ or $-N(R_4)-SO_2R_6$,

R_2 represents either a phenyl which is unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, -CO-alk,

cyano, $-CONR_7R_8$, hydroxyalkyl or $-alk-NR_7R_8$ radicals; or a heteroaromatic chosen from the pyridyl, pyrimidyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with a halogen atom or an alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, $-CONR_7R_8$, $-alk-NR_9R_{10}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl or hydroxyalkyl radical,

R_3 represents either a phenyl which is unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, -CO-alk, cyano, $-CONR_7R_8$, hydroxyalkyl or $-alk-NR_7R_8$ radicals; or a heteroaromatic chosen from the pyridyl, pyrimidyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with a halogen atom or an alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, $-CONR_7R_8$, $-alk-NR_9R_{10}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl or hydroxyalkyl radical,

R_4 represents a radical $-C(R_{11})(R_{12})-Het$, -Het, $-C(R_{11})(R_{12})-Ar$, Ar or norbornyl,

R_5 represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, $-alk-CONR_7R_8$, $-alk-NR_7R_8$, alkoxy, $-CH_2Ar$, $-CH_2Het$ or alkyl radical,

R_6 represents a hydroxyalkyl, -alk-COOalk, $-alk-CONR_7R_8$, $-alk-NR_7R_8$, alkoxy, $-CH_2Ar$, $-CH_2Het$ or alkyl radical,

R_7 and R_8, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_7

and R_8 together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_9 and R_{10}, which are identical or different, represent a hydrogen atom or an alkyl, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl radical or alternatively R_9 and R_{10} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl, -COalk, -COOalk, -CO-NHalk, oxo, hydroxyalkyl or $-CO-NH_2$ radicals,

R_{11} represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, $-alk-CONR_7R_8$, $-alk-NR_7R_8$, alkoxyalkyl, Ar, Het, $-CH_2Ar$, $-CH_2Het$ or alkyl radical optionally substituted with one or more halogen atoms,

R_{12} represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, $-alk-CONR_7R_8$, $-alk-NR_7R_8$, alkoxyalkyl or alkyl radical optionally substituted with one or more halogen atoms,

or alternatively R_{11} and R_{12} together form with the carbon atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic ring, optionally containing another heteroatom chosen from oxygen,

sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

Ar represents a phenyl or naphthyl radical, these different radicals being optionally substituted with one or more halogen atoms or alkyl, alkoxy, -CO-alk, cyano, $-CONR_{13}R_{14}$, alkylsulfonyl, $-alk-NR_{15}R_{16}$, $-NR_{15}R_{16}$, CF_3, OCF_3, SO_2NH_2, hydroxyl or hydroxyalkyl radicals or on 2 adjacent carbon atoms with dioxymethylene,

Het represents a 3- to 10-membered unsaturated or saturated mono- or bicyclic heterocycle containing one or more heteroatoms chosen from oxygen, sulfur and nitrogen optionally substituted with one or more halogen atoms or alkyl, alkoxy, oxo or hydroxyl radicals, the nitrogen-containing heterocycles being optionally in their N-oxidized form and, more particularly, Het represents a heterocycle chosen from benzimidazole, benzoxazole, benzothiazole, benzothiophene, thiophene, quinazoline, quinoxaline, quinoline, pyrrole, pyridine, imidazole, indole, isoquinoline, pyrimidine, thiazole, thiadiazole, furan, tetrahydroisoquinoline and tetrahydroquinoline, these heterocycles being optionally substituted with one or more halogen atoms or alkyl, alkoxy, alkoxycarbonyl, oxo, hydroxyl, OCF_3 or CF_3 radicals.

R_{13} and R_{14}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{13} and R_{14} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono-

or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_{15} and R_{16}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{15} and R_{16} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals.

Still more preferably, the compounds of formula (I) are chosen from the following compounds:

R_1 represents a radical $-N(R_4)-SO_2R_6$,

R_2 represents either a phenyl which is unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, cyano, $-CONR_7R_8$, hydroxyalkyl or $-alk-NR_7R_8$ radicals; or a heteroaromatic chosen from the pyridyl, pyrimidyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with a halogen atom or an alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, $-CONR_7R_8$ or hydroxyalkyl radical,

R_3 represents either a phenyl which is unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, cyano,

$-CONR_7R_8$, hydroxyalkyl or $-alk-NR_7R_8$ radicals; or a heteroaromatic chosen from the pyridyl, pyrimidyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with a halogen atom or an alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, $-CONR_7R_8$ or hydroxyalkyl radical,

R_4 represents -Het or Ar,

R_6 represents a hydroxyalkyl or alkyl radical,

R_7 and R_8, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_7 and R_8 together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

Ar represents a phenyl or naphthyl radical, these different radicals being optionally substituted with one or more halogen atoms or alkyl, alkoxy, -CO-alk, cyano, $-CONR_{13}R_{14}$, $-alk-NR_{15}R_{16}$, $-NR_{15}R_{16}$, CF_3, OCF_3, SO_2NH_2, hydroxyl or hydroxyalkyl radicals,

Het represents a 3- to 10-membered unsaturated or saturated mono- or bicyclic heterocycle containing one or more heteroatoms chosen from oxygen, sulfur and nitrogen optionally substituted with one or more halogen atoms or alkyl, alkoxy, oxo or hydroxyl radicals, and, more particularly, Het represents a

heterocycle chosen from benzimidazole, benzoxazole, benzothiazole, benzothiophene, thiophene, quinazoline, quinoxaline, quinoline, pyrrole, pyridine, imidazole, indole, isoquinoline, thiazole, thiadiazole, furan, tetrahydroisoquinoline and tetrahydroquinoline, these heterocycles being optionally substituted with one or more halogen atoms or alkyl, alkoxy, alkoxycarbonyl, oxo, hydroxyl, OCF_3 or CF_3 radicals,

R_{13} and R_{14}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{13} and R_{14} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_{15} and R_{16}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{15} and R_{16} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals.

Among the preferred compounds, the following compounds may be mentioned:

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(6-chloropyrid-2-yl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(6-ethylpyrid-2-yl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-quinol-6-ylmethylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-quinol-5-ylmethylsulfonamide

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-isoquinol-5-ylmethylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-pyrid-3-ylmethylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(1-oxide-pyrid-3-yl)methylsulfonamide,

N-(1R,2S,4S)-bicyclo[2.2.1]hept-2-yl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonamide,

N-(1R,2R,4S)-bicyclo[2.2.1]hept-2-yl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(thiazol-2-yl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3-methoxyphenyl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3-hydroxyphenyl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3-hydroxymethylphenyl)methylsulfonamide,

Ethyl N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(methylsulfonyl)-3-aminobenzoate,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(1-isobutylpiperid-4-yl)methylsulfonamide,

N-benzyl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}amine,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorobenzyl)amine,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorobenzyl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(pyrid-3-ylmethyl)methylsulfonamide

N-{1-[bis(4-fluorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(RS)-N-{1-[(4-chlorophenyl)pyrid-3-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(R)-N-{1-[(4-chlorophenyl)pyrid-3-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(S)-N-{1-[(4-chlorophenyl)pyrid-3-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(RS)-N-{1-[(4-chlorophenyl)pyrid-4-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(R)-N-{1-[(4-chlorophenyl)pyrid-4-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(S)-N-{1-[(4-chlorophenyl)pyrid-4-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(RS)-N-{1-[(4-chlorophenyl)pyrimid-5-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

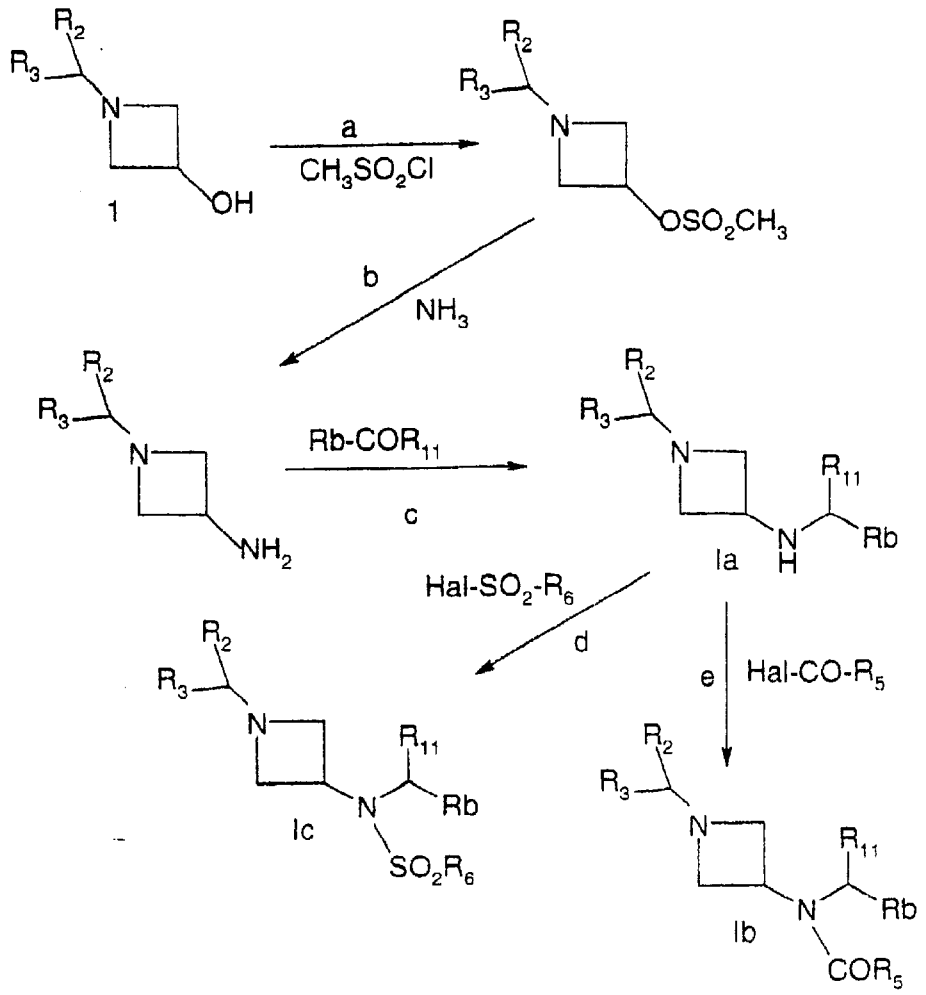
(R)-N-{1-[(4-chlorophenyl)pyrimid-5-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(S)-N-{1-[(4-chlorophenyl)pyrimid-5-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)benzylsulfonamide,

their optical isomers and their pharmaceutically acceptable salts.

The compounds of formula (I) for which R_1 represents the radical $-N(R_4)R_5$ in which R_5 is a hydrogen atom, a radical $-N(R_4)-CO-R_5$ or $-N(R_4)-SO_2R_6$, R_4 is a radical $-C(R_{11})(R_{12})-Ar$ or $-C(R_{11})(R_{12})-Het$ and R_{12} is a hydrogen atom may be prepared according to the following reaction scheme:



In these formulae, R_2, R_3, R_6 and R_{11} have the same meanings as in formula (I), Rb represents an Ar or Het radical, Ar and Het having the same meanings as in formula (I) and Hal represents a halogen atom and preferably chlorine or bromine.

Step a is generally carried out in an inert solvent such as tetrahydrofuran, dioxane, a chlorinated solvent (for example dichloromethane or chloroform), at a temperature of between 15 and 30°C, in the presence of a base such as a trialkylamine (for example

triethylamine or dipropylethylamine) or in pyridine, at a temperature of between 0 and 30°C.

Step b is preferably carried out in methanol, in an autoclave, at a temperature of between 50 and 70°C.

Step c is generally carried out in an inert solvent such as a chlorinated solvent (for example dichloromethane), in the presence of sodium triacetoxyborohydride and acetic acid, at a temperature in the region of 20°C.

Steps d and e are generally carried out in an inert solvent such as tetrahydrofuran, dioxane, a chlorinated solvent (for example dichloromethane or chloroform), in the presence of an amine such as a trialkylamine (for example triethylamine), at a temperature of between 5°C and 20°C.

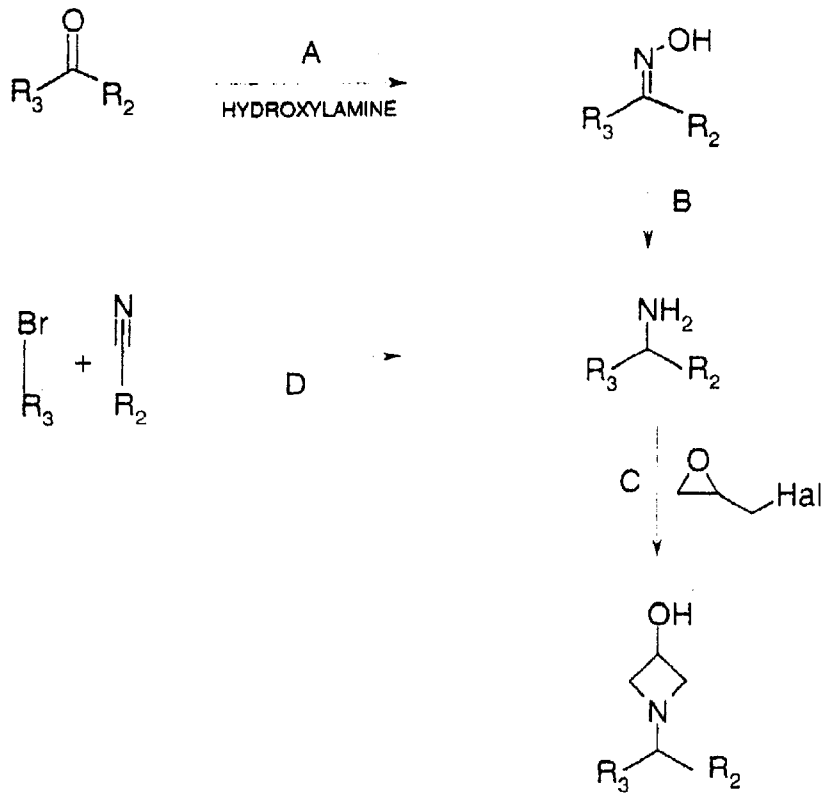
The derivatives $Rb\text{-}COR_{11}$ are commercially available or may be obtained according to the methods described for example by R.C. LAROCK, Comprehensive Organic Transformations, VCH editor.

The derivatives $Hal\text{-}SO_2R_6$ are commercially available or may be obtained by halogenation of the corresponding sulfonic acids, in particular in situ in the presence of chlorosulfonyl isocyanate and alcohol, in a halogenated solvent (for example dichloromethane or chloroform).

The derivatives $Hal\text{-}COR_5$ are commercially available or may be prepared by halogenation of the

corresponding carboxylic acids, in particular in situ in the presence of thionyl chloride in a halogenated solvent (for example dichloromethane or chloroform).

The azetidinols 1 may be obtained by application or adaptation of the methods described by KATRITZKY A.R. et al., J. Heterocycl. Chem., 271 (1994) or DAVE P.R., J. Org. Chem., 61, 5453 (1996) and in the examples. The procedure is generally carried out according to the following reaction scheme:



in these formulae, R_2 and R_3 have the same meanings as in formula (I) and Hal represents a chlorine or bromine atom.

In step A, the procedure is preferably carried out in an inert solvent such as a 1-4C aliphatic alcohol (for example ethanol or methanol), optionally in the presence of an alkali metal hydroxide, at the boiling point of the reaction medium.

In step B, the reduction is generally carried out, by means of lithium aluminum hydride, in tetrahydrofuran at the boiling point of the reaction medium.

In step C, the procedure is preferably carried out in an inert solvent such as a 1-4C aliphatic alcohol (for example ethanol or methanol), in the presence of sodium hydrogen carbonate, at a temperature of between 20°C and the boiling point of the reaction medium.

In step D, the procedure is carried out according to the method described by GRISAR M. et al. in J. Med. Chem., 885 (1973). The magnesium compound of the brominated derivative is formed and then the nitrile is caused to react, in an ether such as ethyl ether, at a temperature of between 0°C and the boiling point of the reaction medium. After hydrolysis with an alcohol, the intermediate imine is reduced *in situ* with sodium borohydride at a temperature of between 0°C and the boiling point of the reaction medium.

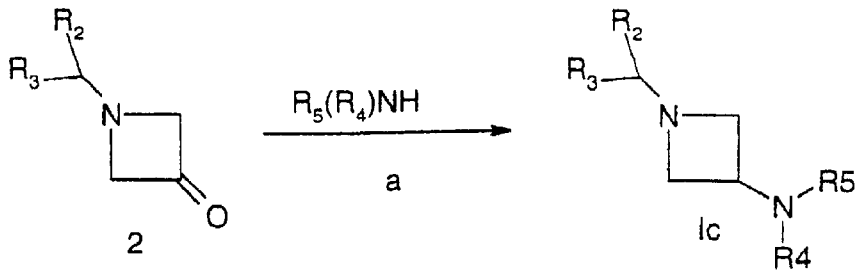
The derivatives R_2-CO-R_3 are commercially available or may be obtained by application or adaptation of the methods described by KUNDER N.G. et

al. J. Chem. Soc. Perkin Trans 1, 2815 (1997); MORENO-MARRAS M., Eur. J. Med. Chem., 23 (5) 477 (1988); SKINNER et al., J. Med. Chem., 14 (6) 546 (1971); HURN N.K., Tet. Lett., 36 (52) 9453 (1995); MEDICI A. et al., Tet. Lett., 24 (28) 2901 (1983); RIECKE R.D. et al., J. Org. Chem., 62 (20) 6921 (1997); KNABE J. et al., Arch. Pharm., 306 (9) 648 (1973); CONSONNI R. et al., J. Chem. Soc. Perkin Trans 1, 1809 (1996); FR-96-2481 and JP-94-261393.

The derivatives R_3Br are commercially available or may be obtained by application or adaptation of the methods described by BRANDSMA L. et al., Synth. Comm., 20 (11) 1697 and 3153 (1990); LEMAIRE M. et al., Synth. Comm., 24 (1) 95 (1994); GODA H. et al., Synthesis, 9 849 (1992); BAEUERLE P. et al., J. Chem. Soc. Perkin Trans 2, 489 (1993).

The derivatives R_2CN are commercially available or may be obtained by application or adaptation of the methods described by BOUYSSOU P. et al., J. Het. Chem., 29 (4) 895 (1992); SUZUKI N. et al., J. Chem. Soc. Chem. Comm., 1523 (1984); MARBURG S. et al., J. Het. Chem., 17 1333 (1980); PERCEC V. et al., J. Org. Chem., 60 (21) 6895 (1995).

The compounds of formula (I) for which R_1 represents a radical $-N(R_4)R_5$ may be prepared according to the following reaction scheme:



In these formulae, R_2, R_3, R_4 and R_5 have the same meanings as in formula (I).

