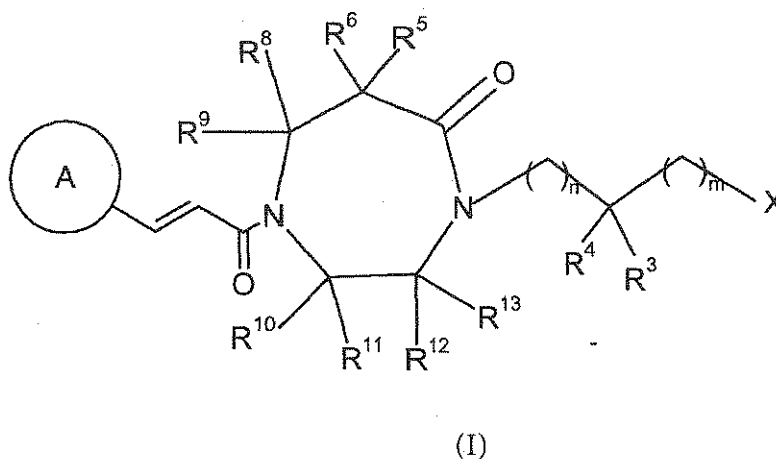


DIAZEPAN DERIVATIVES MODULATORS OF CHEMOKINE RECEPTORS

The invention is concerned with novel diazepan derivatives of formula (I),



wherein

A is aryl or heteroaryl, said aryl and said heteroaryl being optionally substituted by one to three substituents independently selected from the group consisting of halogen, benzyloxy, heteroaryl-C₁₋₆ alkoxy, C₁₋₆ alkyl, C₁₋₆ alkoxy and halo C₁₋₆ alkoxy, or said aryl and said heteroaryl being optionally substituted by C₁₋₆ alkylendioxy;

X is -N(R¹)(R²) or -N⁺(R¹)(R²)(R⁷);

- i) R¹ and R² are, independently to each other, hydrogen, C₁₋₆ alkyl, C₃₋₆ alkenyl, C₃₋₆ alkynyl, hydroxy C₂₋₆ alkyl, C₁₋₆ alkoxy C₂₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₆ alkyl, C₇₋₁₀ bicycloalkyl, phenyl C₁₋₃ alkyl, heteroaryl C₁₋₃ alkyl, heterocyclyl or heterocyclyl C₁₋₆ alkyl, in which the cycloalkyl of said C₃₋₇ cycloalkyl and said C₃₋₇ cycloalkyl C₁₋₆ alkyl, the phenyl of said phenyl C₁₋₃ alkyl, the heteroaryl of said heteroaryl C₁₋₃ alkyl and the heterocyclyl of said heterocyclyl and said heterocyclyl C₁₋₆ alkyl are optionally substituted by one to three substituents independently selected from the group consisting of R^d; or

R¹ and R², together with the nitrogen atom to which they are attached, form heterocyclyl optionally substituted by one to three substituents independently

selected from the group consisting of R^d , and one of the ring carbon atoms of said heterocyclyl formed by R^1 and R^2 being optionally replaced with a carbonyl group; and/or

one of the ring carbon atoms of the heterocyclyl formed by R^1 and R^2 may be a ring carbon atom of another ring which is C_{3-7} cycloalkyl or heterocyclyl, one or two ring carbon atoms of said another ring being optionally replaced by a carbonyl group, and said another ring being optionally substituted by C_{1-6} alkyl;

R^3 and R^4 are, independently to each other, hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-6} alkyl, C_{1-6} alkoxy carbonyl, carboxyl, hydroxy- C_{1-6} alkyl, C_{1-6} alkoxy- C_{1-6} alkyl, halogen or halo C_{1-6} alkyl; or

R^3 and R^4 , together with the carbon atom to which they are attached, form C_{3-7} cycloalkyl or heterocyclyl optionally substituted by one to three substituents independently selected from the group consisting of C_{1-4} alkyl, halo C_{1-4} alkyl and halogen; or

ii) R^1 is hydrogen, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, hydroxy C_{1-6} alkyl, C_{1-6} alkoxy C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-6} alkyl, C_{7-10} bicycloalkyl, phenyl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl, heterocyclyl or heterocyclyl C_{1-6} alkyl, in which the cycloalkyl of said C_{3-7} cycloalkyl and said C_{3-7} cycloalkyl C_{1-6} alkyl, the phenyl of said phenyl C_{1-3} alkyl, the heteroaryl of said heteroaryl C_{1-3} alkyl and the heterocyclyl of said heterocyclyl and said heterocyclyl C_{1-6} alkyl are optionally substituted by one to three substituents independently selected from the group consisting of R^d ;

R^3 is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-6} alkyl, halogen or halo C_{1-6} alkyl;

R^2 and R^4 , together with the nitrogen atom to which R^2 is attached, the carbon atom to which R^4 is attached and the C_{1-2} alkylene between said nitrogen atom and said carbon atom, if any, form heterocyclyl optionally substituted by one to three substituents independently selected from the group consisting of C_{1-6} alkyl and fluorine;

R^5 and R^6 are, independently to each other, hydrogen, fluoro, C_{1-6} alkyl or C_{3-7} cycloalkyl;

R^7 is C_{1-6} alkyl;

R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} are, independently to each other, hydrogen, C_{1-6} alkyl or C_{3-7} cycloalkyl;

R^d is hydroxy, cyano, NR^aR^b , halogen, C_{1-6} alkyl, halo C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy carbonyl, acyl, $-C(O)NR^aR^b$, $-NR^a-C(O)-R^b$, $-NR^a-C(O)-OR^b$, $-NR^a-C(O)-NR^b$, $-NR^a-SO_2-R^b$, $-NR^a-SO_2-NR^bR^c$, $-OC(O)NR^aR^b$, $-OC(O)OR^a$, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylthio, phenyl, phenyl C_{1-3} alkyl, heteroaryl, heteroaryl C_{1-3} alkyl and heterocyclyl, and the phenyl of said phenyl and said phenyl C_{1-3} alkyl, the heteroaryl of said heteroaryl and said heteroaryl C_{1-3} alkyl, and the heterocyclyl being optionally substituted by one to three substituents independently selected from the group consisting of hydroxy, cyano, NR^aR^b , halogen, C_{1-6} alkyl, halo C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkoxy carbonyl, acyl, $-C(O)NR^aR^b$, $-NR^a-C(O)-R^b$, $-NR^a-C(O)-OR^b$, $-NR^a-C(O)-NR^b$, $-NR^a-SO_2-R^b$, $-NR^a-SO_2-NR^bR^c$, $-OC(O)NR^aR^b$, $-OC(O)OR^a$, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl and C_{1-6} alkylthio, and one or two ring carbon atoms of the heterocyclyl being optionally replaced with a carbonyl group;

R^a , R^b and R^c are independently hydrogen or C_{1-6} alkyl;

n is an integer of 0 to 3;

m is an integer of 0 to 3;

$m+n$ is an integer of 1 to 5;

or prodrugs or pharmaceutically acceptable salts thereof.