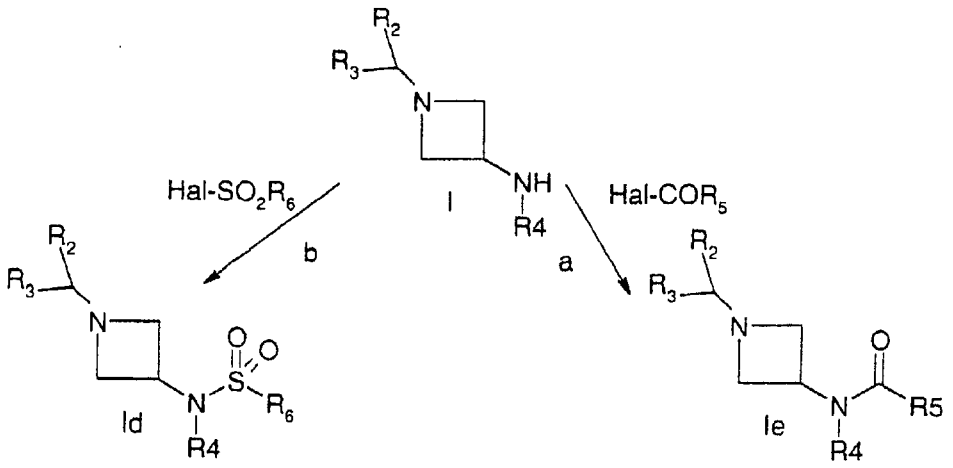
This reaction is generally carried out in an inert solvent such as a chlorinated solvent (for example dichloromethane), in the presence of sodium triacetoxyborohydride and acetic acid, at a temperature in the region of 20°C.

The compounds $HN(R_4)R_5$ are commercially available or may be prepared according to conventional methods known to persons skilled in the art or by application or adaptation of the methods described by Park K.K. et al., J. Org. Chem., 60 (19) 6202 (1995); Kalir A. et al., J. Med. Chem., 12 (3) 473 (1969); Sarges R., J. Org. Chem., 40 (9) 1216 (1975); Zaugg H.E., J. Org. Chem., 33 (5) 2167 (1968); Med. Chem., 10, 128 (1967); J. Am. Chem. Soc., 2244 (1955); Chem. Ber., 106, 2890 (1973); Chem. Pharm. Bull., 16 (10) 1953 (1968); Bull. Soc. Chim. Fr., 835 (1962).

The azetidinones 2 may be obtained by oxidation of the corresponding acetidinols, preferably in dimethyl sulfoxide, by means of the sulfur trioxide-pyridine complex, at a temperature in the region of

20°C or by means of dimethyl sulfoxide, in the presence of oxalyl chloride and triethylamine, at a temperature of between -70°C and -50°C.

The compounds of formula (I) for which R_1 represents a radical $-N(R_4)COR_5$ or $-N(R_4)SO_2R_6$ may be prepared according to the following reaction scheme:

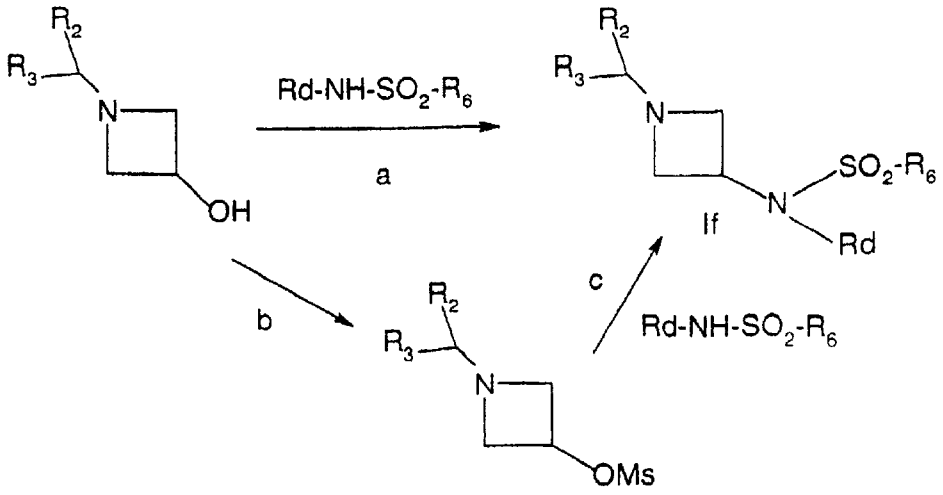


In these formulae, R_2, R_3, R_4, R_5 and R_6 have the same meanings as in formula (I) and Hal represents a halogen atom and preferably chlorine.

Steps a and b are generally carried out in an inert solvent such as tetrahydrofuran, dioxane, a chlorinated solvent (for example dichloromethane or chloroform), in the presence of an amine such as a trialkylamine (for example triethylamine), at a temperature of between 5°C and 20°C.

The compounds of formula (I) for which R_1 represents a radical $-N(R_4)-SO_2-R_6$ for which R_4 is a Het

or Ar radical may be prepared according to the following reaction scheme:



In these formulae, R_2, R_3 and R_6 have the same meanings as in formula (I), Rd represents an Ar or Het radical (Het and Ar having the same meanings as in formula (I)) and Ms represents a methylsulfonyloxy radical.

Step a is generally carried out in an inert solvent such as tetrahydrofuran, in the presence of triphenylphosphine and diethylazodicarboxylate, at a temperature of between 0°C and the boiling point of the reaction medium.

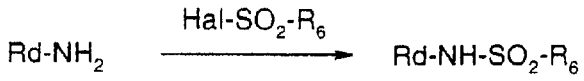
Step b is generally carried out in an inert solvent such as tetrahydrofuran, dioxane, a chlorinated solvent (for example dichloromethane or chloroform), at a temperature of between 15°C and 30°C, in the presence of a base such as a trialkylamine (for example

triethylamine or dipropylethylamine) or in pyridine, at a temperature of between 0°C and 30°C.

Step c is preferably carried out in an inert solvent such as dioxane in the presence of $CsCO_3$, at the reflux temperature of the reaction mixture.

The derivatives for which Rd represents an N-oxidized nitrogen-containing heterocycle may be reduced [lacuna] nonoxidized compound according to the method described by SANGHANEL E. et al., Synthesis 1375 (1996).

The derivatives $Rd\text{-}NH\text{-}SO_2R_6$ may be obtained according to the following reaction scheme:

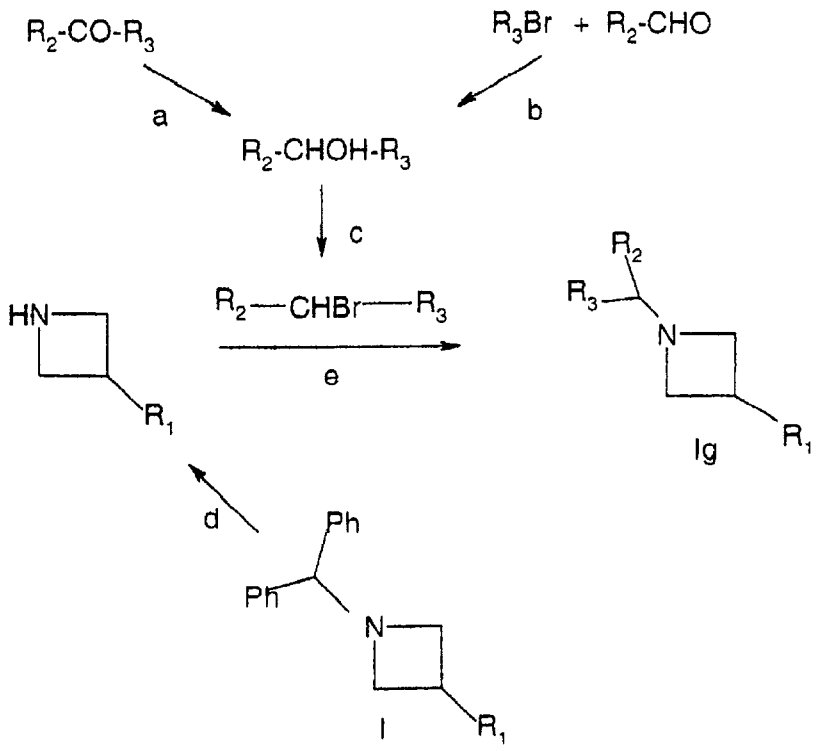


In these formulae, Hal represents a halogen atom, Rd represents a Het or Ar radical. The reaction is carried out in an inert solvent such as tetrahydrofuran, dioxane, a chlorinated solvent (for example dichloromethane or chloroform), at a temperature of between 15°C and 30°C, in the presence of a base such as a trialkylamine (for example triethylamine or dipropylethylamine) or in pyridine, at a temperature of between 0°C and 30°C.

The derivatives for which Rd represents an N-oxidized nitrogen-containing heterocycle may be

obtained according to the method described by RHIE R., Heterocycles, 41 (2) 323 (1995).

The compounds of formula (I) may also be prepared according to the following reaction scheme:



In these formulae, R_1, R_2 and R_3 have the same meanings as in formula (I) and Ph represents a phenyl.

Step a is generally carried out in an alcohol such as methanol, in the presence of sodium borohydride, at a temperature in the region of 20°C.

In step b, the magnesium compound of the brominated derivative is prepared and it is caused to react, in an inert solvent such as ethyl ether or tetrahydrofuran, at a temperature of between 0°C and the boiling point of the reaction medium.

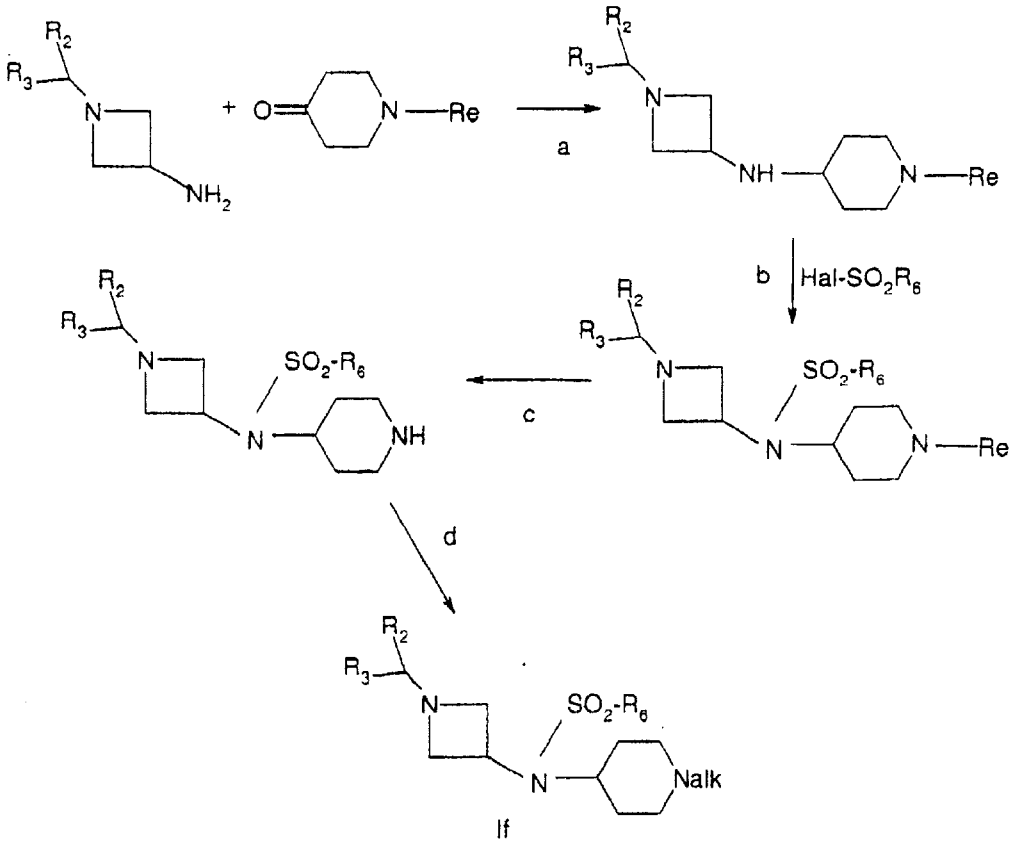
Step c is carried out by means of a halogenating agent such as hydrobromic acid, thionyl bromide, thionyl chloride, a mixture of triphenylphosphine and carbon tetrabromide or tetrachloride, in acetic acid or an inert solvent such as dichloromethane, chloroform, carbon tetrachloride or toluene, at a temperature of between 0°C and the boiling point of the reaction medium.

Step d is carried out by means of hydrogen, in the presence of palladized charcoal, in an alcohol such as methanol, at a temperature in the region of 20°C.

Step e is carried out in an inert solvent such as acetonitrile, in the presence of an alkali metal carbonate (for example potassium carbonate) and potassium iodide, at a temperature of between 20°C and the boiling point of the reaction medium.

The derivatives R_3Br and the derivatives R_2-CHO are commercially available or may be obtained according to the methods described for example by R.C. LAROCK, Comprehensive Organic Transformations, VCH editor.

The compounds of formula (I) for which R_1 represents a radical $-N(R_4)-SO_2-R_6$ for which R_4 is a 4-piperidyl radical optionally substituted on the nitrogen with an alkyl radical may also be prepared according to the following reaction scheme:



In these formulae, R_2, R_3 and R_6 have the same meanings as in formula (I), alk represents an alkyl radical and Re represents a tert-butylcarbonyloxy radical.

Step a is carried out in an inert solvent such as a chlorinated solvent (for example dichloromethane), in the presence of a hydride such as sodium triacetoxyborohydride and acetic acid, at a temperature of between 0°C and the boiling point of the reaction medium.

Step b is generally carried out in an inert solvent such as tetrahydrofuran, dioxane, a chlorinated solvent (for example dichloromethane or chloroform), in

the presence of an amine such as a trialkylamine (triethylamine for example), at a temperature of between 5°C and 20°C.

Step c is carried out by means of hydrochloric acid, in dioxane, at a temperature of between 0°C and the boiling point of the reaction medium.

Step d is carried out by any means known to persons skilled in the art for alkylating an amine without affecting the rest of the molecule. It is possible, for example, to use an alkyl halide, in the presence of an organic base such as triethylamine or an alkali metal hydroxide (for example sodium hydroxide or potassium hydroxide), optionally in the presence of tetrabutylammonium bromide, in an inert solvent such as dimethyl sulfoxide, dimethylformamide or pyridine, at a temperature of between 20 and 50°C.

The compounds of formula (I) for which R_1 represents a radical $-N(R_4)-SO_2-R_6$ for which R_4 is a phenyl radical substituted with a 1-pyrrolidyl radical may also be prepared by the action of pyrrolidine on a corresponding compound of formula (I) for which R_1 represents a radical $-N(R_4)SO_2R_6$ for which R_4 is a phenyl radical substituted with a halogen atom.

This reaction is preferably carried out in dimethyl sulfoxide, at a temperature of between 50 and 95°C.

It is understood for persons skilled in the art that, to carry out the processes according to the invention which are described above, it may be necessary to introduce groups protecting amino, hydroxyl and carboxyl functions in order to avoid side reactions. These groups are those which allow removal without affecting the rest of the molecule. As examples of groups protecting the amino function, there may be mentioned tert-butyl or methyl carbamates which may be regenerated using iodotrimethylsilane or allyl using palladium catalysts. As examples of groups protecting the hydroxyl function, there may be mentioned triethylsilyl and tert-butyldimethylsilyl which may be regenerated using tetrabutylammonium fluoride or alternatively asymmetric acetals (methoxymethyl or tetrahydropyranyl for example) with regeneration using hydrochloric acid. As groups protecting carboxyl functions, there may be mentioned esters (allyl or benzyl for example), oxazoles and 2-alkyl-1,3-oxazolines. Other protecting groups which can be used are described by GREENE T.W. et al., Protecting Groups in Organic Synthesis, second edition, 1991, John Wiley & Sons.

The compounds of formula (I) may be purified by the customary known methods, for example by crystallization, chromatography or extraction.

The enantiomers of the compounds of formula (I) may be obtained by resolution of the racemates for

example by chromatography on a chiral column according to PIRCKLE W.H. et al., Asymmetric synthesis, Vol. 1, Academic Press (1983) or by formation of salts or by synthesis from chiral precursors. The diastereoisomers may be prepared according to known conventional methods (crystallization, chromatography or from chiral precursors).

The compounds of formula (I) may be optionally converted to addition salts with an inorganic or organic acid by the action of such an acid in an organic solvent such as an alcohol, a ketone, an ether or a chlorinated solvent. These salts also form part of the invention.

As examples of pharmaceutically acceptable salts, the following salts may be mentioned: benzenesulfonate, hydrobromide, hydrochloride, citrate, ethanesulfonate, fumarate, gluconate, iodate, isethionate, maleate, methane sulfonate, methylene-bis-b-oxynaphthoate, nitrate, oxalate, pamoate, phosphate, salicylate, succinate, sulfate, tartrate, theophyllineacetate and p-toluenesulfonate.

The compounds of formula (I) exhibit advantageous pharmacological properties. These compounds possess a high affinity for the cannabinoid receptors and particularly those of the CB1 type. They are CBI receptor antagonists and are therefore useful in the treatment and prevention of disorders affecting the central nervous system, the immune system, the

cardiovascular or endocrine system, the respiratory system, the gastrointestinal apparatus and reproductive disorders (Hollister, Pharm. Rev.; 38, 1986, 1-20, Reny and Sinha, Prog. Drug Res., 36, 71-114 (1991), Consroe and Sandyk, in Marijuana/Cannabinoids, Neurobiology and Neurophysiology, 459, Murphy L. and Barthe A. Eds, CRC Press, 1992).

Accordingly, these compounds may be used for the treatment or prevention of psychoses including schizophrenia, anxiety disorders, depression, epilepsy, neurodegeneration, cerebellar and spinocerebellar disorders, cognitive disorders, cranial trauma, panic attacks, peripheral neuropathies, glaucomas, migraine, Parkinson's disease, Alzheimer's disease, Huntington's chorea, Raynaud's syndrome, tremor, obsessive-compulsive disorder, senile dementia, thymic disorders, Tourette's syndrome, tardive dyskinesia, bipolar disorders, cancers, movement disorders induced by medicaments, dystonia, endotoxemic shocks, hemorrhagic shocks, hypotension, insomnia, immunological diseases, multiple sclerosis, vomiting, asthma, appetite disorders (bulimia, anorexia), obesity, memory disorders, in weaning from chronic treatments and alcohol or drug abuse (opioids, barbiturates, cannabis, cocaine, amphetamine, phencyclide, hallucinogens, benzodiazepines for example), as analgesics or potentiators of the analgesic activity of the narcotic

and nonnarcotic drugs. They may also be used for the treatment or prevention of intestinal transit.

The affinity of the compounds of formula (I) for the cannabis receptors has been determined according to the method described by KUSTER J.E., STEVENSON J.I., WARD S.J., D'AMBRA T.E., HAYCOCK D.A. in J. Pharmacol. Exp. Ther., 264 1352-1363 (1993).

In this test, the IC_{50} of the compounds of formula (I) is less than or equal to 1000 nM.

Their antagonist activity has been shown by means of the model of hypothermia induced by an agonist of the cannabis receptors (CP-55940) in mice, according to the method described by Pertwee R.G. in Marijuana, Harvey D.J. eds, 84 Oxford IRL Press, 263-277 (1985).

In this test, the ED_{50} of the compounds of formula (I) is less than or equal to 50 mg/kg.

The compounds of formula (I) exhibit low toxicity. Their LD_{50} is greater than 40 mg/kg by the subcutaneous route in mice.

The following examples illustrate the invention.