Further, the invention is concerned with a process and an intermediate for the manufacture of the above compounds, pharmaceutical preparations which contain such compounds, the use of these compounds for the production of pharmaceutical preparations.

The compounds of formula (I) are CCR2 receptor (Chemokine Receptor 2/Monocyte chemotactic protein 1 receptor) antagonists and also CCR-5 receptor (Chemokine Receptor 5) and/or CCR-3 receptor (Chemokine Receptor 3) antagonists. Chemokines are a family of small, secreted proinflammatory cytokines functioning as chemoattractants for leukocytes. They promote trafficking of leukocytes from vascular beds into surrounding tissues in response to inflammatory signals. Chemotaxis starts upon chemokine binding to receptors (GPCRs) by initiating signaling pathways involving increased Ca-flux, inhibition of cAMP production, rearrangements of the cytoskeleton, activation of integrins and of cell motility processes and an increase in the expression of adhesion proteins.

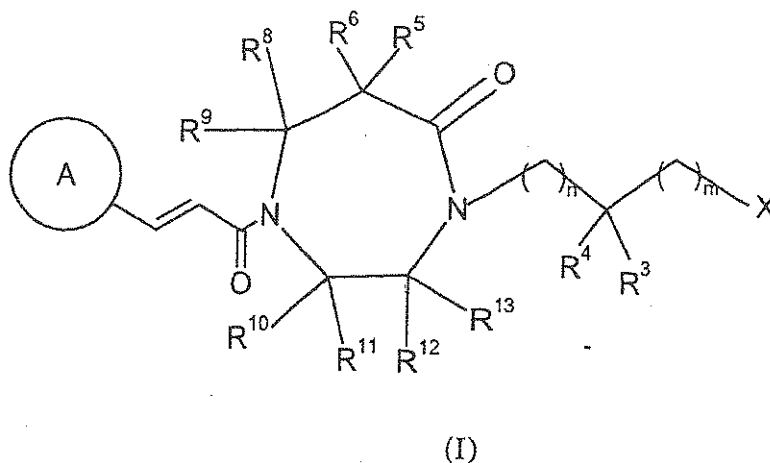
Proinflammatory chemokines are considered to be involved in the development of atherosclerosis and other important diseases with inflammatory components like rheumatoid arthritis, asthma, multiple sclerosis, transplant rejection and ischemia reperfusion injury with specific prominent effects in nephropathy and peripheral vascular diseases. Monocyte

Chemotactic protein 1 is considered to be the major stimulated chemokine mediating inflammatory processes in these diseases through the CCR2 receptor on monocytes and on some T lymphocytes. In addition MCP-1 / CCR2 are in discussion to be related to the progression of the metabolic syndrome to more severe stages of obese and diabetic diseases. CCR2 has also been linked to HIV infection, and consequently the course of autoimmune diseases, through its heterodimerization with CCR5 which has a role as coreceptor for viral entry into host cells.

Thus, CCR2 can be a target of a new medicine for treatment of peripheral vascular diseases, and more specifically for treatment of patients with critical limb ischemia. Furthermore, study results and experiences from the development of a new CCR2 medicine for this indication may facilitate a follow-up development for treatment of atherosclerosis. There is a large body of information from animal models of MCP-1 and CCR2 ko mice in wt or apoE^{-/-} or LDL-R^{-/-} backgrounds showing that the MCP-1/CCR2 pathway is essential for monocyte / macrophage recruitment, and also for intimal hyperplasia and the formation and stability of atherosclerotic lesions. In addition, numerous reports describe involvement of the MCP-1 / CCR2 pathway in man post injury and in various inflammatory processes, including such in vascular beds.

The disclosure provides the novel compounds of formula (I) which are CCR2 receptor antagonists, with some antagonist activity also at CCR-3 and CCR-5.

In a first aspect, there is provided compounds of formula (I)



wherein

A is aryl or heteroaryl, said aryl and said heteroaryl being optionally substituted by one to three substituents independently selected from the group consisting of halogen, benzyloxy, heteroaryl-C₁₋₆ alkoxy, C₁₋₆ alkyl, C₁₋₆ alkoxy and halo C₁₋₆ alkoxy, or said aryl and said heteroaryl being optionally substituted by C₁₋₆ alkylenedioxy;

X is -N(R¹)(R²) or -N⁺(R¹)(R²)(R⁷);

- i) R¹ and R² are, independently to each other, hydrogen, C₁₋₆ alkyl, C₃₋₆ alkenyl, C₃₋₆ alkynyl, hydroxy C₂₋₆ alkyl, C₁₋₆ alkoxy C₂₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₆ alkyl, C₇₋₁₀ bicycloalkyl, phenyl C₁₋₃ alkyl, heteroaryl C₁₋₃ alkyl, heterocyclyl or heterocyclyl C₁₋₆ alkyl, in which the cycloalkyl of said C₃₋₇ cycloalkyl and said C₃₋₇ cycloalkyl C₁₋₆ alkyl, the phenyl of said phenyl C₁₋₃ alkyl, the heteroaryl of said heteroaryl C₁₋₃ alkyl and the heterocyclyl of said heterocyclyl and said heterocyclyl C₁₋₆ alkyl are optionally substituted by one to three substituents independently selected from the group consisting of R^d; or

R¹ and R², together with the nitrogen atom to which they are attached, form heterocyclyl optionally substituted by one to three substituents independently selected from the group consisting of R^d, and one of the ring carbon atoms of

said heterocyclyl formed by R^1 and R^2 being optionally replaced with a carbonyl group; and/or

one of the ring carbon atoms of the heterocyclyl formed by R^1 and R^2 may be a ring carbon atom of another ring which is C_{3-7} cycloalkyl or heterocyclyl, one or two ring carbon atoms of said another ring being optionally replaced by a carbonyl group, and said another ring being optionally substituted by C_{1-6} alkyl;