Example 1

N-{1-[Bis-(4-chlorophenyl)methyl]azetidin-3-yl}-N-(6-chloropyrid-2-yl)methylsulfonamide may be prepared by carrying out the procedure in the following manner: 2.4 cm^3 of diethyl azodicarboxylate and 1.44 g of triphenylphosphine are added, under argon, to a solution of 1.54 g of 1-[bis(4-chlorophenyl)methyl]-

azetidin-3-ol and 1.22 g of N-(6-chloropyrid-2-yl)methylsulfonamide in 120 cm^3 of anhydrous tetrahydrofuran. After stirring for 20 hours at 20°C, the reaction mixture is concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.040-0.063 mm, height 30 cm, diameter 4.5 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (80/20 by volume) and collecting 60-cm^3 fractions. Fractions 6 to 9 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 1.75 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(6-chloropyrid-2-yl)-methylsulfonamide are obtained in the form of a white foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): from 2.85 to 3.00 (mt : 2H); 2.91 (s : 3H); 3.57 (split t, J = 7 and 2 Hz : 2H); 4.25 (s : 1H); 4.64 (mt : 1H); from 7.20 to 7.35 (mt : 9H); 7.36 (dd, J = 8 and 1 Hz : 1H); 7.71 (t, J = 8 Hz : 1H)].

1-[Bis(4-chlorophenyl)methyl]azetidin-3-ol may be prepared according to the procedure described by KATRITZKY A.R. et al., J. Heterocycl. Chem., 271 (1994), starting with 35.5 g of [bis(4-chlorophenyl)-methyl]amine hydrochloride and 11.0 cm^3 of epichlorohydrin. 9.0 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-ol are isolated.

Bis(4-chlorophenyl)methyl]amine hydrochloride may be prepared according to the method described by GRISAR M. et al., J. Med. Chem., 885 (1973).

N-(6-Chloropyrid-2-yl)methylsulfonamide may be prepared by carrying out the procedure in the following manner: 7.8 cm^3 of methylsulfonyl chloride are poured dropwise, over 1 hour, into a solution, cooled to +5°C, of 2-amino-6-chloropyridine in 12.5 cm^3 of pyridine. After returning to room temperature and stirring for 20 hours, the black reaction mixture is supplemented with 140 cm^3 of water and extracted with 200 cm^3 of dichloromethane. The organic phase is separated after settling, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The oily residue obtained is chromatographed on a silica gel column (particle size 0.063-0.200 mm, height 30 cm, diameter 4 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (70/30 by volume) and collecting 60-cm^3 fractions. Fractions 5 to 11 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 17 g of N-(6-chloropyrid-2-yl)methylsulfonamide are obtained in the form of a yellow oil.

Example 2

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(6-ethylpyrid-2-yl)methylsulfonamide may be prepared by carrying out the procedure as described in

Example 1, starting with 0.61 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-ol, 0.40 g of N-(6-ethylpyrid-2-yl)methylsulfonamide, 50 cm^3 of anhydrous tetrahydrofuran, 0.96 cm^3 of diethyl azodicarboxylate and 0.577 g of triphenylphosphine. The crude product is chromatographed on a silica gel column (particle size 0.040-0.063 mm, height 20 cm, diameter 2 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (70/30 by volume) and collecting 30-cm^3 fractions. Fractions 6 to 9 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 0.3 g of an oil is obtained which is triturated in a mixture of 5 cm^3 of diethyl ether and 5 cm^3 of diisopropyl ether. The suspension is filtered, the solid drained and then dried under reduced pressure (2.7 kPa). 0.11 g of N-{1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}-N-(6-ethylpyrid-2-yl)methylsulfonamide is obtained in the form of a white solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 1.26 (t, J = 7.5 Hz : 3H); 2.76 (q, J = 7.5 Hz : 2H); from 2.85 to 2.95 (mt : 2H); 2.90 (s : 3H); 3.53 (split t, J = 7 and 2 Hz : 2H); 4.22 (s : 1H); 4.69 (mt : 1H); 7.07 (d, J = 7.5 Hz : 1H); from 7.15 to 7.30 (mt : 9H); 7.64 (t, J = 7.5 Hz : 1H)].

N-(6-Ethylpyrid-2-yl)methylsulfonamide may be prepared by carrying out the procedure in the following manner: 1.56 cm^3 of methylsulfonyl chloride are poured dropwise into a solution, cooled to +5°C, of 2.50 g of

2-amino-6-ethylpyridine in 2.50 cm^3 of pyridine. After stirring for 20 hours at 20°C, the reaction mixture is supplemented with 8 cm^3 of water and filtered. The filtrate is concentrated to dryness at 50°C under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.040-0.063 mm, height 30 cm, diameter 4 cm), eluting under an argon pressure of 0.5 bar with 1.5 litres of dichloromethane and then with a mixture of dichloromethane and methanol (98/2 by volume) and collecting 60-cm^3 fractions. Fractions 8 to 12 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 2.8 g of N-(6-ethylpyrid-2-yl)methylsulfonamide are obtained in the form of a yellow oil.

Example 3

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-quinol-6-ylmethylsulfonamide may be prepared by carrying out the procedure in the following manner: 0.70 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-ol and 0.597 g of triphenylphosphine are added, under argon, to a solution of 0.50 g of N-quinol-6-ylmethylsulfonamide in 50 cm^3 of anhydrous tetrahydrofuran and then 0.40 cm^3 of diethyl azodicarboxylate is poured in. After stirring for 20 hours at 20°C, the reaction mixture is heated at the reflux temperature for 4 hours and then supplemented with 2.98 g of triphenylphosphine and 2.0 cm^3 of diethyl azodicarboxylate. After stirring for 48 hours at 20°C, the mixture is concentrated to

dryness under reduced pressure (2.7 kPa). The residue is taken up in 30 cm^3 of diethyl ether, the suspension obtained is filtered and the filtrate is concentrated to dryness. A fraction of the residue obtained (0.90 g) is purified on a Bond Elut column of cation exchange sulfonic acid SCX resin (particle size 0.054 mm, height 4 cm, diameter 3 cm), eluting first with methanol and then with a 2 M solution of aqueous ammonia in methanol in order to elute the expected product, collecting 5-cm^3 fractions. Fractions 16 to 19 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 0.33 g of an oil is obtained which is stirred in 10 cm^3 of diisopropyl ether. The resulting suspension is filtered. The filtrate, which is again filtered, gives, after 15 minutes, a solid which is dried at 50°C under reduced pressure (2.7 kPa). 83 mg of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-quinol-6-ylmethylsulfonamide are obtained in the form of a white solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.87 (s : 3H); 2.89 (mt : 2H); 3.55 (split t, J = 7 and 1 Hz : 2H); 4.18 (s : 1H); 4.69 (mt : 1H); from 7.15 to 7.30 (mt : 8H); 7.47 (dd, J = 8.5 and 4 Hz : 1H); 7.58 (dd, J = 9 and 2.5 Hz : 1H); 7.73 (d, J = 2.5 Hz : 1H); 8.10 to 8.20 (mt : 2H); 8.97 (dd, J = 4 and 1.5 Hz : 1H)]

N-Quinol-6-ylmethylsulfonamide may be prepared by carrying out the procedure in the following manner: 1.1 cm^3 of methylsulfonyl chloride are poured

dropwise, over 1 hour, into a solution, cooled to +3°C, of 1.98 g of 6-aminoquinoline in 1.75 cm^3 of pyridine. After stirring for 20 hours at 20°C, the reaction mixture is supplemented with 10 cm^3 of water and 50 cm^3 of dichloromethane, and then filtered. The filtrate is separated after settling, the organic phase is dried over magnesium sulfate, and then filtered and concentrated to dryness under reduced pressure (2.7 kPa). 1.15 g of N-quinol-6-ylmethylsulfonamide are obtained in the form of a cream-yellow solid.

Example 4

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-quinol-6-ylmethylsulfonamide may be prepared by carrying out the procedure in the following manner: 0.70 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-ol and 0.597 g of triphenylphosphine are added, under argon, to a solution of 0.50 g of N-(quinol-5-yl)-methylsulfonamide in 70 cm^3 of anhydrous tetrahydrofuran and then 0.40 cm^3 of diethyl azodicarboxylate and 0.45 g of 1,2-bis(diphenylphosphine)ethane are poured in. After stirring for 20 hours at 20°C, the reaction mixture is concentrated to dryness under reduced pressure (2.7 kPa). The residue is taken up in 70 cm^3 of ethyl acetate, the resulting solution is washed with 30 cm^3 of brine, dried over magnesium sulfate, filtered and then concentrated to dryness at 50°C under reduced pressure (2.7 kPa). The violet oil obtained is purified by chromatography on a silica gel column (particle size

0.063-0.200 mm, height 35 cm, diameter 3.9 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (40/60 then 30/70 and 20/80 by volume) and collecting 50-cm^3 fractions. Fractions 6 to 12 are combined and concentrated to dryness under reduced pressure (2.7 kPa). The residue is taken up in 15 cm^3 of methanol, the resulting white suspension is filtered, the solid drained and then dried at 50°C under reduced pressure (2.7 kPa). 0.35 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-quinol-5-ylmethylsulfonamide is obtained in the form of a white solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.60 (t, J = 7 Hz : 1H); 2.84 (t, J = 7 Hz : 1H); 2.99 (s : 3H); 3.36 (split t, J = 7 and 2.5 Hz : 1H); 3.56 (split t, J = 7 and 2.5 Hz : 1H); 4.01 (s : 1H); 4.85 (mt : 1H); from 7.10 to 7.25 (mt : 8H); 7.40 (dd, J = 7.5 and 1 Hz : 1H); 7.54 (dd, J = 8.5 and 4 Hz : 1H); 7.74 (dd, J = 8 and 7.5 Hz : 1H); 8.20 (broad d, J = 8 Hz : 1H); 8.54 (broad d, J = 9 Hz : 1H); 8.99 (dd, J = 4 and 1.5 Hz : 1H)].

N-(Quinol-5-yl)methylsulfonamide may be prepared by carrying out the procedure as described in Example 3, starting with 2.0 g of 5-aminoquinoline, 3.0 cm^3 of pyridine, 1.1 cm^3 of methylsulfonyl chloride. 2.47 g of N-(quinol-5-yl)methylsulfonamide are obtained in the form of a brown-yellow solid.

Example 5

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-isoquinol-5-ylmethylsulfonamide may be prepared by carrying out the procedure as described in Example 4, starting with 0.497 g of N-(isoquinol-5-yl)methylsulfonamide, 70 cm^3 of anhydrous tetrahydrofuran, 0.712 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-ol, 0.597 g of triphenylphosphine, 0.40 cm^3 of diethyl azodicarboxylate and 0.45 g of 1,2-bis(diphenylphosphine)ethane. The crude brown oil obtained is purified by chromatography on a silica gel column (particle size 0.063-0.200 mm, height 38 cm, diameter 3 cm), eluting with a mixture of cyclohexane and ethyl acetate (30/70 by volume) and collecting 40-cm^3 fractions. Fractions 8 to 23 are combined and concentrated to dryness under reduced pressure (2.7 kPa). The residue is stirred in 15 cm^3 of diethyl ether, the suspension is filtered and the insoluble matter is chromatographed on a column of SCX resin (height 4 cm, diameter 3 cm), washing first with a mixture of methanol and dichloromethane (50/50 by volume) and then eluting with a 2 M solution of aqueous ammonia in methanol and collecting 20-cm^3 fractions. Fractions 1 to 6 are combined and the white insoluble matter which appears is filtered, the solid is drained and then dried at 50°C under reduced pressure (2.7 kPa). 0.169 g of N-{1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}-N-isoquinol-5-ylmethylsulfonamide is

obtained in the form of a white solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.64 (t, J = 7 Hz : 1H); 2.81 (t, J = 7 Hz : 1H); 2.98 (s : 3H); 3.36 (split t, J = 7 and 2 Hz : 1H); 3.55 (split t, J = 7 and 2 Hz : 1H); 4.02 (s : 1H); 4.86 (mt : 1H); from 7.10 to 7.25 (mt : 8H); 7.60 (dd, J = 8 and 1 Hz : 1H); 7.66 (t, J = 8 Hz : 1H); 7.93 (broad d, J = 6 Hz : 1H); 8.06 (broad d, J = 8 Hz : 1H); 8.66 (d, J = 6 Hz : 1H); 9.32 (broad s : 1H)].

N-(Isoquinol-5-yl)methylsulfonamide may be prepared by carrying out the procedure as described in Example 4, starting with 2.0 g of 5-aminoisoquinoline, 3.0 cm^3 of pyridine and 1.1 cm^3 of methylsulfonyl chloride. 2.3 g of N-(isoquinol-5-yl)methylsulfonamide are obtained in the form of a beige solid.

Example 6

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-pyrid-3-ylmethylsulfonamide may be prepared by carrying out the procedure in the following manner: 0.042 cm^3 of phosphorus trichloride is poured into a solution of 0.144 g of N-{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-N-(1-oxide-pyrid-3-yl)methyl-sulfonamide in 5 cm^3 of chloroform and then the mixture is heated to the reflux temperature. After stirring for 1 hour 30 minutes, the reaction mixture is allowed to return to room temperature and is then supplemented with 5 cm^3 of 0.1 N hydrochloric acid, then stirred and separated after settling. The organic phase is diluted

with 20 cm^3 of chloroform, dried over magnesium sulfate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.063-0.200 mm, height 9 cm, diameter 1.8 cm), eluting under an argon pressure of 0.1 bar with a mixture of dichloromethane and methanol (95/5 by volume) and collecting 15-cm^3 fractions. Fractions 2 to 4 are combined and concentrated to dryness under reduced pressure (2.7 kPa). The residue is stirred with 15 cm^3 of diethyl ether, the suspension is filtered, the solid is drained and then dried under reduced pressure (2.7 kPa). 35 mg of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-pyrid-3-ylmethylsulfonamide are obtained in the form of a cream-coloured solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): from 2.80 to 2.95 (mt : 2H); 2.87 (s : 3H); 3.51 (split t, J = 7 and 1.5 Hz : 2H); 4.18 (s : 1H); 4.65 (mt : 1H); from 7.15 to 7.35 (mt : 8H); 7.37 (broad dd, J = 8 and 5 Hz : 1H); 7.64 (decoupled d, J = 8 Hz : 1H); 8.52 (broad d, J = 2 Hz : 1H); 8.61 (broad d, J = 5 Hz : 1H)].

Example 7

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(1-oxide-pyrid-3-yl)methylsulfonamide may be prepared by carrying out the procedure in the following manner: 0.16 cm^3 of diethyl azodicarboxylate and 0.226 g of triphenylphosphine are added, under argon, to a solution of 0.265 g of 1-[bis(4-chlorophenyl)methyl]-

azetidin-3-ol and 0.162 g of N-(1-oxide-pyrid-3-yl)methylsulfonamide, in 25 cm^3 of anhydrous tetrahydrofuran. After stirring for 20 hours at 20°C, and then for 24 hours at the reflux temperature, the reaction mixture is concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.063-0.2 mm, height 20 cm, diameter 1.5 cm), eluting under an argon pressure of 0.5 bar with a mixture of dichloromethane and methanol (98/2 by volume) and collecting 40-cm^3 fractions. Fractions 26 to 64 are combined and concentrated to dryness under reduced pressure (2.7 kPa). The residue is stirred in 10 cm^3 of diethyl ether, the suspension is filtered, the insoluble matter is drained and then dried under reduced pressure (2.7 kPa). 0.1 g of N-{1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}-N-(1-oxide-pyrid-3-yl)methylsulfonamide is obtained in the form of a white solid [^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$ d6, δ in ppm): 2.78 (t, J = 7 Hz : 2H); 3.06 (s : 3H); 3.37 (t, J = 7 Hz : 2H); 4.45 (s : 1H); 4.71 (mt : 1H); from 7.30 to 7.50 (mt : 10H); 8.21 (broad d, J = 6.5 Hz : 1H); 8.27 (broad s : 1H)].

N-(1-Oxide-pyrid-3-yl)methylsulfonamide may be prepared by carrying out the procedure in the following manner: 7.1 g of 50-55% 3-chloroperoxybenzoic acid are added, in fractions, to a solution of 1.81 g of N-pyrid-3-ylmethylsulfonamide in 71 cm^3 of

N,N-dimethylformamide and 3 cm^3 of methanol, followed by 0.56 cm^3 of 40% hydrofluoric acid. After stirring for 1 hour at 20°C, the reaction mixture is poured into 500 g of ice, stirred and then filtered. The filtrate is concentrated to dryness at 60°C under reduced pressure (2.7 kPa). The residue is taken up in 50 cm^3 of a mixture of dichloromethane and methanol (98/2 by volume) and then filtered. The filtrate is chromatographed on a silica gel column (particle size 0.063-0.2 mm, height 27 cm, diameter 4 cm), eluting under an argon pressure of 0.5 bar with a mixture of dichloromethane and methanol (98/2, 97/3 and then 50/50 by volume) and collecting 60-cm^3 fractions. Fraction 62 is concentrated to dryness under reduced pressure (2.7 kPa). 0.96 g of N-(1-oxide-pyrid-3-yl)methyl-sulfonamide is obtained in the form of a yellowish solid.

N-Pyrid-3-ylmethylsulfonamide may be prepared by carrying out the procedure as described in Example 1, starting with 2 g of 3-aminopyridine, 5 cm^3 of pyridine and 1.8 cm^3 of methylsulfonyl chloride. The crude product obtained is stirred in 40 cm^3 of diethyl ether, the suspension is filtered and then the solid is drained and dried under reduced pressure (2.7 kPa). 2.47 g of N-pyrid-3-ylmethylsulfonamide are obtained in the form of a pinkish solid.

Example 8

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-cyclohexylmethylsulfonamide may be prepared by carrying out the procedure in the following manner:

0.4 cm^3 of methylsulfonyl chloride is added, with stirring, to a solution of 1.8 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-cyclohexylamine, 0.7 cm^3 of triethylamine and 20 mg of 4-dimethylaminopyridine in 25 cm^3 of dichloromethane. After stirring for 48 hours at 20°C, 20 cm^3 of dichloromethane and 20 cm^3 of water are added to the reaction mixture and it is stirred and separated after settling. The organic phase is dried over magnesium sulfate and concentrated at 50°C under reduced pressure (2.7 kPa). The brown oily residue is chromatographed on a silica gel column (particle size 0.063-0.2 mm, height 20 cm, diameter 2.0 cm), eluting under an argon pressure of 0.1 bar with a mixture of dichloromethane and methanol (96/4 by volume) and collecting 10-cm^3 fractions. Fractions 2 to 4 and 5 to 10 are combined and concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.063-0.2 mm, height 30 cm, diameter 1.5 cm), eluting under an argon pressure of 0.1 bar with a mixture of cyclohexane and ethyl acetate (70/30 by volume) and collecting 5-cm^3 fractions. Fractions 7 to 10 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 0.10 g of N-{1-[bis(4-chloro-

phenyl)methyl]azetidin-3-yl}-N-cyclohexylmethyl-sulfonamide is obtained in the form of a cream-coloured foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): from 0.80 to 1.90 (mt : 10H); 2.82 (s : 3H); 3.36 (broad t, J = 7.5 Hz : 2H); 3.46 (broad t, J = 7.5 Hz : 2H); 3.59 (mt : 1H); 4.08 (mt : 1H); 4.42 (s : 1H); from 7.20 to 7.40 (mt : 8H)].

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-cyclohexylamine may be prepared by carrying out the procedure in the following manner: 0.5 g of cyclohexylamine, 1 g of sodium triacetoxyborohydride and 0.3 cm^3 of 100% acetic acid are added to a solution of 1.5 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-one in 25 cm^3 of 1,2-dichloroethane. After stirring for 20 hours at 20°C, 20 cm^3 of dichloromethane and 10 cm^3 of water are added to the reaction mixture, with stirring, and then the mixture is neutralized to pH 7 to 8 with a 1 N aqueous sodium hydroxide solution. The mixture is separated after settling, the organic phase is dried over magnesium sulfate and concentrated to dryness at 50°C under reduced pressure (2.7 kPa). 1.8 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-cyclohexylamine are obtained in the form of a cream-coloured paste which will be used as it is in the next step.

1-[Bis(4-chlorophenyl)methyl]azetidin-3-one may be prepared according to the following procedure: a solution of 8.1 cm^3 of dimethyl sulfoxide in 17.6 cm^3 of dichloromethane is added to a solution of 5.0 cm^3 of

oxalyl chloride in 73 cm^3 of dichloromethane cooled to -78°C. After 0.5 hour at -78°C, a solution of 16.0 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-ol, dissolved in 50 cm^3 of dichloromethane, is poured in. After 5 hours at -78°C, 26.6 cm^3 of triethylamine are added dropwise and the reaction mixture is allowed to return to room temperature. After 16 hours, the reaction mixture is washed with 4 times 200 cm^3 of water and then with 200 cm^3 of a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is chromatographed on a silica gel column (particle size 0.04-0.06 mm, diameter 9.2 cm, height 21 cm), under an argon pressure of 0.5 bar with a mixture of ethyl acetate and cyclohexane (40/60 by volume) as eluents and collecting 200-cm^3 fractions. Fractions 15 to 25 are combined and then concentrated to dryness under reduced pressure (2.7 kPa). 8.9 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-one are obtained in the form of pale yellow crystals melting at 111°C.

Example 9

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-cyclopropylmethylsulfonamide may be prepared by carrying out the procedure as described in Example 8, starting with 1.6 g of N-{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-N-cyclopropylamine, 25 cm^3 of dichloromethane, 0.7 cm^3 of triethylamine, 20 mg of 4-

dimethylaminopyridine and 0.4 cm^3 of methylsulfonyl chloride, while the mixture is stirred for 20 hours at 20°C. The crude product is chromatographed on a silica gel column (particle size 0.063-0.2 mm, height 30 cm, diameter 2.0 cm), eluting under an argon pressure of 0.1 bar with a mixture of dichloromethane and methanol (97/3 by volume) and collecting 10-cm^3 fractions. Fractions 6 to 9 and 10 to 20 are combined and concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is chromatographed on a silica gel column (particle size 0.063-0.2 mm, height 30 cm, diameter 2.0 cm), eluting under an argon pressure of 0.1 bar with a mixture of cyclohexane and ethyl acetate (70/30 by volume) and collecting 10-cm^3 fractions. Fractions 6 to 11 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 0.14 g of N-{1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}-N-cyclopropylmethylsulfonamide is obtained in the form of a cream-coloured foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 0.79 (mt : 2H); 0.95 (mt : 2H); 2.11 (mt : 1H); 2.84 (s : 3H); 3.17 (broad t, J = 7 Hz : 2H); 3.50 (mt : 2H); 4.18 (mt : 1H); 4.29 (s : 1H); from 7.20 to 7.40 (mt : 8H)].

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-cyclopropylamine may be prepared by carrying out the procedure as described in Example 8, starting with 1.5 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-one, 25 cm^3 of 1,2-dichloroethane, 0.37 cm^3 of

cyclopropylamine, 1 g of sodium triacetoxyborohydride and 0.3 cm^3 of 100% acetic acid. 1.6 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-cyclopropylamine are obtained in the form of a brown oil which will be used as it is in the next step.

Example 10

N-(1R,2S,4S)Bicyclo[2.2.1]hept-2-yl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}methyl-sulfonamide may be prepared by carrying out the procedure as described in Example 8, starting with 2.0 g of N-(1R,2S,4S)bicyclo[2.2.1]hept-2-yl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}amine, 25 cm^3 of dichloromethane, 0.7 cm^3 of triethylamine, 20 mg of 4-dimethylaminopyridine and 0.4 cm^3 of methylsulfonyl chloride, with stirring for 20 hours. The brown oily residue is chromatographed on a silica gel column (particle size 0.063-0.2 mm, height 30 cm, diameter 2.0 cm), eluting under an argon pressure of 0.1 bar with a mixture of dichloromethane and methanol (97/3 by volume) and collecting 10-cm^3 fractions. Fractions 6 to 18 are combined and concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.063-0.2 mm, height 30 cm, diameter 2.0 cm), eluting under an argon pressure of 0.1 bar with a mixture of cyclohexane and ethyl acetate (70/30 by volume) and collecting 10-cm^3 fractions. Fractions 8 to 14 are combined and concentrated to dryness under reduced

pressure (2.7 kPa). 0.70 g of N-(1R,2S,4S)bicyclo-[2.2.1]hept-2-yl-N-{1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}methylsulfonamide is obtained in the form of a cream-coloured foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): from 1.20 to 1.75 (mt : 7H); 1.84 (broad t, J = 12.5 Hz : 1H); 2.29 (mt : 1H); 2.35 (mt : 1H); 2.82 (s : 3H); from 3.35 to 3.55 (mt : 3H); 3.66 (mt : 1H); from 3.90 to 4.05 (mt : 2H); 4.51 (s : 1H); from 7.20 to 7.45 (mt : 8H)].

N-(1R,2S,4S)Bicyclo[2.2.1]hept-2-yl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}amine may be prepared by carrying out the procedure as described in Example 8, starting with 1.5 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-one, 25 cm^3 of 1,2-dichloroethane, 1.5 g of (1R,2S,4S)bicyclo[2.2.1]hept-2-ylamine, 1 g of sodium triacetoxyborohydride and 0.3 cm^3 of 100% acetic acid. 2 g of N-(1R,2S,4S)bicyclo[2.2.1]-hept-2-yl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}amine are obtained in the form of a brown oil which will be used as it is in the next step.

Example 11

N-(1R,2R,4S)Bicyclo[2.2.1]hept-2-yl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonamide may be prepared by carrying out the procedure as described in Example 8, starting with 1.8 g of N-(1R,2R,4S)bicyclo[2.2.1]hept-2-yl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}amine, 25 cm^3 of dichloromethane, 0.7 cm^3 of triethylamine, 20 mg of

4-dimethylaminopyridine and 0.4 cm^3 of methylsulfonyl chloride, with stirring for 20 hours. The brown oily residue is chromatographed on a silica gel column (particle size 0.063-0.2 mm, height 30 cm, diameter 2.0 cm), eluting under an argon pressure of 0.1 bar with a mixture of cyclohexane and ethyl acetate (60/40 by volume) and collecting 10-cm^3 fractions. Fractions 3 to 12 are combined and concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.063-0.2 mm, height 30 cm, diameter 2.0 cm), eluting under an argon pressure of 0.1 bar with a mixture of cyclohexane and ethyl acetate (70/30 by volume) and collecting 10-cm^3 fractions. Fractions 4 to 10 are combined and concetrated to dryness under reduced pressure (2.7 kPa). 0.10 g of N-(1R,2R,4S)bicyclo-[2.2.1]hept-2-yl-N-{1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}methylsulfonamide is obtained in the form of a yellow foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): from 1.00 to 1.85 (mt : 8H); 2.14 (mt : 1H); 2.33 (mt : 1H); 2.82 (s : 3H); from 3.40 to 3.60 (mt : 4H); 3.71 (broad dd, J = 8 and 6 Hz : 1H); 4.10 (mt : 1H); 4.47 (s : 1H); from 7.20 to 7.40 (mt : 8H)].

N-(1R,2R,4S)Bicyclo[2.2.1]hept-2-yl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}amine may be prepared by carrying out the procedure as described in Example 8, starting with 1.5 g of 1-[bis(4-chloro-phenyl)methyl]azetidin-3-one, 25 cm^3 of 1,2-dichloro-

ethane, 0.6 g of (1R,2R,4S)bicyclo[2.2.1]hept-2-ylamine, 1 g of sodium triacetoxyborohydride and 0.3 cm^3 of 100% acetic acid. 1.8 g of N-(1R,2R,4S)bicyclo-[2.2.1]hept-2-yl-N-{1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}amine are obtained in the form of a cream-coloured paste which will be used as it is in the next step.

Example 12

N-[(1-Benzhydryl)azetidin-3-yl]-N-phenyl-methylsulfonamide may be prepared by carrying out the procedure in the following manner: 0.7 cm^3 of methylsulfonyl chloride is poured into a solution of 2 g of 1-benzhydryl-3-anilinoazetidine in 40 cm^3 of dichloromethane and then 1.34 cm^3 of triethylamine are added. After stirring for 4 hours and 15 minutes at 20°C, the reaction mixture is washed with twice 20 cm^3 of water, the organic phase is dried over magnesium sulfate and then concentrated to dryness at 50°C under reduced pressure (2.7 kPa). The brown oil obtained is chromatographed on a silica gel column (particle size 0.063-0.2 mm, height 26 cm, diameter 3.6 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (70/30 by volume) and collecting 50-cm^3 fractions. Fractions 10 to 15 are combined and concentrated to dryness under reduced pressure (2.7 kPa), the residue is triturated in diethyl ether, the suspension is filtered, the solid is drained and then dried under reduced pressure

(2.7 kPa). 35 mg of N-[(1-benzhydryl)azetidin-3-yl]-N-phenylmethylsulfonamide are obtained in the form of a white solid [^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6 with addition of a few drops of CD_3COOD d4, δ in ppm): 2.72 (mt : 2H); 2.92 (s : 3H); 3.36 (mt : 2H); 4.32 (s : 1H); 4.73 (mt : 1H); from 7.10 to 7.45 (mt : 15H)].

1-Benzhydryl-3-anilinoazetidine may be prepared by carrying out the procedure as described in Example 8, starting with 5 g of 1-benzhydrylazetidin-3-one, 1.92 cm^3 of aniline, 74 cm^3 of 1,2-dichloroethane, 6.3 g of sodium triacetoxyborohydride and 1.2 cm^3 of 100% acetic acid. 8.81 g of 1-benzhydryl-3-anilinoazetidine are obtained in the form of a brown gum which will be used as it is in the next step.

Example 13

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide may be prepared by carrying out the procedure in the following manner: 1.0 g of cesium carbonate is added to a mixture of 1.23 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-yl methylsulfonate and 0.66 g of N-(3,5-difluorophenyl)-methylsulfonamide, in 25 cm^3 of dioxane. After stirring for 5 hours at the reflux temperature, and then for 20 hours at 20°C, the reaction mixture is supplemented with 50 cm^3 of diethyl ether and 30 cm^3 of brine, and is then stirred and separated after settling. The organic phase is dried over magnesium sulfate, filtered and then concentrated to dryness at 50°C under reduced

pressure (2.7 kPa). The orange-colored oil obtained is chromatographed on a silica gel column (particle size 0.040-0.063 mm, height 25 cm, diameter 2.0 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (65/35 by volume) and collecting 10-cm^3 fractions. Fractions 6 to 10 are combined and concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.040-0.063 mm, height 15 cm, diameter 1.0 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (65/35 by volume) and collecting 5-cm^3 fractions. Fraction 7 is concentrated to dryness under reduced pressure (2.7 kPa). 0.11 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide is obtained in the form of a white powder [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.82 (s : 3H); 2.85 (mt : 2H); 3.52 (split t, J = 7 and 2 Hz : 2H); 4.22 (s : 1H); 4.47 (mt : 1H); from 6.75 to 6.90 (mt : 3H); from 7.20 to 7.35 (mt : 8H)].

Method 2

0.78 cm^3 of diethyl azodicarboxylate and 1.31 g of triphenylphosphine are added, under argon, to a solution of 1.41 g of 1-[bis(4-chlorophenyl)-methyl]azetidin-3-ol and 0.95 g of N-(3,5-difluorophenyl)methylsulfonamide in 100 cm^3 of anhydrous tetrahydrofuran. After stirring for 16 hours at 20°C, 300 cm^3 of ethyl acetate are added, the reaction mixture

is washed twice with 100 cm^3 of water, dried over magnesium sulfate and concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.20-0.063 mm, height 50 cm, diameter 4 cm), eluting under an argon pressure of 0.6 bar with a mixture of cyclohexane and ethyl acetate (75/25 by volume) and collecting 125-cm^3 fractions. Fractions 6 to 12 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 1.8 g of a solid are obtained, which solid is dissolved hot in an ethyl acetate/diisopropyl ether (15/2 by volume) mixture, cooled and diluted with 100 cm^3 of pentane in order to initiate the crystallization. After filtration and drying, 1.0 g of N-{1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide is obtained in the form of white crystals melting at 154°C.

N-(3,5-Difluorophenyl)methylsulfonamide may be prepared by carrying out the procedure in the following manner: 2.0 cm^3 of methylsulfonyl chloride, 3.8 cm^3 of triethylamine and 20 mg of 4-dimethylamino-pyridine are slowly added to a solution of 3.5 g of 3,5-difluoroaniline in 75 cm^3 of dichloromethane. After stirring for 20 hours at 20°C, the reaction mixture, supplemented with 20 cm^3 of dichloromethane and 20 cm^3 of water, is stirred and then separated after settling. The organic phase is dried over magnesium sulfate,

filtered and then concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.063-0.200 mm, height 20 cm, diameter 2.0 cm), eluting under an argon pressure of 0.1 bar with dichloromethane and collecting 25-cm^3 fractions. Fractions 14 to 20 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 0.66 g of N-(3,5-difluorophenyl)methyl-sulfonamide is obtained in the form of a white powder.

1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl methyl sulfonate may be prepared by carrying out the procedure in the following manner: 3.5 cm^3 of methyl-sulfonyl chloride are added, under argon and over 10 minutes, to a solution of 12 g of 1-[bis(4-chloro-phenyl)methyl]azetidin-3-ol in 200 cm^3 of dichloro-methane, then the mixture is cooled to +5°C and 3.8 cm^3 of pyridine are poured in over 10 minutes. After stirring for 30 minutes at +5°C and then for 20 hours at 20°C, the reaction mixture is diluted with 100 cm^3 of water and 100 cm^3 of dichloromethane. The mixture, which is first filtered, is separated after settling. The organic phase is washed with water, then dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The oil obtained is chromatographed on a silica gel column (particle size 0.063-0.200 mm, height 40 cm, diameter 3.0 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (70/30 by volume) and

collecting 100-cm^3 fractions. Fractions 4 to 15 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 6.8 g of 1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl methyl sulfonate are obtained in the form of a yellow oil.

1-[Bis(4-chlorophenyl)methyl]azetidin-3-ol may be prepared according to the procedure described by KATRITZKY A.R. et al., J. Heterocycl. Chem., 271 (1994), starting with 35.5 g of [bis(4-chlorophenyl)-methyl]amine hydrochloride and 11.0 cm^3 of epichlorohydrin. 9.0 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-ol are isolated.

[Bis(4-chlorophenyl)methyl]amine hydrochloride may be prepared according to the method described by GRISAR M. et al., J. Med. Chem., 885 (1973).

Example 14

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(4,6-dimethylpyrimid-2-yl)methylsulfonamide may be prepared by carrying out the procedure as described in Example 13 (method 2), starting with 0.20 g of N-(4,6-dimethylpyrimid-2-yl)methylsulfonamide and 0.308 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-ol. After chromatography on a silica gel column (particle size 0.06-0.04 mm, height 50 cm, diameter 2 cm), eluting under an argon pressure of 0.6 bar with dichloromethane and then a mixture of dichloromethane + 1% methanol and then a mixture of dichloromethane + 2% methanol and

collecting 200-cm^3 fractions, fractions 4 to 7 are combined and concentrated to dryness under reduced pressure (2.7 kPa). After crystallization from diisopropyl ether, filtration and drying, 0.20 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(4,6-dimethylpyrimid-2-yl)methylsulfonamide is obtained in the form of a white solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.39 (s : 6H); 2.89 (broad t, J = 7.5 Hz : 2H); 3.51 (s : 3H); 3.77 (mt : 2H); 4.27 (s : 1H); 4.77 (mt : 1H); 6.73 (s : 1H); from 7.20 to 7.35 (mt : 8H)].

N-(4,6-Dimethylpyrimid-2-yl)methylsulfonamide may be prepared by carrying out the procedure in the following manner: 1.4 cm^3 of triethylamine are added, at 0°C, to a mixture of 1.23 g of 2-amino-4,6-dimethylpyrimidine, 0.77 cm^3 of methylsulfonyl chloride and 50 mg of 4-dimethylaminopyridine dissolved in 50 cm^3 of dichloromethane. After 16 hours at room temperature, the reaction medium is washed with twice 100 cm^3 of water, dried over magnesium sulfate, filtered and then evaporated to dryness under reduced pressure (2.7 kPa). 1.0 g of a yellow powder is obtained which is treated with 15 cm^3 of 10% sodium hydroxide at 100°C for 1 hour. After cooling, the reaction mixture is extracted with twice 50 cm^3 of dichloromethane. The aqueous phase is acidified to pH = 1 with 5 cm^3 of 10 N hydrochloric acid and extracted with twice 50 cm^3 of dichloromethane. The organic phases obtained are combined, washed with 50 cm^3

of water, dried over magnesium sulfate, filtered and concentrated. 0.20 g of N-(4,6-dimethylpyrimid-2-yl)-methylsulfonamide is obtained in the form of a yellow powder.

Example 15

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(1,3,4-thiadiazol-2-yl)methylsulfonamide may be prepared by carrying out the procedure as described in Example 13 (method 2), from 0.10 g of N-(1,3,4-thiadiazol-2-yl)methylsulfonamide and 0.215 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-ol. After chromatography on a silica gel column (particle size 0.06-0.04 mm, height 25 cm, diameter 1 cm), eluting under an argon pressure of 0.8 bar with an ethyl acetate/cyclohexane 20/80 and then 40/60 by volume mixture and collecting 60-cm^3 fractions, fractions 26 to 31 are combined and concentrated to dryness under reduced pressure (2.7 kPa). After crystallization from diisopropyl ether, filtration and drying, 40 mg of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(1,3,4-thiadiazol-2-yl)methylsulfonamide are obtained in the form of a white solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 3.01 (s : 3H); 3.09 (split t, J = 7 and 1.5 Hz : 2H); 3.70 (split t, J = 7 and 1.5 Hz : 2H); 4.28 (s : 1H); 4.76 (mt : 1H); from 7.20 to 7.35 (mt : 8H); 9.01 (s : 1H)].

N-(1,3,4-Thiadiazol-2-yl)methylsulfonamide may be prepared by carrying out the procedure in the

following manner: 1.5 cm^3 of methylsulfonyl chloride are added to a mixture of 2.02 g of 2-amino-1,3,4-thiadiazole in 10 cm^3 of pyridine. After 2 hours at room temperature, 60 cm^3 of water are added and the reaction medium is filtered. The aqueous phase collected is acidified to pH = 2 with 1 N hydrochloric acid, extracted with twice 50 cm^3 of ethyl acetate, the organic phase washed with twice 50 cm^3 of water, dried over magnesium sulfate, filtered and then evaporated to dryness under reduced pressure (2.7 kPa). 0.1 g of a yellow powder is obtained.