R^3 and R^4 are, independently to each other, hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-6} alkyl, C_{1-6} alkoxy carbonyl, carboxyl, hydroxy- C_{1-6} alkyl, C_{1-6} alkoxy- C_{1-6} alkyl, halogen or halo C_{1-6} alkyl; or

R^3 and R^4 , together with the carbon atom to which they are attached, form C_{3-7} cycloalkyl or heterocyclyl optionally substituted by one to three substituents independently selected from the group consisting of C_{1-4} alkyl, halo C_{1-4} alkyl and halogen; or

- ii) R^1 is hydrogen, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, hydroxy C_{1-6} alkyl, C_{1-6} alkoxy C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-6} alkyl, C_{7-10} bicycloalkyl, phenyl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl, heterocyclyl or heterocyclyl C_{1-6} alkyl, in which the cycloalkyl of said C_{3-7} cycloalkyl and said C_{3-7} cycloalkyl C_{1-6} alkyl, the phenyl of said phenyl C_{1-3} alkyl, the heteroaryl of said heteroaryl C_{1-3} alkyl and the heterocyclyl of said heterocyclyl and said heterocyclyl C_{1-6} alkyl are optionally substituted by one to three substituents independently selected from the group consisting of R^d ;

R^3 is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-6} alkyl, halogen or halo C_{1-6} alkyl;

R^2 and R^4 , together with the nitrogen atom to which R^2 is attached, the carbon atom to which R^4 is attached and the C_{1-2} alkylene between said nitrogen atom and said carbon atom, if any, form heterocyclyl optionally substituted by one to three substituents independently selected from the group consisting of C_{1-6} alkyl and fluorine;

R^7 is C_{1-6} alkyl;

$R^8, R^9, R^{10}, R^{11}, R^{12}$ and R^{13} are, independently to each other, hydrogen, C_{1-6} alkyl or C_{3-7} cycloalkyl;

R^d is hydroxy, cyano, NR^aR^b , halogen, C_{1-6} alkyl, halo C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkoxycarbonyl, acyl, $-C(O)NR^aR^b$, $-NR^a-C(O)-R^b$, $-NR^a-C(O)-OR^b$, $-NR^a-C(O)-NR^b$, $-NR^a-SO_2-R^b$, $-NR^a-SO_2-NR^bR^c$, $-OC(O)NR^aR^b$, $-OC(O)OR^a$, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylthio, phenyl, phenyl C_{1-3} alkyl, heteroaryl, heteroaryl C_{1-3} alkyl and heterocyclyl, and the phenyl of said phenyl and said phenyl C_{1-3} alkyl, the heteroaryl of said heteroaryl and said heteroaryl C_{1-3} alkyl, and the heterocyclyl being optionally substituted by one to three substituents independently selected from the group consisting of hydroxy, cyano, NR^aR^b , halogen, C_{1-6} alkyl, halo C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkoxycarbonyl, acyl, $-C(O)NR^aR^b$, $-NR^a-C(O)-R^b$, $-NR^a-C(O)-OR^b$, $-NR^a-C(O)-NR^b$, $-NR^a-SO_2-R^b$, $-NR^a-SO_2-NR^bR^c$, $-OC(O)NR^aR^b$, $-OC(O)OR^a$, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl and C_{1-6} alkylthio, and one or two ring carbon atoms of the heterocyclyl being optionally replaced with a carbonyl group;

R^a, R^b and R^c are independently hydrogen or C_{1-6} alkyl;

n is an integer of 0 to 3;

m is an integer of 0 to 3;

$m+n$ is an integer of 1 to 5;

or pharmaceutically acceptable salts thereof;

wherein, unless otherwise indicated,

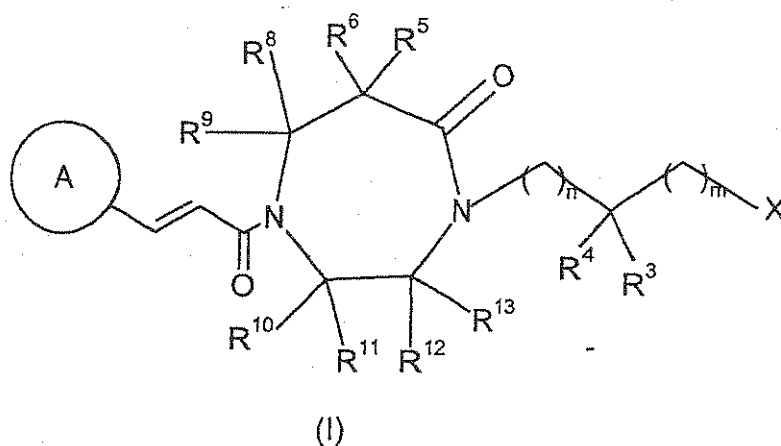
the term "aryl" means phenyl or naphthyl;

the term "heterocyclyl" means non-aromatic mono- or bi-cyclic radicals of four to nine ring atoms in which one to three ring atoms are heteroatoms independently selected from N, O and S(O)_n (where n is an integer from 0 to 2), the remaining ring atoms being C;

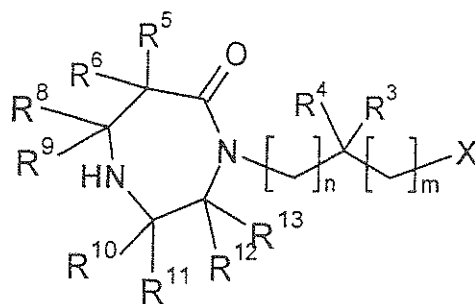
the term "heteroaryl" means a monocyclic or bicyclic radical of 5 to 10 ring atoms having one to three ring heteroatoms independently selected from N, O, and S, the remaining ring atoms being C;

the term "acyl" means R-C(O)-, in which R is C₁₋₆ alkyl, halo C₁₋₆ alkyl, C₃₋₇ cycloalkyl or C₃₋₇ cycloalkyl C₁₋₆ alkyl.

In a second aspect, there is provided a process for manufacturing compounds of formula (I)

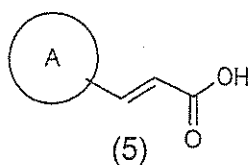


comprising a step of reacting compounds of formula (4)



(4)

with compounds of formula (5)



(5)

, wherein A, X, R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, m and n are as defined above.

In a third aspect, there is provided pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable excipient.

In a fourth aspect, there is provided the compounds as defined above for use as therapeutic active substances.