Example 16

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(thiazol-2-yl)methylsulfonamide may be prepared by carrying out the procedure as described in Example 15, starting with 0.50 g of N-(thiazol-2-yl)methylsulfonamide and 0.5 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-ol. After chromatography on a silica gel column (particle size 0.06-0.04 mm, height 60 cm, diameter 2 cm), eluting under an argon pressure of 0.9 bar with an ethyl acetate/cyclohexane 20/80 and then 40/60 by volume mixture and collecting 30-cm^3 fractions, fractions 9 to 12 are combined and concentrated to dryness under reduced pressure (2.7 kPa). After crystallization from diisopropyl ether, filtration and drying, 0.21 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(thiazol-2-yl)methylsulfonamide is obtained in the form of a white

solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): from 2.95 to 3.10 (mt : 2H); 3.00 (s : 3H); 3.59 (mt : 2H); 4.22 (broad s : 1H); 4.69 (mt : 1H); from 7.20 to 7.35 (mt : 9H); 7.60 (mt : 1H)].

N-(Thiazol-2-yl)methylsulfonamide may be prepared by carrying out the procedure in the following manner: 1.15 g of methylsulfonyl chloride are added to a mixture of 1.0 g of 2-aminothiazole in 5 cm^3 of pyridine. After 2 hours at room temperature, 20 cm^3 of water are added, the reaction medium is filtered and the solid collected (0.35 g). The aqueous phase collected is acidified to pH = 2 with 1 N hydrochloric acid, extracted with twice 40 cm^3 of ethyl acetate, the organic phase washed with twice 30 cm^3 of water, dried over magnesium sulfate, filtered and then evaporated to dryness under reduced pressure (2.7 kPa). 0.15 g of a white solid is obtained which has spectral characteristics similar to the filtered solid corresponding to an N-(thiazol-2-yl)methylsulfonamide and N-(thiazol-2-yl)di(methylsulfonyl)imide mixture which is used as it is for the next step.

Example 17

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3-hydroxyphenyl)methylsulfonamide may be prepared by carrying out the procedure in the following manner: 7.63 cm^3 of a 1 M boron tribromide solution are added dropwise at 2°C to a mixture of 0.5 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3-methoxy-

phenyl)methylsulfonamide in 20 cm^3 of dichloromethane. After 20 hours at room temperature, the reaction medium is poured over ice and extracted with 60 cm^3 of dichloromethane. The organic phase [lacuna] washed with 3 times 80 cm^3 of water and then twice with 80 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and then evaporated to dryness under reduced pressure (2.7 kPa). 0.33 g of a white foam is obtained which is taken up in acetonitrile, filtered and dried in order to obtain 0.20 g of a white solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.81 (s : 3H); 2.86 (broad t, J = 7.5 Hz : 2H); 3.50 (broad t, J = 7.5 Hz : 2H); 4.20 (s : 1H); 4.53 (mt : 1H); 5.36 (unresolved complex : 1H); from 6.70 to 6.85 (mt : 3H) from 7.15 to 7.35 (mt : 9H)].

Example 18

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3-methoxyphenyl)methylsulfonamide may be prepared by carrying out the procedure as described in Example 15, starting with 1.58 g of N-(3-methoxyphenyl)methylsulfonamide and 2.0 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-ol. After chromatography on a silica gel column (particle size 0.06-0.04 mm, height 24 cm, diameter 7.8 cm), eluting under an argon pressure of 0.7 bar with an ethyl acetate/cyclohexane 50/50 and then 40/60 by volume mixture and collecting 100-cm^3 fractions, fractions 7 to 10 are combined and

concentrated to dryness under reduced pressure (2.7 kPa). (2.05 g). After crystallization from diisopropyl ether, filtration and drying, 0.21 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3-methoxyphenyl)methylsulfonamide is obtained.

N-(3-Methoxyphenyl)methylsulfonamide may be prepared by carrying out the procedure in the following manner: 3.14 cm^3 of methylsulfonyl chloride are added at 3°C to a mixture of 5.0 g of 3-methoxyaniline in 150 cm^3 of pyridine. After 20 hours at room temperature, 200 cm^3 of water and 400 cm^3 of ethyl acetate are added and the reaction medium is separated after settling. The organic phase is washed with 3 times 400 cm^3 of water and 400 cm^3 of a saturated sodium chloride solution, dried over magnesium sulfate, filtered and then evaporated to dryness under reduced pressure (2.7 kPa). After chromatography on a silica gel column (particle size 0.06-0.04 mm, height 23 cm, diameter 7.8 cm), eluting under an argon pressure of 0.7 bar with an ethyl acetate/cyclohexane 25/75 by volume mixture and collecting 100-cm^3 fractions, fractions 24 to 36 are combined and concentrated to dryness under reduced pressure (2.7 kPa), 6.21 g of N-(3-methoxyphenyl)methylsulfonamide are obtained in the form of an orange-colored oil.

Example 19

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3-hydroxymethylphenyl)methylsulfonamide may be

prepared by carrying out the procedure in the following manner: 1.46 cm^3 of a 20% toluenic solution of diisopropylaluminum hydride are added dropwise at -50°C to a mixture of 0.5 g of ethyl N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(methylsulfonyl)-3-aminobenzoate in 20 cm^3 of toluene. After 1.5 hours at 0°C and 1.5 hours at 10°C, the reaction medium is cooled to 0°C and 20 cm^3 of water are added slowly. After filtration of the precipitate and extraction with ethyl acetate, the organic phase is washed with twice 80 cm^3 of water and then 80 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and then evaporated to dryness under reduced pressure (2.7 kPa). 0.46 g of an oil is obtained which is chromatographed on a silica gel column (particle size 0.06-0.04 mm, height 16 cm, diameter 4 cm), eluting under an argon pressure of 0.7 bar with an ethyl acetate/cyclohexane 40/60 by volume mixture and collecting 20-cm^3 fractions, fractions 72 to 76 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 0.20 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3-hydroxymethylphenyl)methylsulfonamide is obtained in the form of a white solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 1.80 (mt : 1H); 2.83 (s : 3H); 2.87 (mt : 2H); 3.52 (mt : 2H); 4.21 (broad s : 1H); 4.60 (mt : 1H); 4.74 (broad t, J = 4 Hz : 2H) from 7.10 to 7.45 (mt : 12H)].

Example 20

Ethyl N-{1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}-N-(methylsulfonyl)-3-aminobenzoate may be prepared by carrying out the procedure as described in Example 15, starting with 1.58 g of ethyl N-(methylsulfonyl)-3-aminobenzoate and 2.0 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-ol. After chromatography on a silica gel column (particle size 0.06-0.04 mm, height 24 cm, diameter 7.8 cm), eluting under an argon pressure of 0.7 bar with an ethyl acetate/cyclohexane 50/50 and then 40/60 by volume mixture and collecting 100-cm^3 fractions, fractions 7 to 10 are combined and concentrated to dryness under reduced pressure (2.7 kPa) to give 2.0 g of a yellow oil.

Ethyl N-(methylsulfonyl)-3-aminobenzoate may be prepared by carrying out the procedure in the following manner: 2.35 cm^3 of methylsulfonyl chloride are added at 3°C to a mixture of 5.0 g of ethyl 3-aminobenzoate in 150 cm^3 of pyridine. After 20 hours at room temperature, 200 cm^3 of water and 400 cm^3 of ethyl acetate are added and the reaction medium is separated after settling. The organic phase is washed with 3 times 400 cm^3 of water and 400 cm^3 of a saturated sodium chloride solution, dried over magnesium sulfate, filtered and then evaporated to dryness under reduced pressure (2.7 kPa). After chromatography on a silica gel column (particle size 0.06-0.04 mm, height 25 cm, diameter 7.8 cm), eluting under an argon pressure of

0.7 bar with an ethyl acetate/cyclohexane 25/75 by volume mixture and collecting 100-cm^3 fractions, fractions 27 to 36 are combined and concentrated to dryness under reduced pressure (2.7 kPa), 5.24 g of ethyl N-(methylsulfonyl)-3-aminobenzoate are obtained in the form of an orange-colored oil.

Example 21

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(1-isobutylpiperid-4-yl)methylsulfonamide may be prepared by carrying out the procedure in the following manner: 0.11 cm^3 of isobutyraldehyde, 0.057 cm^3 of 100% acetic acid and 320 mg of sodium triacetoxyborohydride are added to a solution of 0.47 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(piperid-4-yl)methylsulfonamide in 20 cm^3 of dichloromethane. After stirring for 20 hours at 20°C, the reaction mixture is supplemented with 50 cm^3 of a saturated aqueous sodium hydrogen carbonate solution and separated after settling. The organic phase is dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue is purified by chromatography on a silica gel column (particle size 0.063-0.200 mm, height 20 cm, diameter 2 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (40/60 by volume) and collecting 30-cm^3 fractions. Fractions 3 to 15 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 0.22 g of N-{1-[bis(4-chloro-

phenyl)methyl]azetidin-3-yl}-N-(1-isobutylpiperid-4-yl)methylsulfonamide is obtained in the form of a white foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 0.87 (d, J = 7 Hz : 6H); from 1.60 to 1.90 (mt : 5H); 1.93 (broad t, J = 11.5 Hz : 2H); 2.03 (d, J = 7.5 Hz : 2H); 2.84 (s, 3H); 2.89 (broad d, J = 11.5 Hz : 2H); 3.38 (broad t, J = 7 Hz : 2H); 3.47 (broad t, J = 7 Hz : 2H); 3.62 (mt : 1H); 4.08 (mt : 1H); 4.43 (s : 1H); from 7.20 to 7.40 (mt : 8H)].

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(piperid-4-yl)methylsulfonamide may be prepared by carrying out the procedure in the following manner: 50 cm^3 of a 6 N hydrochloric acid solution in dioxane is poured slowly into a solution of 19 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(1-tert-butoxy-carbonylpiperid-4-yl)methylsulfonamide in 100 cm^3 of dioxane. After stirring for 20 hours at 20°C, the reaction mixture is concentrated at 50°C under reduced pressure (2.7 kPa). The residue is taken up in 200 cm^3 of ethyl acetate and in 200 cm^3 of water. The aqueous phase is alkalinized with a 4 N aqueous sodium hydroxide solution and then extracted with 200 cm^3 of ethyl acetate. This organic phase is dried over magnesium sulfate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa). 15.5 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(piperid-4-yl)methylsulfonamide are obtained in the form of a cream-colored foam.

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(1-tert-butoxycarbonylpiperid-4-yl)methyl-sulfonylamide may be prepared by carrying out the procedure in the following manner: 4.60 cm^3 of methyl-sulfonyl chloride are added slowly to a solution of 14.7 g of 4-{1-[bis(4-chlorophenyl)methyl]azetidin-3-ylamino}-(1-tert-butoxycarbonyl)piperidine in 250 cm^3 of dichloromethane followed by 4.60 cm^3 of triethylamine and 100 mg of 4-dimethylaminopyridine. After stirring for 20 hours at 20°C, the reaction mixture is supplemented with 200 cm^3 of a saturated aqueous sodium hydrogen carbonate solution and then stirred for 30 minutes and separated after settling. The organic phase is dried over magnesium sulfate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa). The foam obtained, taken up in 250 cm^3 of dichloromethane, is again supplemented slowly with 4.60 cm^3 of methylsulfonyl chloride and then with 4.60 cm^3 of triethylamine and 100 mg of 4-dimethyl-aminopyridine. After stirring for 20 hours at 20°C, the mixture is supplemented with 200 cm^3 of a saturated aqueous sodium hydrogen carbonate solution and then stirred for 30 minutes and separated after settling. The organic phase is dried over magnesium sulfate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa). The residue is purified by chromatography on a silica gel column (particle size 0.063-0.200 mm, height 35 cm, diameter 5 cm), eluting

under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (70/30 by volume) and collecting 250-cm^3 fractions. Fractions 4 to 18 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 19 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(1-tert-butoxycarbonylpiperid-4-yl)methylsulfonylamide are obtained in the form of a cream-colored foam which will be used as it is in the next step.

4-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-ylamino}-(1-tert-butoxycarbonyl)piperidine may be prepared by carrying out the procedure in the following manner: 6.58 g of 1-tert-butoxycarbonylpiperidin-4-one are added to a solution of 9.22 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-ylamine in 300 cm^3 of dichloromethane. 9.54 g of sodium triacetoxyborohydride are added, in two portions, to the mixture, cooled to +5°C, and then 1.72 cm^3 of 100% acetic acid are poured in. After stirring for 20 hours at 20°C, the reaction mixture is supplemented slowly with 500 cm^3 of a saturated aqueous sodium hydrogen carbonate solution and then thoroughly stirred and separated after settling. The organic phase is dried over magnesium sulfate, filtered and concentrated to dryness at 50°C under reduced pressure (2.7 kPa). 15 g of 4-{1-[bis(4-chlorophenyl)methyl]azetidin-3-ylamino}-(1-tert-butoxycarbonyl)piperidine are obtained in the form of a

cream-colored foam which will be used as it is in the next step.

Example 22

N-Benzyl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}amine: 0.134 cm^3 of benzaldehyde is added, at room temperature under an argon atmosphere, to a solution of 369 mg of 1-[bis(4-chlorophenyl)methyl]azetidin-3-ylamine in 15 cm^3 of dichloromethane. The mixture is cooled to around 0°C, before gradually adding thereto 382 mg of sodium triacetoxyborohydride, and then 70 mm^3 of acetic acid. After stirring for 16 hours at room temperature, the mixture is poured over 50 cm^3 of a saturated aqueous sodium hydrogen carbonate solution and then extracted with twice 25 cm^3 of dichloromethane. The combined organic phases are dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is purified by flash chromatography on silica gel [eluent: dichloromethane/methanol (95/5 by volume)]. 0.29 g of N-benzyl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}amine is obtained in the form of a colorless oil [^1H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.71 (broad t, J = 7 Hz : 2H); 3.42 (mt : 2H); 3.49 (mt : 1H); 3.70 (s : 2H); 4.25 (s : 1H); from 7.20 to 7.40 (mt : 13H)].

1-[Bis(4-chlorophenyl)methyl]azetidin-3-ylamine may be obtained in the following manner: 400 cm^3 of a mixture of methanol and liquid ammonia (50/50 by

volume) are added to 27 g of 1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl methylsulfonate contained in an autoclave previously cooled to around -60°C. The reaction medium is then stirred at 60°C for 24 hours and then abandoned in the open air in order to allow the evaporation of the ammonia and finally concentrated under reduced pressure (2.7 kPa). The residue is taken up in 500 cm^3 of a 0.37 N aqueous sodium hydroxide solution and extracted with four times 500 cm^3 of ethyl ether. The combined organic phases are washed successively with twice 100 cm^3 of distilled water and 100 cm^3 of a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated under reduced pressure (2.7 kPa). The residue obtained is purified by flash chromatography on silica gel [eluent: dichloromethane/methanol (95/5 by volume)]. 14.2 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-ylamine are obtained in the form of an oil which solidifies into a cream-colored solid.

Example 23

N-Benzyl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonamide:

104 mm^3 of triethylamine are added, at room temperature under an argon atmosphere, to a solution of 120 mg of N-benzyl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}amine in 5 cm^3 of dichloromethane. The mixture is cooled to around 0°C before adding thereto 46.4 mm^3 of methylsulfonyl chloride, and then it is stirred at room

temperature for 16 hours. The reaction mixture is diluted with 20 cm^3 of dichloromethane and then is washed with twice 15 cm^3 of distilled water. The organic phase is dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa), providing a lacquer which is crystallized by trituration in methanol. 42 mg of N-benzyl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonamide are thus obtained in the form of a cream-colored powder melting at 171°C.

Example 24

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorobenzyl)amine may be prepared as in Example 22, but using 188 mg of 3,5-difluoro-benzaldehyde and 369 mg of 1-[bis(4-chlorophenyl)-methyl]azetidin-3-ylamine and 382 mg of sodium triacetoxyborohydride, without purification by flash chromatography. 0.48 g of N-{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-N-(3,5-difluorobenzyl)amine is obtained in the form of a colorless oil [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.73 (mt : 2H); from 3.40 to 3.55 (mt : 3H); 3.70 (s : 2H); 4.26 (s : 1H); 6.69 (tt, J = 9 and 2 Hz : 1H); 6.83 (mt : 2H); from 7.20 to 7.35 (mt : 8H)].

Example 25

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorobenzyl)methylsulfonamide

347 mm^3 of triethylamine are added, at room temperature under an argon atmosphere, to a solution of 433 mg of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorobenzyl)amine in 30 cm^3 of dichloromethane. The mixture is cooled to around 0°C before adding thereto a solution of 46.4 mm^3 of methylsulfonyl chloride in 5 cm^3 of dichloromethane, and then it is stirred at room temperature for 1 hour. The reaction mixture is diluted with 20 cm^3 of dichloromethane and is then washed with twice 20 cm^3 of distilled water. The organic phase is dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue is introduced into solution in methanol on a Bond Elut® SCX cartridge (10 g), eluting successively with methanol and with a 1 M solution of ammonia in methanol. The ammoniacal fractions are pooled and concentrated to dryness under reduced pressure (2.7 kPa). 0.44 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorobenzyl)-methylsulfonamide is thus obtained in the form of a cream-colored foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.81 (s : 3H); 3.02 (broad t, J = 7.5 Hz : 2H); 3.38 (broad t, J = 7.5 Hz : 2H); 4.23 (s : 1H); 4.40 (mt : 1H); 4.54 (s : 2H); 6.75 (tt, J = 9 and 2 Hz : 1H); 6.95 (mt : 2H); 7.25 (mt : 8H)].

Example 26

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorobenzyl)acetamide

1.6 cm^3 of triethylamine are added, at room temperature under an argon atmosphere, to a solution of 2 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorobenzyl)amine in 75 cm^3 of dichloromethane. The mixture is cooled to around 0°C before adding dropwise thereto 0.66 cm^3 of acetyl chloride, and then it is stirred at room temperature for 16 hours. The reaction mixture is diluted with 50 cm^3 of dichloromethane and is then washed with twice 20 cm^3 of distilled water. The organic phase is dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is purified by flash chromatography on silica gel [eluent: dichloromethane/methanol (98/2 by volume)]. 1.2 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorobenzyl)acetamide are obtained in the form of a colorless oil [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm). A mixture of rotamers is observed. * 2.06 and 2.14 (2s : 3H in total); 2.97 (mt : 2H); 3.43 (mt : 2H); 4.20 and 4.25 (2s : 1H in total); 4.54 and from 4.75 to 4.80 (mt : 1H in total); 4.68 and 4.78 (broad 2s : 2H in total); 6.70 (mt : 3H); 7.24 (broad s : 8H)].

Example 27

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(pyrid-4-ylmethyl)methylsulfonamide

346 mm^3 of triethylamine are added, at room temperature under an argon atmosphere, to a solution of

398 mg of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(pyrid-4-ylmethyl)amine in 8 cm^3 of dichloromethane. The mixture is cooled to around 0°C before adding thereto 155 mm^3 of methylsulfonyl choride, and then it is stirred at room temperature for 3 hours. The reaction mixture is diluted with 35 cm^3 of dichloromethane and is then washed with twice 20 cm^3 of distilled water. The organic phase is dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is purified by flash chromatography on silica gel [eluent: dichloromethane/methanol (97/3 by volume)]. 288 mg of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(pyrid-4-ylmethyl)methylsulfonamide are obtained in the form of a cream-colored foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.83 (s : 3H); 3.02 (broad t, J = 7.5 Hz : 2H); 3.40 (broad t, J = 7.5 Hz : 2H); 4.23 (s : 1H); 4.43 (mt : 1H); 4.57 (s : 2H); from 7.20 to 7.35 (mt : 8H); 7.32 (broad d, J = 5.5 Hz : 2H); 8.60 (broad d, J = 5.5 Hz : 2H)].