In a fifth aspect, there is provided the compounds as defined above for use as therapeutic active substances for the treatment and/or prophylaxis of diseases treatable by a CCR-2 receptor antagonist, CCR-3 receptor antagonist or CCR-5 receptor antagonist.

In a sixth aspect, there is provided the use of compounds as defined above for the preparation of medicaments for the therapeutic and/or prophylactic treatment of diseases selected from the group consisting of peripheral arterial occlusive disease, critical limb ischemia, vulnerable atherosclerotic plaque patients, unstable angina, congestive heart failure, left ventricular hypertrophy, ischemia reperfusion injury, stroke, cardiomyopathy, restenosis, rheumatoid arthritis, diabetic nephropathy, irritable Bowel Disease, Crohns' disease, multiple sclerosis, neuropathic pain, atherothrombosis and/or burns/ulcers in Diabetes/CLI or asthma.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The term “halogen” or “halo” means fluorine, chlorine, bromine and iodine, with chlorine and fluorine being preferred.

The term “C₁₋₆ alkyl”, alone or in combination with other groups, means a branched or straight-chain monovalent alkyl radical, having one to six carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, t-butyl. C₁₋₄ alkyl or C₁₋₃ alkyl is more preferred. The term “C₂₋₆ alkyl” means the same as “C₁₋₆ alkyl”, except that C₂₋₆ alkyl has two to six carbon atoms.

The term “hydroxy C₁₋₆ alkyl” means C₁₋₆ alkyl substituted by one or more, preferably one hydroxy group(s).

The term “halo C₁₋₆ alkyl” means C₁₋₆ alkyl substituted by one or more same or different halogen atoms.

The term "C₁₋₂ alkylene" means a linear saturated divalent hydrocarbon radical of one to two carbon atoms, such as methylene, ethylene.

The term "C₃₋₇ cycloalkyl", alone or in combination with other groups, means a saturated monovalent mono-cyclic hydrocarbon radical of three to seven ring carbons, e.g., cyclopropyl, cyclobutyl, cyclohexyl.

The term "C₇₋₁₀ bicycloalkyl", alone or in combination with other groups, means a saturated monovalent cyclic hydrocarbon radical of seven to ten ring carbons, having two rings, in which two or more ring carbon atoms of one ring are ring carbon atoms of the other ring, e.g., bicyclo[2.2.1]heptyl.

The term "C₁₋₆ alkoxy", alone or in combination with other groups, means the group R'-O-, wherein R' is a C₁₋₆ alkyl.

The term "halo C₁₋₆ alkoxy", alone or in combination with other groups, means C₁₋₆ alkoxy substituted by one or more, preferably one to three halogens.

The term "C₁₋₆ alkylenedioxy" means -O-C₁₋₆ alkyl-O-. Methylenedioxy or 1,2-ethylenedioxy are preferred.

The term "C₃₋₆ alkenyl", alone or in combination with other groups, means a straight-chain or branched hydrocarbon residue comprising a carbon-carbon double bond, having three to six carbon atoms, provided that the carbon atom of the attachment point of the C₃₋₆ alkenyl to the rest of the molecule is not bonded to another carbon atom of the C₃₋₆ alkenyl by a carbon-carbon double bond. An example of C₃₋₆ alkenyl is 2-propenyl.

The term "C₃₋₆-alkynyl", alone or in combination with other groups, means a straight-chain or branched hydrocarbon residue comprising a carbon-carbon triple bond, having three to six carbon atoms, provided that the carbon atom of the attachment point of the C₃₋₆ alkynyl to the rest of the molecule is not bonded to another carbon atom of the C₃₋₆ alkynyl by a carbon-carbon triple bond. An example of C₃₋₆ alkynyl is 2-propynyl.

The term "acyl" means R-C(O)-, in which R is C₁₋₆ alkyl, halo C₁₋₆ alkyl, C₃₋₇ cycloalkyl or C₃₋₇ cycloalkyl C₁₋₆ alkyl.

The term "heterocyclyl", alone or combination with other groups, means non-aromatic mono- or bi-cyclic radicals of four to nine ring atoms in which one to three ring atoms are heteroatoms independently selected from N, O and S(O)_n (where n is an integer from 0 to 2), the remaining ring atoms being C.

The term "aryl", alone or combination with other groups, means phenyl or naphthyl.

The term "heteroaryl", alone or combination with other groups, means a monocyclic or bicyclic radical of 5 to 10 ring atoms having one to three ring heteroatoms independently selected from N, O, and S, the remaining ring atoms being C.

The term "bicyclic radicals" means radicals having two rings, in which two or more ring atoms of one ring are ring carbon atoms of the other ring.

The term, "C₁₋₆ alkylsulfonyl", "C₁₋₆ alkylsulfinyl" and "C₁₋₆ alkylthio" means C₁₋₆ alkyl-SO₂-, C₁₋₆ alkyl-SO- and C₁₋₆ alkyl-S-, respectively.

Preferred radicals for the chemical groups whose definitions are given above are those specifically exemplified in Examples.

Compounds of formula (I) can form pharmaceutically acceptable acid addition salts. Examples of such pharmaceutically acceptable salts are salts of compounds of formula (I) with physiologically compatible mineral acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, sulphurous acid or phosphoric acid; or with organic acids, such as methanesulphonic acid, p-toluenesulphonic acid, acetic acid, lactic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. The term "pharmaceutically acceptable salts" refers to such salts.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "aryl group optionally substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the aryl group is substituted with an alkyl group and situations where the aryl group is not substituted with the alkyl group.

"Pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

Compounds that have the same molecular Formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers."

Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers".

Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a

compound has an asymmetric center, for example, if a carbon atom is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn, Ingold and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

The compounds of formula (I) can possess one or more asymmetric centers. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof, as well as individual epimers and mixture thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 1992).

While the broadest definition of this invention is described before, certain compounds of formula (I) are preferred.

i) A preferred compound of the invention is a compound of formula (I), wherein A is phenyl optionally substituted by one to three substituents independently selected from the group consisting of halogen, benzyloxy, heteroaryl- C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy and halo C_{1-6} alkoxy, or A is phenyl optionally substituted by C_{1-6} alkylenedioxy. More preferably, A is phenyl substituted by one or two halogen atoms independently selected from the group consisting of chlorine and fluorine. Further more preferably, A is phenyl substituted by two halogen atoms independently selected from the group consisting of chlorine and fluorine at its 3,4 or 3,5 position.

ii) Another preferred compound of the invention is a compound of formula (I), wherein X is $-N(R^1)(R^2)$. Preferably, at least one of R^1 and R^2 is other than hydrogen. R^1 is preferably hydrogen, C_{1-6} alkyl, or hydroxy C_{2-6} alkyl, more preferably hydrogen or C_{1-6} alkyl, especially hydrogen, and R^2 is preferably C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-6} alkyl, C_{7-10} bicycloalkyl, hydroxy C_{2-6} alkyl or C_{1-6} alkoxy C_{2-6} alkyl, especially heterocyclyl, in which the cycloalkyl and the heterocyclyl of said heterocyclyl and said heterocyclyl C_{1-6} alkyl are optionally substituted by one or two substituents independently selected from the group consisting of C_{1-6} alkyl, hydroxy, heteroaryl and C_{1-6} alkoxy. When X is $-N(R^1)(R^2)$, m+n is preferably an integer of 1 or 2, especially 1, and/or R^3 , R^4 , R^5 and R^6 are preferably hydrogen.

In this group ii), preferably A is phenyl optionally substituted by one to three substituents independently selected from the group consisting of halogen, benzyloxy, heteroaryl- C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy and halo C_{1-6} alkoxy, or A is phenyl optionally substituted by C_{1-6} alkylendioxy. More preferably, A is phenyl substituted by one or two halogen atoms independently selected from the group consisting of chlorine and fluorine. Further more preferably, A is phenyl substituted by two halogen atoms independently selected from the group consisting of chlorine and fluorine at its 3,4 or 3,5 position.

iii) Another preferred compound of the invention is a compound of formula (I), wherein X is $-N(R^1)(R^2)$, and R^1 and R^2 , together with the nitrogen atom to which they are attached, form heterocyclyl optionally substituted by one to three substituents independently selected from the group consisting of R^d , and one of the ring carbon atoms of said heterocyclyl formed by R^1 and R^2 being optionally replaced with a carbonyl group; and/or

one of the ring carbon atoms of the heterocyclyl formed by R^1 and R^2 may be a ring carbon atom of another ring which is C_{3-7} cycloalkyl or heterocyclyl, one or two ring carbon atoms of said another ring being optionally replaced by a carbonyl group, and said another ring being optionally substituted by C_{1-6} alkyl.

The heterocyclyl formed by R^1 and R^2 , together with the nitrogen atom to which they are attached, is preferably a mono-cyclic radical of five or six ring atoms in which one more ring atom, in addition of the nitrogen atom, may be a heteroatom independently selected from N, O and $S(O)_n$ (where n is an integer from 0 to 2), such as piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl or 1,1-dioxo-thiomorpholinyl. The heterocyclyl formed by R^1 and R^2 , together with the nitrogen atom to which they are attached, is preferably piperidyl or pyrrolidinyl.

More preferably, the heterocyclyl formed by R^1 and R^2 , together with the nitrogen atom to which they are attached, is optionally substituted by one or two substituents independently selected from the group consisting of hydroxy, phenyl and hydroxy C_{1-6} alkyl, and/or

one of the ring carbon atoms of the heterocyclyl formed by R^1 and R^2 may be a ring carbon atom of another ring which is five or six membered mono-cyclic heterocyclyl, one or two ring carbon atoms of said another ring being optionally replaced by a carbonyl group.

In this group iii), $m+n$ is preferably an integer of 1 to 3, and R^3 , R^4 , R^5 and R^6 are hydrogen.

Moreover, in this group iii), preferably A is phenyl optionally substituted by one to three substituents independently selected from the group consisting of halogen, benzyloxy, heteroaryl- C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy and halo C_{1-6} alkoxy, or A is phenyl optionally

substituted by C₁₋₆ alkylendioxy. More preferably, A is phenyl substituted by one or two halogen atoms independently selected from the group consisting of chlorine and fluorine. Further more preferably, A is phenyl substituted by two halogen atoms independently selected from the group consisting of chlorine and fluorine at its 3,4 or 3,5 position.

iv) Another preferred compound of the invention is a compound of formula (I), which is

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(4-piperidin-1-yl-butyl)-[1,4]diazepan-5-one,

1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one,

1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one,

8-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione,

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-hydroxy-4-phenyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one,

(+/-)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-hydroxy-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one,

8-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-1-oxa-3,8-diaza-spiro[4.5]decan-2-one,

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(tetrahydro-pyran-4-ylamino)-ethyl]-[1,4]diazepan-5-one,

(S)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(2-hydroxymethyl-pyrrolidin-1-yl)-ethyl]-[1,4]diazepan-5-one, or

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(2-pyrrolidin-1-yl-ethyl)-[1,4]diazepan-5-one, or

1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-((-, cis)-3-hydroxy-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one. or

1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(3-hydroxy-4,4-dimethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one, or

(cis)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(3-hydroxy-5-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one, or

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(3-hydroxy-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one, or

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one, or

1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-(3-hydroxy-4,4-dimethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one, or

1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-(cis-3-hydroxy-5-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one, or

1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-[4-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-butyl]-[1,4]diazepan-5-one, or

(cis)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(3-hydroxy-5-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one, or

1-[(E)-3-(3-Chloro-phenyl)-acryloyl]-4-[3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one, or

1-[(E)-3-(5,6-Dichloro-pyridin-3-yl)-acryloyl]-4-[3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one, or

1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one, or

1-[(E)-3-(3-Chloro-phenyl)-acryloyl]-4-[3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one, or