Example 28

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(pyrid-4-ylmethyl)amine may be prepared in the following manner: 0.126 cm^3 of pyrid-4-ylcarboxaldehyde is added, at room temperature under an argon atmosphere, to a solution of 369 mg of 1-[bis(4-chlorophenyl)methyl]azetidin-3-ylamine in 15 cm^3 of dichloromethane. The mixture is cooled to around 0°C,

before gradually adding thereto 382 mg of sodium triacetoxyborohydride, and then 70 mm^3 of acetic acid. After stirring for 72 hours at room temperature, the mixture is poured over 100 cm^3 of a saturated aqueous sodium hydrogen carbonate solution and then extracted with twice 100 cm^3 of dichloromethane. The combined organic phases are washed with 50 cm^3 of distilled water, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue is introduced into solution in 5 cm^3 of methanol on a Bond Elut® SCX cartridge (10 g), eluting successively with 50 cm^3 of methanol and with 60 cm^3 of a 1 M solution of ammonia in methanol. The ammoniacal fractions are pooled and concentrated to dryness under reduced pressure (2.7 kPa). 0.48 g of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(pyrid-4-ylmethyl)amine is thus obtained in the form of a colorless oil.

Example 29

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(pyrid-3-ylmethyl)methylsulfonamide

By carrying out the operation according to the procedure of Example 27, but starting with 380 mg of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(pyrid-3-ylmethyl)amine, 319 mg of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(pyrid-3-ylmethyl)-methylsulfonamide are obtained in the form of a cream-colored foam [^1H NMR spectrum (300 MHz, $CDCl_3$, δ in

ppm): 2.80 (s : 3H); 3.02 (split t, J = 7 and 1.5 Hz : 2H); 3.38 (split t, J = 7 and 1.5 Hz : 2H); 4.22 (s : 1H); 4.35 (mt : 1H); 4.56 (s : 2H); 7.23 (broad s : 8H); 7.31 (dd, J = 8 and 5 Hz : 1H); 7.80 (broad d, J = 8 Hz : 1H); 8.57 (dd, J = 5 and 1.5 Hz : 1H); 8.63 (broad d, J = 1.5 Hz : 1H)].

Example 30

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(pyrid-3-ylmethyl)amine may be prepared as in Example 28, but starting with 0.124 cm^3 of pyrid-3-ylcarboxaldehyde, 0.36 g of 1-[bis(4-chlorophenyl)-methyl]azetidin-3-ylamine and 0.38 g of sodium triacetoxyborohydride. 0.44 g of N-{1-[bis(4-chloro-phenyl)methyl]azetidin-3-yl}-N-(pyrid-3-ylmethyl)amine is thus obtained in the form of a colorless oil.

Example 31

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(1,1-dioxo-1H-1λ^6-benzo[d]isothiazol-3-yl)amine

182 mg of 1,2-benzisothiazol-3-amine 1,1-dioxide and 326 mg of cesium carbonate are added to 386 mg of 1-[bis(4-chlorophenyl)methyl]azetidin-3-yl methylsulfonate in solution in 10 cm^3 of dimethyl-formamide. The reaction medium is then stirred at 100°C for 9 hours and then concentrated under reduced pressure (2.7 kPa). The residue is washed four times with 5 cm^3 of boiling distilled water, disintegrated by stirring in 5 cm^3 of distilled water at room temperature and then recovered by filtration and purified by flash

chromatography on silica gel [eluent: dichloromethane/methanol (98/2 by volume)]. 53 mg of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(1,1-dioxo-1H-1λ^6-benzo[d]isothiazol-3-yl)amine are obtained in the form of a pasty product [[^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 3.17 (mt : 2H); 3.61 (broad t, J = 7.5 Hz : 2H); 4.37 (s : 1H); 4.75 (mt : 1H); from 6.30 to 6.40 (unresolved complex : 1H); from 7.20 to 7.35 (mt : 8H); 7.62 (broad d, J = 7.5 Hz : 1H); 7.69 (broad t, J = 7.5 Hz : 1H); 7.76 (broad t, J = 7.5 Hz : 1H); 7.93 (broad d, J = 7.5 Hz : 1H)].

1,2-Benzisothiazol-3-amine 1,1-dioxide may be prepared according to the method described by Stoss, P. et al., Chem. Ber. (1975), 108(12), 3855-63.

Example 32

N-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)-N'-tert-butyloxycarbonyl-sulfamide may be prepared in the following manner: 0.048 cm^3 of chlorosulfonyl isocyanate is added to a solution of 0.095 cm^3 of tert-butyl alcohol in 2 cm^3 of anhydrous dichloromethane, and after stirring for 2 minutes 0.21 g of {1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}-(3,5-difluorophenyl)amine in 1.25 cm^3 of anhydrous dichloromethane and then 0.084 cm^3 of triethylamine are successively added. After stirring for 1 hour at a temperature in the region of 20°C, 2 cm^3 of a saturated sodium bicarbonate solution are added with vigorous stirring. The reaction medium is

separated after settling, dried over magnesium sulfate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is chromatographed on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm), conditioned and then eluted with a petroleum ether-ethyl acetate mixture with the aid of a Duramat pump, collecting 2-cm^3 fractions. Fractions 6 to 17 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C for 2 hours. 61 mg of N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)-N'-tert-butyloxycarbonylsulfamide are thus obtained in the form of a white foam [^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ in ppm): 1.47 (s : 9H); 2.77 (broad t, J = 8 Hz : 2H); 3.52 (mt : 2H); 4.19 (s : 1H); 5.06 (mt : 1H); from 6.75 to 6.90 (mt : 3H); from 7.15 to 7.35 (mt : 8H].

Example 33

(RS)-N-{1-[(4-Chlorophenyl)pyridin-3-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide may be obtained in the following manner: 0.2 g of potassium carbonate and 23 mg of potassium iodide are added to a mixture of 0.2 g of 3-[bromo-(4-chlorophenyl)methyl]pyridine and 0.22 g of N-azetidin-3-yl-N-(3,5-difluorophenyl)methylsulfonamide hydrochloride in 10 cm^3 of acetonitrile, and then the mixture is heated under reflux for 3 hours. After adding 0.2 g of potassium carbonate, the mixture is heated under

reflux for an additional 15 hours. After cooling to 21°C, the insoluble materials are removed by filtration and then the filtrate is concentrated to dryness at 40°C under 2.7 kPa. 170 mg of a colorless lacquer are obtained, which lacquer is purified by chromatography on a silica cartridge (reference SIL-020-005, FlashPack, Jones Chromatography Limited, New Road, Hengoed, Mid Glamorgan, CF82 8AU, United Kingdom) eluting with a cyclohexane:ethyl acetate 1:1 mixture (6 cm^3/min, 5-cm^3 fractions). The fractions with an Rf=5/57 (cyclohexane:ethyl acetate 1:1, silica plate, Merck reference 1.05719, Merck KGaA, 64271 Darmstatd, Germany) are combined and concentrated under 2.7 kPa at 40°C to give 100 mg of (RS)-N-{1-[(4-chlorophenyl)-pyridin-3-ylmethyl]azetidin-3-yl}-N-(3,5-difluoro-phenyl)methylsulfonamide melting at 110°C [^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): 2.77 (mt : 2H); 2.98 (s : 3H); 3.38 (mt : 2H); 4.50 (s : 1H); 4.70 (mt : 1H); 7.11 (mt : 2H); from 7.20 to 7.40 (mt : 2H); 7.34 (d, J = 8 Hz : 2H); 7.41 (d, J = 8 Hz : 2H); 7.72 (broad d, J = 8 Hz : 1H); 8.40 (dd, J = 5 and 1.5 Hz : 1H); 8.58 (d, J = 1.5 Hz : 1H)].

The two isomers of (RS)-N-{1-[(4-chlorophenyl)pyridin-3-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methanesulfonamide may be separated on a CHIRACEL OD chiral stationary phase.

First isomer: ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.82 (s : 3H); 2.87 (mt : 2H); 3.53 (mt :

2H); 4.29 (s : 1H); 4.47 (mt : 1H); 6.80 (mt : 3H); 7.19 (dd, J = 8 and 5 Hz : 1H); from 7.20 to 7.35 (mt : 4H); 7.62 (broad d, J = 8 Hz : 1H); 8.45 (broad d, J = 5 Hz : 1H); 8.59 (broad s : 1H).

Second isomer: ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.82 (s : 3H); 2.87 (mt : 2H); 3.54 (mt : 2H); 4.29 (s : 1H); 4.48 (mt : 1H); 6.80 (mt : 3H); 7.19 (broad dd, J = 8 and 5 Hz : 1H); from 7.25 to 7.35 (mt : 4H); 7.62 (dt, J = 8 and 2 Hz : 1H); 8.46 (dd, J = 5 and 2 Hz : 1H); 8.59 (broad d, J = 2 Hz : 1H).

N-Azetidin-3-yl-N-(3,5-difluorophenyl)methylsulfonamide hydrochloride is obtained in the following manner: in a 500-cm^3 hydrogenator, a solution of 1 g of N-(1-benzhydrylazetidin-3-yl)-N-(3,5-difluorophenyl)-methylsulfonamide in a mixture of 2.5 cm^3 of 1M hydrochloric acid and 0.41 cm^3 of acetic acid is hydrogenated in the presence of 0.161 g of palladium hydroxide at a hydrogen pressure of 30 bar for 4 hours. The catalyst is removed by filtration on a celite bed and then the filtrate is concentrated to dryness at 40°C under 2.7 kPa to give 630 mg of N-azetidin-3-yl-N-(3,5-difluorophenyl)methylsulfonamide, melting at 216°C.

N-(1-Benzhydrylazetidin-3-yl)-N-(3,5-difluorophenyl)methylsulfonamide may be obtained by carrying out the procedure as in Example 13 (method 2) in the following manner: 0.86 g of N-(3,5-difluoro-

phenyl)methylsulfonamide, 3.28 g of triphenylphosphine and then 2 ml of diethyl azodicarboxylate are added successively to a solution of 2 g of 1-benzhydryl-azetidin-3-ol in 100 cm^3 of tetrahydrofuran. An increase in the temperature, which passes from 22°C to 29°C, as well as the formation of a precipitate immediately following the addition of the diethyl azodicarboxylate are observed. After 20 h at 22°C, the precipitate is removed by filtration and the filtrate is concentrated to dryness at 40°C under 2.7 kPa. The residue is triturated with 5 cm^3 of methanol for 20 minutes at 21°C, providing 1.07 g of N-(1-benzhydrylazetidin-3-yl)-N-(3,5-difluorophenyl)methylsulfonamide in the form of a white amorphous solid.

1-Benzhydrylazetidin-3-ol may be prepared according to the procedure described by KATRITZKY A.R. et al., J. Heterocycl. Chem., 271 (1994).

3-[Bromo(4-chlorophenyl)methyl]pyridine is obtained in the following manner: 3.5 cm^3 of a 48% solution of hydrobromic acid in acetic acid and 1 cm^3 of acetyl bromide are added to 1.5 g of (4-chlorophenyl)-pyridin-3-ylmethanol. The amber-colored mixture thus obtained is heated under reflux for 4 hours and then cooled to 20°C, concentrated to dryness at 40°C under 2.7 kPa, giving 1.53 g of 3-[bromo(4-chlorophenyl)-methyl]pyridine (Rf=75/90, 254 nm, Silica Plates, reference 1.05719, Merck KGaA, 64271 Darmstatd, Germany).

4-(Chlorophenyl)pyridin-3-ylmethanol is obtained in the following manner: 20 cm^3 of a molar solution of 4-chlorophenylmagnesium bromide in ethyl ether are added to a solution of 3 g of 3-pyridine-carboxaldehyde in tetrahydrofuran at 5°C. After heating to 20°C, the mixture is allowed to react for 15 hours, with stirring. 20 cm^3 of a saturated ammonium chloride solution are then added, followed by 20 cm^3 of ethyl acetate. The mixture is separated after settling and the organic phases are extracted with an additional 20 cm^3 of ethyl acetate. The organic extracts are combined, dried over magnesium sulfate and then concentrated to dryness at 40°C under 2.7 kPa. The residue obtained is chromatographed on silica (Amicon, 20-45 µm, 500 g silica, column diameter 5 cm), eluting with a cyclohexane:ethyl acetate mixture from 80:20 to 50:50 under an argon pressure of 0.4 bar. The fractions containing the compound with an Rf=13/53 (Merck Silica Plates, reference 1.05719, Merck KGaA, 64271 Darmstatd, Germany) are combined and evaporated to dryness at 40°C under 2.7 kPa to give 2.53 g of 4-chlorophenyl)pyridin-3-ylmethanol.

Example 34

N-{1-[Bis(4-fluorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide is obtained in the following manner: 0.36 g of potassium carbonate and 27 mg of potassium iodide are added to a mixture of 0.2 g of 4,4'-difluorobenzhydryl chloride and 0.26 g of

N-azetidin-3-yl-N-(3,5-difluorophenyl)- hydrochloride in 10 cm^3 of acetonitrile and then the mixture is heated under reflux for 3 hours. After cooling to 21°C, the insoluble materials are removed by filtration and then the filtrate is concentrated to dryness at 40°C under 2.7 kPa. The residue is triturated with 30 cm^3 of ethyl acetate and then the solid is removed by filtration. The filtrate is concentrated to dryness at 40°C under 2.7 kPa and 90 mg of a pale yellow solid are obtained, which solid is purified by chromatography on BondElut SCX cartridge containing 2 g of graft silica (reference 1225-6019, Varian Associates, Inc. 24201 Frampton Avenue, Harbor City, CA90710, USA) eluting with a 2 M solution of methanolic aqueous ammonia. The fractions with an Rf=16/82 (cyclohexane:ethyl acetate 7:3, silica plate, reference 1.05719, Merck KGaA, 64271 Darmstatd, Germany) are combined and concentrated under 2.7 kPa at 40°C to give 243 mg of N-{1-[bis(4-fluorophenyl)-methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methyl-sulfonamide melting at 98°C [^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): 2.74 (broad t, J = 7 Hz : 2H); 3.00 (s : 3H); 3.37 (broad t, J = 7 Hz : 2H); 4.43 (s : 1H); 4.69 (mt : 1H); from 7.05 to 7.20 (mt : 6H); 7.28 (tt, J = 9 and 2.5 Hz : 1H); 7.40 (mt : 4H)].

Example 35

(RS)-N-{1-[(4-Chlorophenyl)pyridin-4-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methyl-sulfonamide may be obtained in the following manner: a

mixture of about 100 mg of (4-pyridyl)(4-chlorophenyl)-chloromethane, 143 mg of N-azetidin-3-yl-N-(3,5-difluorophenyl)methylsulfonamide hydrochloride, 17 mg of potassium iodide and 200 mg of potassium carbonate in 5 cm^3 of acetonitrile is stirred for about 18 hours at a temperature in the region of 20°C. The reaction mixture is then heated under reflux for 3 hours, supplemented with 17 mg of potassium iodide and kept under reflux for an additional 2 hours. After cooling to a temperature in the region of 20°C, the reaction medium is filtered on sintered glass. The solid is rinsed with acetonitrile and then with twice 3 cm^3 of ethyl acetate. The filtrates are concentrated to dryness under reduced pressure. 230 mg of a pale yellow paste are obtained, which paste is purified by preparative thin-layer chromatography on silica [4 Merck Kieselgel 60F254 preparative plates; 20x20 cm; thickness 0.5 mm], eluting with a methanol-dichloromethane (5-95 by volume) mixture. After elution of the zone corresponding to the desired product, filtration on sintered glass and then evaporation of the solvents under reduced pressure at a temperature in the region of 40°C, 12 mg of (RS)-N-{1-[(4-chlorophenyl)pyridin-4-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide are obtained [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.82 (s : 3H); 2.96 (unresolved complex : 2H); from 3.50 to 3.80 (mt : 2H); 4.33 (unresolved complex : 1H); 4.54 (mt : 1H); 6.82

(mt : 3H); from 7.20 to 7.45 (mt : 6H); 8.53 (broad d, J = 5.5 Hz : 2H)].

The two isomers of (RS)-N-{1-[(4-chlorophenyl)pyridin-4-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methanesulfonamide may be separated on a CHIRACEL OJ chiral stationary phase.

First isomer: ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.83 (s : 3H); 2.87 (broad t, J = 7.5 Hz : 2H); 3.51 (mt : 1H); 3.60 (mt : 1H); 4.24 (s : 1H); 4.50 (mt : 1H); 6.82 (mt : 3H); from 7.20 to 7.35 (mt : 6H); 8.50 (broad d, J = 5.5 Hz : 2H).

Second isomer: ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.83 (s : 3H); 2.88 (t, J = 7.5 Hz : 2H); 3.51 (mt : 1H); 3.61 (mt : 1H); 4.25 (s : 1H); 4.51 (mt : 1H); 6.81 (mt : 3H); from 7.20 to 7.35 (mt : 6H); 8.50 (broad d, J = 5.5 Hz : 2H).

(4-Pyridyl)(4-chlorophenyl)chloromethane may be prepared in the following manner: 0.0598 cm^3 of thionyl choride is added to a suspension of 100 mg of (4-pyridyl)(4-chlorophenyl)methanol in 2 cm^3 of toluene, cooled to a temperature in the region of 0°C. After 2 hours at a temperature in the region of 0°C and 1 hour at a temperature in the region of 20°C, the reaction medium is concentrated under reduced pressure. About 100 mg of (4-pyridyl)(4-chlorophenyl)chloromethane are obtained in the form of a white solid.

(4-Pyridyl)(4-chlorophenyl)methanol may be prepared in the following manner: 348 mg of sodium

tetraborohydride are added, at a temperature in the region of 20°C, to a solution of 2 g of 4-(4-chlorobenzoyl)pyridine in 160 cm^3 of ethanol. After stirring for 2 hours at a temperature in the region of 20°C, 90 mg of sodium tetraborohydride are added. After about 1.5 hours at the same temperature, the reaction medium is diluted with 200 cm^3 of dichloromethane and 200 cm^3 of water. The pH of the aqueous phase is adjusted to a value of about 5 by addition of about 13 cm^3 of a 1 N aqueous hydrochloric acid solution. After decantation, the aqueous phase is extracted with 3 times 100 cm^3 of dichloromethane. The organic phases are combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. 2 g of (4-pyridyl)(4-chlorophenyl)-methanol are thus obtained in the form of a white powder.

Example 36

24.4 mg of a 75% dispersion of sodium hydride in mineral oil are added, at room temperature under an argon atmosphere, to a solution of 330 mg of {1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}(3,5-difluorobenzyl)amine in 25 cm^3 of tetrahydrofuran. The mixture is stirred at room temperature for 1 hour before adding thereto 59 mm^3 of methyl chloroformate, and then the stirring is maintained for 18 hours under the same conditions. The reaction mixture is supplemented with 0.3 cm^3 of distilled water and the tetrahydrofuran is expelled in a rotary evaporator. The residue obtained is extracted with dichloromethane, the organic phase is dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is purified by flash chromatography on silica gel [eluent: dichloromethane/methanol (97.5/2.5 by volume)]. 328 mg of methyl {1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-(3,5-difluorobenzyl)carbamate are obtained in the form of a colorless oil [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.97 (mt : 2H); 3.39 (mt : 2H); 3.71 (s : 3H); 4.24 (broad s : 1H); 4.45 (unresolved complex : 1H); 4.57 (s : 2H); from 6.65 to 6.80 (mt : 3H); from 7.15 to 7.30 (mt : 8H)].