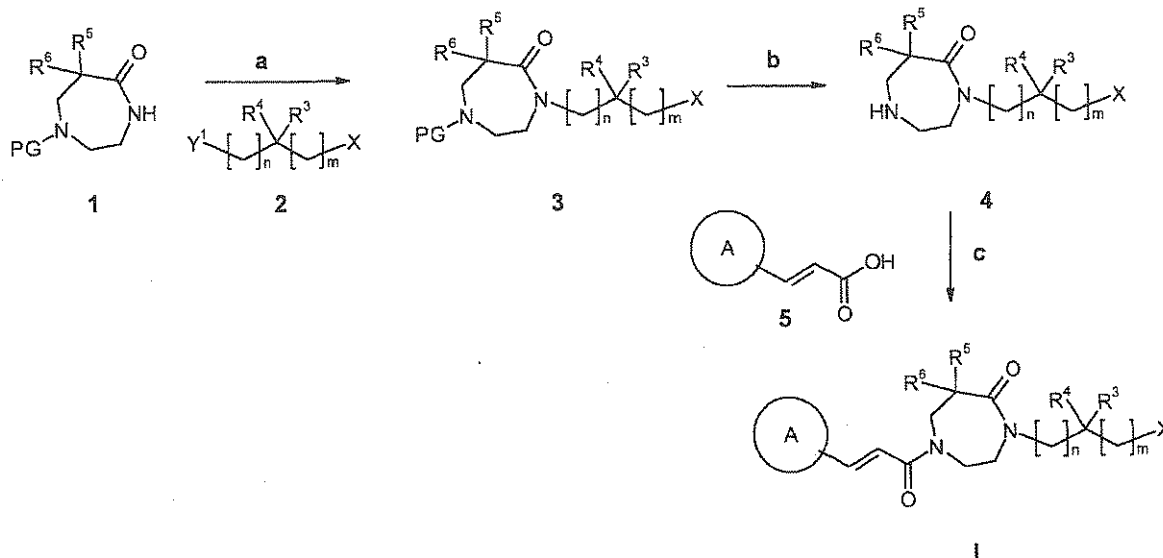
1-[(E)-3-(5,6-Dichloro-pyridin-3-yl)-acryloyl]-4-[3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one.

General Synthetic Procedures

The compounds of the present invention can be prepared, for example, by the general synthetic procedures described below. Appropriate reaction conditions for the individual reaction steps

are known to a person skilled in the art. Starting materials are either commercially available or can be prepared by methods known in the art.

Scheme 1

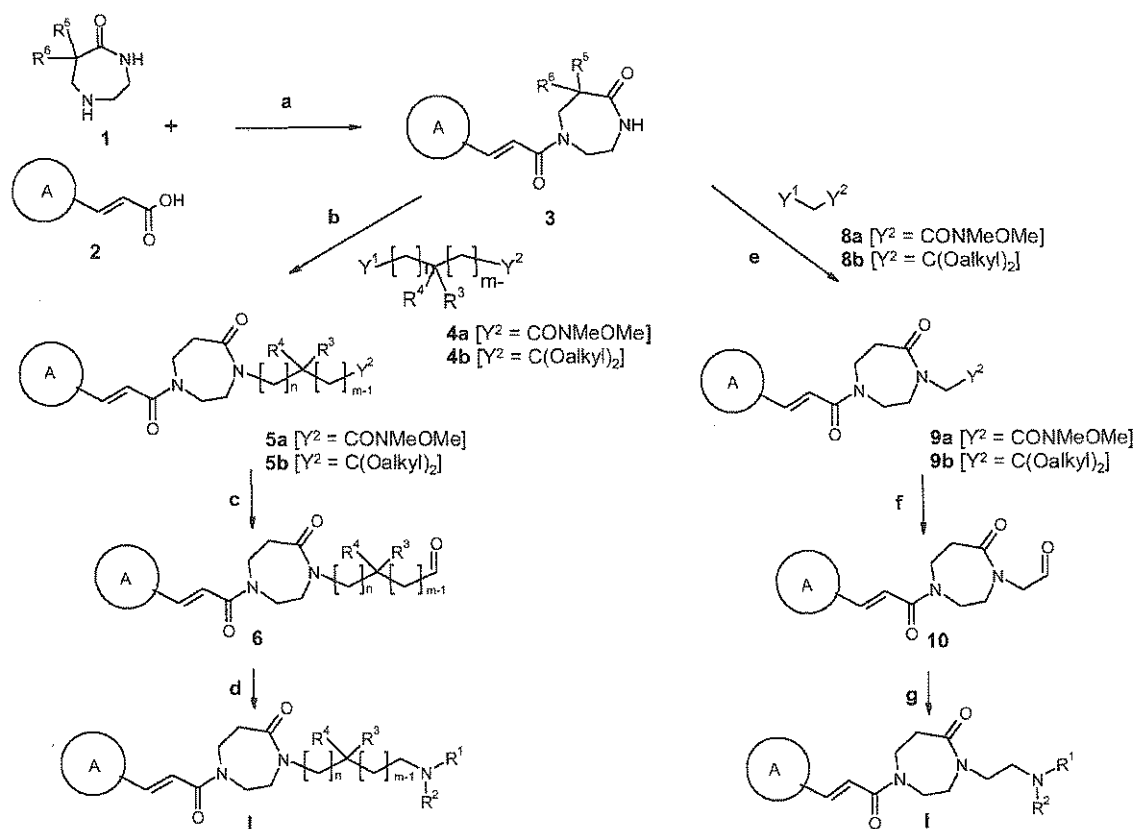


In Scheme 1, PG means protecting group, such as BOC(tert-butyloxy carbonyl), Z(benzyloxy carbonyl). Y^1 means bromide, iodide, mesylate or triflate, A, X, R^3 , R^4 , R^5 and R^6 , m and n are as defined before. The same reactions described in scheme 1 can be performed with 1 being substituted with R^5 , R^6 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} , as defined before.

Protected 5-oxo-[1,4]diazepanes 1 of scheme 1 are commercially available or can be synthesized by methods known in the art (see e.g. Dickerman, S. C.; Lindwall, H. G. Piperidone chemistry. I. Synthesis of 5-homopiperazinones. *Journal of Organic Chemistry* (1949), 14 530-6). R^5 , R^6 can be introduced on a suitably protected 5-oxo-[1,4]diazepanes through deprotonation at low temperature and alkylation or fluorination followed by a second deprotonation and alkylation or fluorination, or can also be synthesized from the corresponding piperazinone (see e.g. Design and synthesis of combinatorial scaffolds-diazepinone and homopiperazine. Sun, Chung-Ming. Department of Chemistry, National Dong-Hwa University, Hualien, Taiwan. *Letters in Drug Design & Discovery* (2005), 2(1), 48-50). Y^1 activated building block 2 is commercially available or can be synthesized as described below. The corresponding none activated precursor amines can be synthesized from acids via amide and reduction with methods known in the art, followed optionally by quaternisation. The corresponding acids are commercially available or can be synthesized from epsilon-hydroxy acids via R^3 and then R^4 alkylation followed optionally by $[CH_2]_{m-1}$ elongation. The Y^1 for the amine can then be introduced by activation of the epsilon-hydroxyl group to Y^1