Example 37

(RS)-N-{1-[(4-chlorophenyl)pyrimidin-5-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)-methylsulfonamide may be obtained by carrying out the

procedure as in Example 33, starting with 0.16 g of (RS)-5-[bromo-(4-chlorophenyl)methyl]pyrimidine hydrobromide, 0.131 g of N-azetidin-3-yl-N-(3,5-difluorophenyl)methanesulfonamide hydrochloride in 5 cm^3 of acetonitrile, 303 mg of potassium carbonate and 95 mg of potassium iodide; 26 mg of (RS)-N-{1-[(4-chlorophenyl)pyrimidin-5-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide are thus obtained in the form of a yellow foam [^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ in ppm): 2.83 (s : 3H); 2.91 (mt : 2H); 3.57 (mt : 2H); 4.31 (s : 1H); 4.50 (mt : 1H); from 6.75 to 6.90 (mt : 3H); 7.29 (s : 4H); 8.71 (s : 2H); 9.08 (s : 1H)].

The medicaments according to the invention consist of at least one compound of formula (I) or an isomer or a salt of such a compound, in the pure state or in the form of a composition in which it is combined with any other pharmaceutically compatible product which may be inert or physiologically active. The medicaments according to the invention may be used orally, parenterally, rectally or topically.

As solid compositions for oral administration, tablets, pills, powders (gelatine capsules, sachets) or granules may be used. In these compositions, the active ingredient according to the invention is mixed with one or more inert diluents, such as starch, cellulose, sucrose, lactose or silica, under an argon stream. These compositions may also

comprise substances other than diluents, for example one or more lubricants such as magnesium stearate or talc, a coloring, a coating (sugar-coated tablet) or a glaze.

As liquid compositions for oral administration, there may be used pharmaceutically acceptable solutions, suspensions, emulsions, syrups and elixirs containing inert diluents such as water, ethanol, glycerol, vegetable oils or paraffin oil. These compositions may comprise substances other than diluents, for example wetting, sweetening, thickening, flavoring or stabilizing products.

Sterile compositions for parenteral administration may be preferably solutions which are aqueous or nonaqueous, suspensions or emulsions. As solvent or vehicle, there may be used water, propylene glycol, polyethylene glycol, vegetable oils, in particular olive oil, injectable organic esters, for example ethyl oleate or other suitable organic solvents. These compositions may also contain adjuvants, in particular wetting, isotonizing, emulsifying, dispersing and stabilizing agents. Sterilization may be carried out in several ways, for example by asepticizing filtration, by incorporating sterilizing agents into the composition, by irradiation or by heating. They may also be prepared in the form of sterile solid compositions which may be dissolved at

the time of use in sterile water or any other injectable sterile medium.

Compositions for rectal administration are suppositories or rectal capsules which contain, in addition to the active product, excipients such as cocoa butter, semisynthetic glycerides or polyethylene glycols.

Compositions for topical administration may be, for example, creams, lotions, collyria, collutoria, nasal drops or aerosols.

In human therapy, the compounds according to the invention are particularly useful for the treatment and/or prevention of psychoses including schizophrenia, anxiety disorders, depression, epilepsy, neurodegeneration, cerebellar and spinocerebellar disorders, cognitive disorders, cranial trauma, panic attacks, peripheral neuropathies, glaucomas, migraine, Parkinson's disease, Alzheimer's disease, Huntington's chorea, Raynaud's syndrome, tremor, obsessive-compulsive disorder, senile dementia, thymic disorders, Tourette's syndrome, tardive dyskinesia, bipolar disorders, cancers, movement disorders induced by medicaments, dystonia, endotoxemic shocks, hemorrhagic shocks, hypotension, insomnia, immunological diseases, multiple sclerosis, vomiting, asthma, appetite disorders (bulimia, anorexia), obesity, memory disorders, intestinal transit disorders, in weaning from chronic treatments and alcohol or drug abuse

(opioids, barbiturates, cannabis, cocaine, amphetamine, phencyclide, hallucinogens, benzodiazepines for example), as analgesics or potentiators of the analgesic activity of the narcotic and nonnarcotic drugs.

The doses depend on the desired effect, the duration of the treatment and the route of administration used; they are generally between 5 mg and 1000 mg per day orally for an adult with unit doses ranging from 1 mg to 250 mg of active substance.

In general, the doctor will determine the appropriate dosage depending on the age, weight and any other factors specific to the subject to be treated.

The following examples illustrate the compositions according to the invention:

EXAMPLE A

Gelatin capsules containing a dose of 50 mg of active product and having the following composition are prepared according to the usual technique:

- Compound of formula (I) ..... 50 mg
- Cellulose ..... 18 mg
- Lactose ..... 55 mg
- Colloidal silica ..... 1 mg
- Sodium carboxymethylstarch ..... 10 mg
- Talc ..... 10 mg
- Magnesium stearate ..... 1 mg

EXAMPLE B

Tablets containing a dose of 50 mg of active product and having the following composition are prepared according to the usual technique:

- Compound of formula (I) ..... 50 mg
- Lactose ..... 104 mg
- Cellulose ..... 40 mg
- Polyvidone ..... 10 mg
- Sodium carboxymethylstarch ..... 22 mg
- Talc ..... 10 mg
- Magnesium stearate ..... 2 mg
- Colloidal silica ..... 2 mg
- Mixture of hydroxymethylcellulose, glycerin, titanium oxide (72-3.5-24.5) qs 1 finished film-coated tablet containing 245 mg

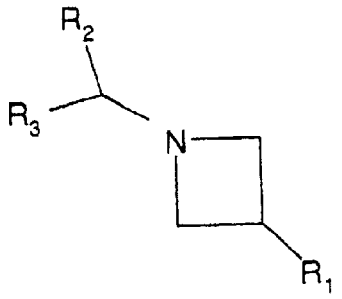
EXAMPLE C

An injectable solution containing 10 mg of active product and having the following composition is prepared:

- Compound of formula (I) ..... 10 mg
- Benzoic acid ..... 80 mg
- Benzyl alcohol ..... 0.06 ml
- Sodium benzoate ..... 80 mg
- Ethanol, 95% ..... 0.4 ml
- Sodium hydroxide ..... 24 mg
- Propylene glycol ..... 1.6 ml
- Water ..... qs 4 ml

CLAIMS

1. Pharmaceutical composition containing as active ingredient at least one compound of formula:



(I)

in which

R_1 represents a radical $-N(R_4)R_5$, $-N(R_4)-CO-R_5$, $-N(R_4)-SO_2R_6$,

R_2 and R_3, which are identical or different, represent either an aromatic chosen from phenyl, naphthyl and indenyl, these aromatics being unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, formyl, hydroxyl, trifluoromethyl, trifluoromethoxy, -CO-alk, cyano, -COOH, COOalk, $-CONR_7R_8$, $-CO-NH-NR_9R_{10}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkyl or $-alk-NR_7R_8$ radicals; or a heteroaromatic chosen from benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, 2,3-dihydrobenzofuryl, 2,3-dihydrobenzothienyl, furyl, imidazolyl, isochromanyl, isoquinolyl, pyrrolyl, pyridyl, pyrimidyl, quinolyl, 1,2,3,4-tetrahydroiso-

quinolyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with a halogen atom or an alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, -COOH, COOalk, -CO-NH-NR_9R_{10}, -$CONR_7R_8$, -alk-NR_9R_{10}, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl or hydroxyalkyl radical,

R_4 represents a radical -$C(R_{11})(R_{12})$-Het, -Het, -$(CR_{11})(R_{12})$-Ar, Ar, cycloalkyl or norbornyl,

R_5 represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, -alk-$CONR_7R_8$, -alk-NR_7R_8, alkoxy, Ar, Het, -CH_2Ar, -CH_2Het or alkyl radical optionally substituted with one or more halogen atoms,

R_6 represents a hydroxyalkyl, -alk-COOalk, -alk-$CONR_7R_8$, -alk-NR_7R_8, alkoxy, Ar, Het, -CH_2Ar, -CH_2Het or alkyl radical optionally substituted with 1 or more halogen atoms,

R_7 and R_8, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_7 and R_8 together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_9 and R_{10}, which are identical or different, represent a hydrogen atom or an alkyl, -COOalk, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl radical or alternatively R_9 and R_{10} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl, -COalk, -COOalk, -CO-NHalk, -CS-NHalk, oxo, hydroxyalkyl, -alk-O-alk or $-CO-NH_2$ radicals,

R_{11} represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, $-alk-CONR_7R_8$, $-alk-NR_7R_8$, alkoxyalkyl, Ar, Het, $-CH_2Ar$, $-CH_2Het$ or alkyl radical optionally substituted with one or more halogen atoms,

R_{12} represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, $-alk-CONR_7R_8$, $-alk-NR_7R_8$, alkoxyalkyl or alkyl radical optionally substituted with one or more halogen atoms,

or alternatively R_{11} and R_{12} together form with the carbon atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic ring, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

Ar represents a phenyl, naphthyl or indenyl radical, these different radicals being optionally substituted with one or more halogen atoms or alkyl, alkoxy, -CO-alk, cyano, -COOH, -COOalk, -$CONR_{13}R_{14}$, -$CO-NH-NR_{15}R_{16}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, -$alk-NR_{15}R_{16}$, -$NR_{15}R_{16}$, alkylthioalkyl, formyl, CF_3, OCF_3, Het, -O-alk-NH-cycloalkyl, SO_2NH_2, hydroxyl, hydroxyalkyl, -NHCOalk, NHCOOalk radicals or on 2 adjacent carbon atoms with dioxymethylene,

Het represents a 3- to 10-membered unsaturated or saturated mono- or bicyclic heterocycle containing one or more heteroatoms chosen from oxygen, sulfur and nitrogen optionally substituted with one or more halogen atoms or alkyl, alkoxy, alkoxycarbonyl, oxo or hydroxyl radicals, the nitrogen-containing heterocycles being optionally in their N-oxidized form,

R_{13} and R_{14}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{13} and R_{14} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_{15} and R_{16}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{15}

and R_{16} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

alk represents an alkyl or alkylene radical,

the alkyl and alkylene radicals and portions and the alkoxy radicals and portions are in the form of a straight or branched chain and contain 1 to 6 carbon atoms and the cycloalkyl radicals contain 3 to 10 carbon atoms,

the optical isomers of these compounds and their salts with a pharmaceutically acceptable inorganic or organic acid.

2. Pharmaceutical composition according to claim 1, for which in formula (I) Het is chosen from benzimidazole, benzoxazole, benzothiazole, benzothiophene, cinnoline, thiophene, quinazoline, quinoxaline, quinoline, pyrazole, pyrrole, pyridine, imidazole, indole, isoquinoline, pyrimidine, thiazole, thiadiazole, piperidine, piperazine, triazole, furan, tetrahydroisoquinoline, tetrahydroquinoline, these heterocycles being optionally substituted with one or more halogen atoms or alkyl, alkoxy, alkoxycarbonyl, oxo, hydroxyl, OCF_3 or CF_3 radicals.

3. Pharmaceutical composition according to claim 1, for which in the compound of formula (I)

R_1 represents a radical $-N(R_4)R_5$ or $-N(R_4)-SO_2R_6$,

R_2 represents either a phenyl which is unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, -CO-alk, cyano, $-CONR_7R_8$, hydroxyalkyl or $-alk-NR_7R_8$ radicals; or a heteroaromatic chosen from the pyridyl, pyrimidyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with a halogen atom or an alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, $-CONR_7R_8$, $-alk-NR_9R_{10}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl or hydroxyalkyl radical,

R_3 represents either a phenyl which is unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, -CO-alk, cyano, $-CONR_7R_8$, hydroxyalkyl or $-alk-NR_7R_8$ radicals; or a heteroaromatic chosen from the pyridyl, pyrimidyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with a halogen atom or an alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, $-CONR_7R_8$, $-alk-NR_9R_{10}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl or hydroxyalkyl radical,

R_4 represents a radical $-C(R_{11})(R_{12})$-Het, -Het, $-C(R_{11})(R_{12})$-Ar, Ar or norbornyl,

R_5 represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, -alk-$CONR_7R_8$, -alk-NR_7R_8, alkoxy, $-CH_2Ar$, $-CH_2$Het or alkyl radical,

R_6 represents a hydroxyalkyl, -alk-COOalk, -alk-$CONR_7R_8$, -alk-NR_7R_8, alkoxy, $-CH_2Ar$, $-CH_2$Het or alkyl radical,

R_7 and R_8, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_7 and R_8 together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_9 and R_{10}, which are identical or different, represent a hydrogen atom or an alkyl, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl radical or alternatively R_9 and R_{10} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl, -COalk, -COOalk, -CO-NHalk, oxo, hydroxyalkyl or $-CO-NH_2$ radicals,

R_{11} represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, -alk-$CONR_7R_8$, -alk-NR_7R_8, alkoxyalkyl, Ar, Het, -CH_2Ar, -CH_2Het or alkyl radical optionally substituted with one or more halogen atoms,

R_{12} represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, -alk-$CONR_7R_8$, -alk-NR_7R_8, alkoxyalkyl or alkyl radical optionally substituted with one or more halogen atoms,

or alternatively R_{11} and R_{12} together form with the carbon atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic ring, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

Ar represents a phenyl or naphthyl radical, these different radicals being optionally substituted with one or more halogen atoms or alkyl, alkoxy, -CO-alk, cyano, -$CONR_{13}R_{14}$, alkylsulfonyl, -alk-$NR_{15}R_{16}$, -$NR_{15}R_{16}$, CF_3, OCF_3, SO_2NH_2, hydroxyl or hydroxyalkyl radicals or on 2 adjacent carbon atoms with dioxymethylene,

Het represents a heterocycle chosen from benzimidazole, benzoxazole, benzothiazole, benzothiophene, thiophene, quinazoline, quinoxaline, quinoline, pyrrole, pyridine, imidazole, indole, isoquinoline, pyrimidine, thiazole, thiadiazole, furan, tetrahydroisoquinoline and tetrahydroquinoline, these heterocycles being

optionally substituted with one or more halogen atoms or alkyl, alkoxy, alkoxycarbonyl, oxo, hydroxyl, OCF_3 or CF_3 radicals,

R_{13} and R_{14}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{13} and R_{14} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_{15} and R_{16}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{15} and R_{16} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

the optical isomers of these compounds and their salts with a pharmaceutically acceptable inorganic or organic acid.

4. Pharmaceutical composition according to claim 1, for which in the compound of formula (I)

R_1 represents a radical $-N(R_4)-SO_2R_6$,

R_2 represents either a phenyl which is unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, cyano, $-CONR_7R_8$, hydroxyalkyl or $-alk-NR_7R_8$ radicals; or a heteroaromatic chosen from the pyridyl, pyrimidyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with a halogen atom or an alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, $-CONR_7R_8$ or hydroxyalkyl radical,

R_3 represents either a phenyl which is unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, cyano, $-CONR_7R_8$, hydroxyalkyl or $-alk-NR_7R_8$ radicals; or a heteroaromatic chosen from the pyridyl, pyrimidyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with a halogen atom or an alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, $-CONR_7R_8$ or hydroxyalkyl radical,

R_4 represents -Het or Ar,

R_6 represents a hydroxyalkyl or alkyl radical,

R_7 and R_8, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_7 and R_8 together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono-

or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

Ar represents a phenyl or naphthyl radical, these different radicals being optionally substituted with one or more halogen atoms or alkyl, alkoxy, -CO-alk, cyano, $-CONR_{13}R_{14}$, $-alk-NR_{15}R_{16}$, $-NR_{15}R_{16}$, CF_3, OCF_3, SO_2NH_2, hydroxyl or hydroxyalkyl radicals,

Het represents represents a heterocycle chosen from benzimidazole, benzoxazole, benzothiazole, benzothiophene, thiophene, quinazoline, quinoxaline, quinoline, pyrrole, pyridine, imidazole, indole, isoquinoline, thiazole, thiadiazole, furan, tetrahydroisoquinoline and tetrahydroquinoline, these heterocycles being optionally substituted with one or more halogen atoms or alkyl, alkoxy, alkoxycarbonyl, oxo, hydroxyl, OCF_3 or CF_3 radicals,

R_{13} and R_{14}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{13} and R_{14} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_{15} and R_{16}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{15} and R_{16} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

the optical isomers of these compounds and their salts with a pharmaceutically acceptable inorganic or organic acid.

5. Composition according to claim 1, for which the compound of formula (I) is chosen from the following compounds:

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(6-chloropyrid-2-yl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(6-ethylpyrid-2-yl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-quinol-6-ylmethylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-quinol-5-ylmethylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-isoquinol-5-ylmethylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-pyrid-3-ylmethylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(1-oxide-pyrid-3-yl)methylsulfonamide,

N-(1R,2S,4S)-bicyclo[2.2.1]hept-2-yl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonamide,

N-(1R,2R,4S)-bicyclo[2.2.1]hept-2-yl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(thiazol-2-yl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3-methoxyphenyl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3-hydroxyphenyl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3-hydroxymethylphenyl)methylsulfonamide,

Ethyl N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(methylsulfonyl)-3-aminobenzoate,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(1-isobutylpiperid-4-yl)methylsulfonamide,

N-benzyl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}amine,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorobenzyl)amine,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorobenzyl)methylsulfonamide,

N-{1-[bis(4-chloprophenyl)methyl]azetidin-3-yl}-N-(pyrid-3-ylmethyl)methylsulfonamide,

N-{1-[bis(4-fluorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(RS)-N-{1-[(4-chlorophenyl)pyrid-3-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(R)-N-{1-[(4-chlorophenyl)pyrid-3-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(S)-N-{1-[(4-chlorophenyl)pyrid-3-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(RS)-N-{1-[(4-chlorophenyl)pyrid-4-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(R)-N-{1-[(4-chlorophenyl)pyrid-4-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(S)-N-{1-[(4-chlorophenyl)pyrid-4-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(RS)-N-{1-[(4-chlorophenyl)pyrimid-5-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

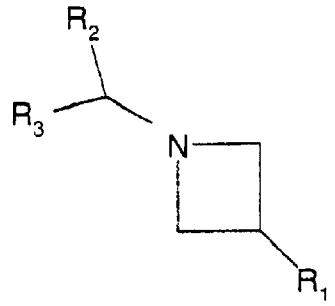
(R)-N-{1-[(4-chlorophenyl)pyrimid-5-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(S)-N-{1-[(4-chlorophenyl)pyrimid-5-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)benzylsulfonamide,

their optical isomers and their salts with a pharmaceutically acceptable inorganic or organic acid.