(Y¹ = Cl, e.g. reaction of the alcohol with thionyl chloride in THF 0 °C to 50 °C gives the corresponding chloride). Deprotonation of protected 5-oxo-[1,4]diazepanes 1 in solvents like DMF with e.g. NaH as base at 0 °C to RT followed by reaction with building block 2 at 0 °C to 75 °C, preferably 50 °C gives the protected intermediate 3 (step a). Deprotection (e.g. for BOC protected 3, with HCl in dioxane, in CH₂Cl₂ and methanol as solvents) gives intermediate 4 as hydrochloride salt (step b) which can be coupled with all possible acids 5 to give the final compound I (step c). Acid 5 can be activated e.g. with oxalyl chloride and catalytic amount of DMF to the ciannamic acid chloride and then reacted with amine 4 in the presence of a base like triethyl amine, or CDI activation DCC, HATU coupling are possible alternatives. Acids 5 can be synthesized from the corresponding aldehydes, or from the corresponding alcohols via oxidation and subsequent Wittig reaction or subsequent Knoevenagel reaction with malonate. The compounds I with X = -N(R¹)(R²) can optionally be converted to X = -N⁺(R¹)(R²)(R³) with R³-halogenide in a solvent like methanol as described in scheme 5 shown below.

Scheme 2

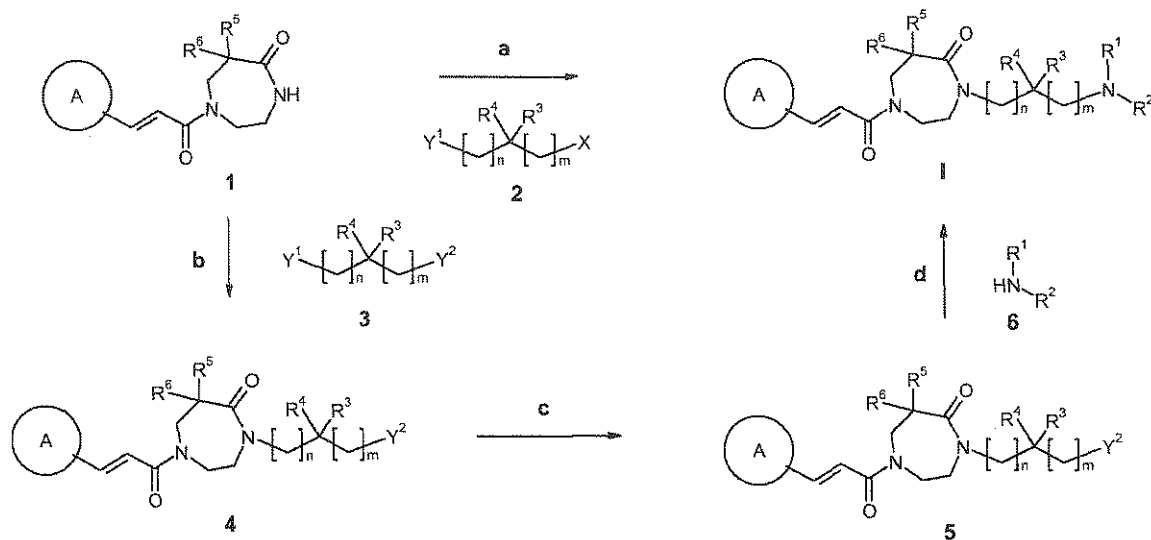


In Scheme 2, Y¹ means bromide, iodide, mesylate or triflate, A, R¹, R², R³, R⁴, R⁵ and R⁶, m and n are as defined before. The same reactions described in scheme 2 can be performed with 1 being substituted with R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³, as defined before.

The free 5-oxo-[1,4]diazepane 1 of scheme 2 is commercially available. R⁵, R⁶ can be introduced on a suitable protected 5-oxo-[1,4]diazepanes through deprotonation at low temperature and alkylation or fluorination followed by a second deprotonation and alkylation or fluorination, or can also be synthesized from the corresponding piperazinone (see e.g. Design and synthesis of combinatorial scaffolds-diazepinone and homopiperazine. Sun, Chung-Ming. Department of Chemistry, National Dong-Hwa University, Hualien, Taiwan. Letters in Drug Design & Discovery (2005), 2(1), 48-50). Acids 2 can be synthesized from the corresponding alcohols or aldehyde (via oxidation, for the alcohols) followed by Wittig reaction. Acid 2 can then be activated e.g. with oxalyl chloride and catalytic amount of DMF to the ciannamic acid chloride and then reacted with 5-oxo-[1,4]diazepanes 1 in the presence of a base like triethyl amine, alternatively CDI activation of the acid 2 or DCC or HATU coupling is possible to give intermediate 3 (step a). Y¹ activated Weinreb building blocks 4a or 8a are synthesized from the corresponding acids by treatment with N,O-dimethyl-hydroxylamine-hydrochloride with EDCI and HOBT in CH₂Cl₂ at 0 °C to room temperature. The acids are commercial available or can be synthesized from epsilon-hydroxy acids via R³, R⁴ alkylation followed optionally by [CH₂]_{m-1} elongation and activation of the hydroxyl group to Y¹. The elongation reaction can also lead to aldehydes, which can be transformed to acetals 4b. Y¹ activated acetals are also commercial available. Deprotonation of the 5-oxo-[1,4]diazepanes 3 in the presence of 4a, 4b or 8a, 8b in solvents like THF with e.g. NaH as base at 0 °C to RT and then at 50 °C to 75 °C gave intermediate 5a, 5b or 9a, 9b respectively (step b or e). In case of 3-bromo-N-methoxy-N-methyl-propionamide 4a, the first equivalent of NaH is forming the corresponding acrylamide which reacts after additional addition of NaH to the final amide 5a. An LAH- solution, preferable in THF was added to the cooled (preferable at -30 °C) suspension of amide 5a or 9a. After 5 to 15 min, the reaction was cooled (-78 °C) and quenched with acetone and acetic acid to give aldehyde 6 or 10. Aldehydes 6 and 10 are also received from acetal-protected 5b or 9b after cleavage with e.g. formic acid in a mixture of toluene water (step c or f). Reductive amination with R¹R²NH in CH₂Cl₂ with a slight excess of acetic acid and NaHB(OAc)₃ at room temperature gives the final compounds I (step d or g).

The compounds I with X = -N(R¹)(R²) can optionally be converted to X = -N⁺(R¹)(R²)(R³) with R³-halogenide in a solvent like methanol as described in scheme 5 shown below.