6. Compound of formula:



(I)

in which

R_1 represents a radical $-N(R_4)R_5$, $-N(R_4)-CO-R_5$, $-N(R_4)-SO_2R_6$,

R_2 and R_3, which are identical or different, represent either an aromatic chosen from phenyl, naphthyl and indenyl, these aromatics being unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, formyl, hydroxyl, trifluoromethyl, trifluoromethoxy, -CO-alk, cyano, -COOH, COOalk, $-CONR_7R_8$, $-CO-NH-NR_9R_{10}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkyl or $-alk-NR_7R_8$ radicals; or a heteroaromatic chosen from benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, 2,3-dihydrobenzofuryl, 2,3-dihydrobenzothienyl, furyl, imidazolyl, isochromanyl, isoquinolyl, pyrrolyl, pyridyl, pyrimidyl, quinolyl, 1,2,3,4-tetrahydroisoquinolyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with a halogen atom or alkyl, alkoxy,

hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, -COOH, COOalk, -CO-NH-NR_9R_{10}, -$CONR_7R_8$, -alk-NR_9R_{10}, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl or hydroxyalkyl radical,

R_4 represents a radical -$C(R_{11})(R_{12})$-Het, -Het, -$(CR_{11})(R_{12})$-Ar, Ar, cycloalkyl or norbornyl,

R_5 represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, -alk-$CONR_7R_8$, -alk-NR_7R_8, alkoxy, Ar, Het, -CH_2Ar, -CH_2Het or alkyl radical optionally substituted with one or more halogen atoms,

R_6 represents a hydroxyalkyl, -alk-COOalk, -alk-$CONR_7R_8$, -alk-NR_7R_8, alkoxy, Ar, Het, -CH_2Ar, -CH_2Het or alkyl radical optionally substituted with 1 or more halogen atoms,

R_7 and R_8, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_7 and R_8 together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_9 and R_{10}, which are identical or different, represent a hydrogen atom or an alkyl, -COOalk, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl radical or

alternatively R_9 and R_{10} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl, -COalk, -COOalk, -CO-NHalk, -CS-NHalk, oxo, hydroxyalkyl, -alk-O-alk or $-CO-NH_2$ radicals

R_{11} represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, $-alk-CONR_7R_8$, $-alk-NR_7R_8$, alkoxyalkyl, Ar, Het, $-CH_2Ar$, $-CH_2Het$ or alkyl radical optionally substituted with one or more halogen atoms,

R_{12} represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, $-alk-CONR_7R_8$, $-alk-NR_7R_8$, alkoxyalkyl or alkyl radical optionally substituted with one or more halogen atoms,

or alternatively R_{11} and R_{12} together form with the carbon atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic ring, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

Ar represents a phenyl, naphthyl or indenyl radical, these different radicals being optionally substituted with one or more halogen atoms or alkyl, alkoxy, -CO-alk, cyano, -COOH, -COOalk, $-CONR_{13}R_{14}$,

-CO-NH-$NR_{15}R_{16}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, -alk-$NR_{15}R_{16}$, -$NR_{15}R_{16}$, alkylthioalkyl, formyl, CF_3, OCF_3, Het, -O-alk-NH-cycloalkyl, SO_2NH_2, hydroxyl, hydroxyalkyl, -NHCOalk, NHCOOalk radicals or on 2 adjacent carbon atoms with dioxymethylene,

Het represents a 3- to 10-membered unsaturated or saturated mono- or bicyclic heterocycle containing one or more heteroatoms chosen from oxygen, sulfur and nitrogen optionally substituted with one or more halogen atoms or alkyl, alkoxy, alkoxycarbonyl, oxo or hydroxyl radicals, the nitrogen-containing heterocycles being optionally in their N-oxidized form,

R_{13} and R_{14}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{13} and R_{14} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_{15} and R_{16}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{15} and R_{16} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and

being optionally substituted with one or more alkyl radicals,

alk represents an alkyl or alkylene radical,

the alkyl and alkylene radicals and portions and the alkoxy radicals and portions are in the form of a straight or branched chain and contain 1 to 6 carbon atoms and the cycloalkyl radicals contain 3 to 10 carbon atoms,

the optical isomers of these compounds and their salts with a pharmaceutically acceptable inorganic or organic acid,

with the exception of the compound for which R_2 and R_3 represent phenyl radicals, R_1 represents a radical $-N(R_4)SO_2R_6$ for which R_4 represents a phenyl radical and R_6 represents a methyl radical.

7. Compound of formula (I) according to claim 6, for which Het is chosen from benzimidazole, benzoxazole, benzothiazole, benzothiophene, cinnoline, thiophene, quinazoline, quinoxaline, quinoline, pyrazole, pyrrole, pyridine, imidazole, indole, isoquinoline, pyrimidine, thiazole, thiadiazole, piperidine, piperazine, triazole, furan, tetrahydro-isoquinoline, tetrahydroquinoline, these heterocycles being optionally substituted with one or more halogen atoms or alkyl, alkoxy, alkoxycarbonyl, oxo, hydroxyl, OCF_3 or CF_3 radicals.

8. Compound of formula (I) according to claim 6, for which

R_1 represents a radical $-N(R_4)R_5$ or $-N(R_4)-SO_2R_6$,

R_2 represents either a phenyl which is unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, -CO-alk, cyano, $-CONR_7R_8$, hydroxyalkyl or $-alk-NR_7R_8$ radicals; or a heteroaromatic chosen from the pyridyl, pyrimidyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with a halogen atom or an alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, $-CONR_7R_8$, $-alk-NR_9R_{10}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl or hydroxyalkyl radical,

R_3 represents either a phenyl which is unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, -CO-alk, cyano, $-CONR_7R_8$, hydroxyalkyl or $-alk-NR_7R_8$ radicals; or a heteroaromatic chosen from the pyridyl, pyrimidyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with a halogen atom or an alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, $-CONR_7R_8$, $-alk-NR_9R_{10}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl or hydroxyalkyl radical,

R_4 represents a radical $-C(R_{11})(R_{12})$-Het, -Het, $-C(R_{11})(R_{12})$-Ar, Ar or norbornyl,

R_5 represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, -alk-$CONR_7R_8$, -alk-NR_7R_8, alkoxy, $-CH_2Ar$, $-CH_2$Het or alkyl radical,

R_6 represents a hydroxyalkyl, -alk-COOalk, -alk-$CONR_7R_8$, -alk-NR_7R_8, alkoxy, $-CH_2Ar$, $-CH_2$Het or alkyl radical,

R_7 and R_8, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_7 and R_8 together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_9 and R_{10}, which are identical or different, represent a hydrogen atom or an alkyl, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl radical or alternatively R_9 and R_{10} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl, -COalk, -COOalk, -CO-NHalk, oxo, hydroxyalkyl or $-CO-NH_2$ radicals,

R_{11} represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, -alk-$CONR_7R_8$, -alk-NR_7R_8, alkoxyalkyl, Ar, Het, -CH_2Ar, -CH_2Het or alkyl radical optionally substituted with one or more halogen atoms,

R_{12} represents a hydrogen atom or a hydroxyalkyl, -alk-COOalk, -alk-$CONR_7R_8$, -alk-NR_7R_8, alkoxyalkyl or alkyl radical optionally substituted with one or more halogen atoms,

or alternatively R_{11} and R_{12} together form with the carbon atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic ring, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

Ar represents a phenyl or naphthyl radical, these different radicals being optionally substituted with one or more halogen atoms or alkyl, alkoxy, -CO-alk, cyano, -$CONR_{13}R_{14}$, alkylsulfonyl, -alk-$NR_{15}R_{16}$, -$NR_{15}R_{16}$, CF_3, OCF_3, SO_2NH_2, hydroxyl or hydroxyalkyl radicals or on 2 adjacent carbon atoms with dioxymethylene,

Het represents a heterocycle chosen from benzimidazole, benzoxazole, benzothiazole, benzothiophene, thiophene, quinazoline, quinoxaline, quinoline, pyrrole, pyridine, imidazole, indole, isoquinoline, pyrimidine, thiazole, thiadiazole, furan, tetrahydroisoquinoline and tetrahydroquinoline, these heterocycles being

optionally substituted with one or more halogen atoms or alkyl, alkoxy, alkoxycarbonyl, oxo, hydroxyl, OCF_3 or CF_3 radicals,

R_{13} and R_{14}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{13} and R_{14} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_{15} and R_{16}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{15} and R_{16} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

the optical isomers of these compounds and their salts with a pharmaceutically acceptable inorganic or organic acid,

with the exception of the compound for which R_2 and R_3 represent phenyl radicals, R_1 represents a radical $-N(R_4)SO_2R_6$ for which R_4 represents a phenyl radical and R_6 represents a methyl radical.

9. Compound of formula (I) according to claim 6, in which

R_1 represents a radical $-N(R_4)-SO_2R_6$,

R_2 represents either a phenyl which is unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, cyano, $-CONR_7R_8$, hydroxyalkyl or $-alk-NR_7R_8$ radicals; or a heteroaromatic chosen from the pyridyl, pyrimidyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with a halogen atom or an alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, $-CONR_7R_8$ or hydroxyalkyl radical,

R_3 represents either a phenyl which is unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, cyano, $-CONR_7R_8$, hydroxyalkyl or $-alk-NR_7R_8$ radicals; or a heteroaromatic chosen from the pyridyl, pyrimidyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with a halogen atom or an alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, $-CONR_7R_8$ or hydroxyalkyl radical,

R_4 represents -Het or Ar,

R_6 represents a hydroxyalkyl or alkyl radical,

R_7 and R_8, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_7 and R_8 together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

Ar represents a phenyl or naphthyl radical, these different radicals being optionally substituted with one or more halogen atoms or alkyl, alkoxy, -CO-alk, cyano, $-CONR_{13}R_{14}$, $-alk-NR_{15}R_{16}$, $-NR_{15}R_{16}$, CF_3, OCF_3, SO_2NH_2, hydroxyl or hydroxyalkyl radicals,

Het represents represents a heterocycle chosen from benzimidazole, benzoxazole, benzothiazole, benzothiophene, thiophene, quinazoline, quinoxaline, quinoline, pyrrole, pyridine, imidazole, indole, isoquinoline, thiazole, thiadiazole, furan, tetrahydro-isoquinoline and tetrahydroquinoline, these heterocycles being optionally substituted with one or more halogen atoms or alkyl, alkoxy, alkoxycarbonyl, oxo, hydroxyl, OCF_3 or CF_3 radicals,

R_{13} and R_{14}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{13} and R_{14} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono-

or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_{15} and R_{16}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{15} and R_{16} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

the optical isomers of these compounds and their salts with a pharmaceutically acceptable inorganic or organic acid,

with the exception of the compound for which R_2 and R_3 represent phenyl radicals, R_1 represents a radical $-N(R_4)SO_2R_6$ for which R_4 represents a phenyl radical and R_6 represents a methyl radical.

10. Compound of formula (I) according to claim 6, chosen from the following compounds:

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(6-chloropyrid-2-yl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(6-ethylpyrid-2-yl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-quinol-6-ylmethylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-quinol-5-ylmethylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-isoquinol-5-ylmethylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-pyrid-3-ylmethylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(1-oxide-pyrid-3-yl)methylsulfonamide,

N-(1R,2S,4S)-bicyclo[2.2.1]hept-2-yl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonamide,

N-(1R,2R,4S)-bicyclo[2.2.1]hept-2-yl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(thiazol-2-yl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3-methoxyphenyl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3-hydroxyphenyl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3-hydroxymethylphenyl)methylsulfonamide,

Ethyl N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(methylsulfonyl)-3-aminobenzoate,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(1-isobutylpiperid-4-yl)methylsulfonamide,

N-benzyl-N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}amine,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorobenzyl)amine,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorobenzyl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(pyrid-3-ylmethyl)methylsulfonamide,

N-{1-[bis(4-fluorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(RS)-N-{1-[(4-chlorophenyl)pyrid-3-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(R)-N-{1-[(4-chlorophenyl)pyrid-3-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(S)-N-{1-[(4-chlorophenyl)pyrid-3-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(RS)-N-{1-[(4-chlorophenyl)pyrid-4-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(R)-N-{1-[(4-chlorophenyl)pyrid-4-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(S)-N-{1-[(4-chlorophenyl)pyrid-4-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(RS)-N-{1-[(4-chlorophenyl)pyrimid-5-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

(R)-N-{1-[(4-chlorophenyl)pyrimid-5-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

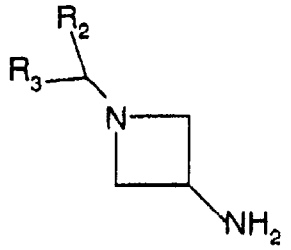
(S)-N-{1-[(4-chlorophenyl)pyrimid-5-ylmethyl]azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide,

N-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-N-(3,5-difluorophenyl)benzylsulfonamide,

their optical isomers and their salts with a pharmaceutically acceptable inorganic or organic acid.

11. N-{1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}-N-(3,5-difluorophenyl)methylsulfonamide, its optical isomers and its salts with a pharmaceutically acceptable inorganic or organic acid.

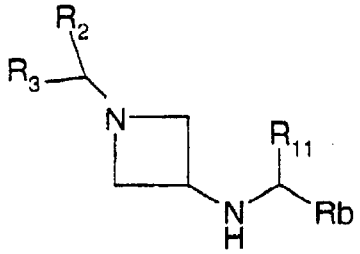
12. Process for preparing the compounds of formula (I) according to claim 6, for which R_1 represents a radical $-N(R_4)R_5$ in which R_5 is a hydrogen atom, R_4 is a radical $-CR_{11}R_{12}-Ar$ or $-CR_{11}R_{12}-Het$ and R_{12} is a hydrogen atom, characterized in that a derivative $Rb-COR_{11}$ for which R_{11} has the same meanings as in claim 6 is reacted with a derivative of formula:



Rb represents a radical Ar or Het, R_2, R_3, R_{11} Ar and Het have the same meanings as in claim 6, the product is

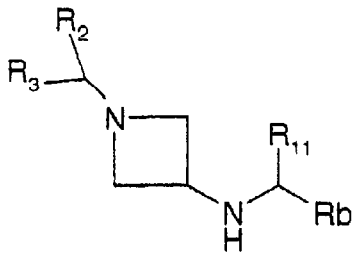
isolated and it is optionally converted to a pharmaceutically acceptable salt.

13. Process for preparing compounds of formula (I) according to claim 6, for which R_1 represents a radical $-N(R_4)-CO-R_5$ in which R_4 is a radical $-C(R_{11})(R_{12})-Het$ or $-C(R_{11})(R_{12})-Ar$ and R_{12} is a hydrogen atom, characterized in that a derivative $Hal-COR_5$ is reacted with a derivative of formula:



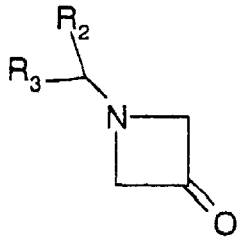
Hal represents a halogen atom Rb represents a radical Ar or Het and R_2, R_3, R_5, R_{11}, Ar and Het have the same meanings as in claim 6, the product is isolated and it is optionally converted to a pharmaceutically acceptable salt.

14. Process for preparing the compounds of formula (I) according to claim 6, for which R_1 represents a radical $-N(R_4)-SO_2R_6$ in which R_4 is a radical $-C(R_{11})(R_{12})-Ar$ or $-C(R_{11})(R_{12})-Het$ and R_{12} is a hydrogen atom, characterized in that a derivative $Hal-SO_2R_6$ is reacted with a derivative of formula:



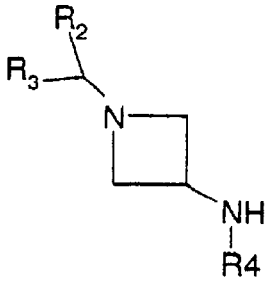
R_2, R_3, R_{11} and R_5 have the same meanings as in claim 6, Hal represents a halogen atom and Rb represents a radical Ar and Het, the product is isolated and it is optionally converted to a pharmaceutically acceptable salt.

15. Process for preparing the compounds of formula (I) according to claim 6 for which R_1 represents a radical $-N(R_4)R_5$, characterized in that a derivative $R_5(R_4)NH$ is reacted with a derivative of formula:



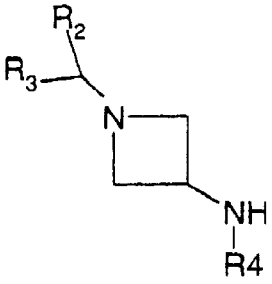
R_2, R_3, R_4 and R_5 have the same meanings as in claim 6, the product is isolated and it is optionally converted to a pharmaceutically acceptable salt.

16. Process for preparing the compounds of formula (I) according to claim 6 for which R_1 represents a radical $-N(R_4)SO_2R_6$, characterized in that a derivative $Hal-SO_2R_6$ is reacted with a derivative of formula:



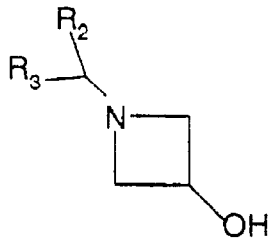
R_2, R_3, R_4 and R_6 have the same meanings as in claim 6 and Hal represents a halogen atom, the product is isolated and optionally converted to a pharmaceutically acceptable salt.

17. Process for preparing the compounds of formula (I) according to claim 6 for which R_1 represents a radical $-N(R_4)COR_5$, characterized in that a derivative $Hal-COR_6$ is reacted with a derivative of formula:

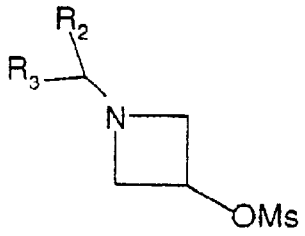


R_2, R_3, R_4 and R_5 have the same meanings as in claim 6 and Hal represents a halogen atom, the product is isolated and optionally converted to a pharmaceutically acceptable salt.

18. Process for preparing the compounds of formula (I) according to claim 6 for which R_1 represents a radical $-N(R_4)-SO_2-R_6$, R_4 is a radical Het or Ar, characterized in that a derivative $Rd-NH-SO_2-R_6$ is reacted with a derivative of formula:

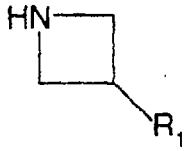


or



Rd represents a radical Ar or Het, R_2, R_3 and R_6 have the same meanings as in claim 6 and Ms represents a methylsulfonyloxy radical, the product is isolated and it is optionally converted to a pharmaceutically acceptable salt.

19. Process for preparing the compounds of formula (I) according to claim 6, characterized in that a derivative R_2-CHBr-R_3 is reacted with a derivative of formula:



R_1, R_2 and R_3 have the same meanings as in claim 6, the product is isolated and it is optionally converted to a pharmaceutically acceptable salt.

20. Process for preparing the compounds of formula (I) according to claim 6 for which R_1 represents a radical $-N(R_4)-SO_2-R_6$ for which R_4 is a piperid-4-yl radical substituted on the nitrogen with an alkyl radical, characterized in that a corresponding compound of formula (I) for which R_1 represents a radical

$-N(R_4)-SO_2-R_6$ for which R_4 is a piperid-4-yl radical is alkylated, the product is isolated and it is optionally converted to a pharmaceutically acceptable salt.

21. Process for preparing the compounds of formula (I) according to claim 6, for which R_1 represents a radical $-N(R_4)-SO_2-R_6$ for which R_4 is a phenyl radical substituted with a pyrrolid-1-yl radical, characterized in that pyrrolidine is reacted with a corresponding compound of formula (I) for which R_1 represents a radical $-N(R_4)SO_2R_6$ for which R_4 is a phenyl radical substituted with a halogen atom, the product is isolated and it is optionally converted to a pharmaceutically acceptable salt.