Scheme 3



In Scheme 3, Y¹ means bromide, iodide, mesylate or triflate, Y¹ can be additionally tosylate, Y² is chloride or ester, or when m is 1, R³, together with Y² forms epoxy group or -O-C(CH₃)₂-O-group, Y² can be additionally bromide or iodide, A, X, R¹, R², R³, R⁴, R⁵ and R⁶, m and n are as defined before. The same reactions described in scheme 3 can be performed with 1 being substituted with R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³, as defined before.

The acylated 5-oxo-[1,4]diazepanes 1 of scheme 3 (corresponds to compound 3 described in scheme 2) can be reacted in two ways to the final compound I. Either directly, where building block 1 was deprotonated e.g. with NaH or potassium tert-butyrate in DMA or THF at 0 °C to 65 °C and then reacted with the activated amine 2 (step a). Deprotonation can be carried out with potassium tert-butyrate, and THF can be also used as a solvent. Amine 2 is commercially available or can be synthesized by methods known in the art. Amines can be synthesized from acids via amide and reduction to the corresponding amines 2 with methods known in the art followed optionally by quaternisation. The corresponding acids are commercial available or can be synthesized from suitably protected epsilon-hydroxy acids via R³ and then R⁴ alkylation followed optionally by [CH₂]_{m-1} elongation or R³ modification (e.g. reduction of the ester to the alcohol and protecting it orthogonally to the epsilon-hydroxy group or alkylation of the alcohol) and activation of the deprotected epsilon-hydroxyl group to Y¹ (Y¹ = Cl, e.g. reaction of the alcohol with thionyl chloride in THF 0 °C to 50 °C gives the corresponding chloride, followed optionally by Finkelstein reaction to the corresponding Y¹ = Br or Y¹ = I). Amine 2 can also be synthesized from building block 3 when Y² is more reactive than Y¹ (e.g. Y² = Y¹ but preferred reactivity through steric control with the corresponding amine 6). Another possibility is to react the deprotonated acylated 5-oxo-[1,4]diazepanes 1 with building block 3,

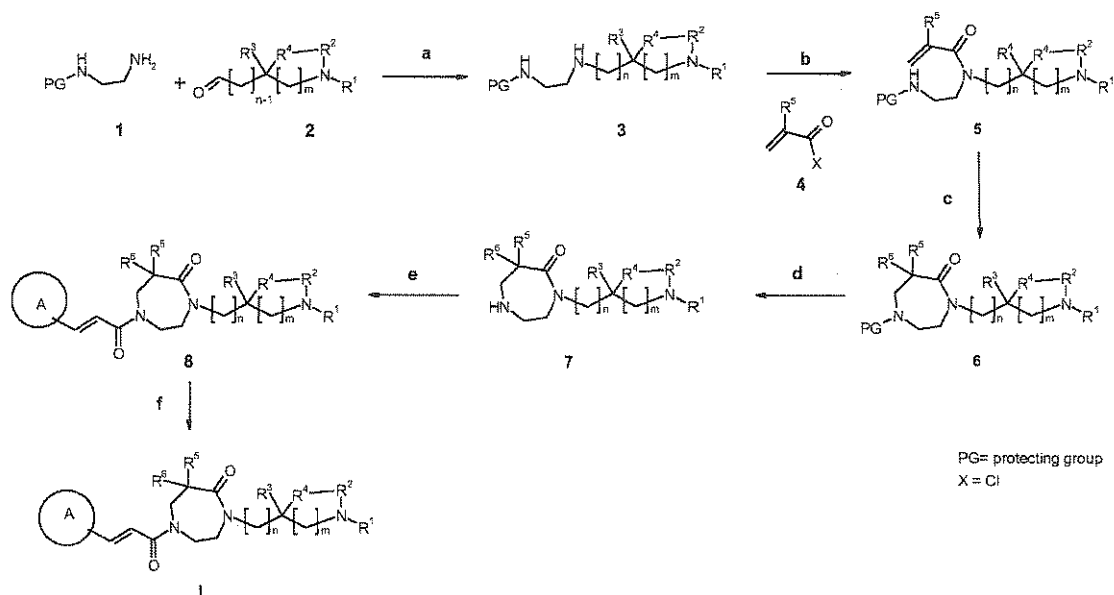
where the Y^1 and Y^2 are groups as indicated in the scheme 3 to give intermediate 4 (step b). Building block 3 is commercial available or can be synthesized from epsilon-hydroxy acids via R^3 and then R^4 alkylation followed optionally by $[CH_2]_{m-1}$ elongation, optionally by introduction of Y^2 , which is a group with a lower reactivity than Y^1 . Transformation of the epsilon hydroxyl group to Y^1 gives 3. For Y^2 = chloride, a better leaving group has to be synthesized via Finkelstein reaction (NaI in 2-butanone at 95 °C) to give compound 5 (step c). In case for Y^2 = ester, sodium borohydride reduction gives the alcohol, which is transferred to the chloride (methansulfonyl chloride / Et_3N in CH_2Cl_2) to give 5 (Y^2 = Cl) (step c). Chloride can optionally be transformed to the iodide 5 (Y^2 = I) under Finkelstein conditions. Reaction of 5 with an optionally excess of amine 6 in the presence of NaI (for Y^2 = Cl) or optionally of Et_3N , in DMF or DMA gives the final compound I (step d).

In case m is 1, R^3 , together with Y^2 forms epoxy group and Y^1 =Br or I, building block 3 is an epoxide which reacts with 5-oxo-[1,4]diazepan 1 as described above to the corresponding epoxide 5 (R^3 and Y^2 form epoxy group and m is 1). Reaction with amine 6 in ethanol or with Cs_2CO_3 in DMF or DMA at RT to 80 °C gives the final compound I, which optionally can be separated on a chiral column in the enantiomers. Epoxides 3 are commercially available or can be synthesized from the corresponding alkenes with e.g. m-chloroperbenzoic acid in dichloromethane. For the chiral synthesis, the corresponding commercially available or synthesized chiral 2,2-dimethyl-[1,3]dioxalane 3 ($-R^3-Y^2-$ is $-O-C(Me)_2-O-$) was used. Acetal 4 (R^3 and Y^2 form $-O-C(Me)_2-O-$) can be cleaved (Dowex H^+ in methanol under reflux), mono mesylated (4, $R^3=OH$, $Y^2=OMes$) and in situ cyclised to the epoxide 5 (R^3 and Y^2 form epoxy group and m is 1; e.g. mesylchlorid and excess collidine, followed by addition of NaH in DMA at 0 °C). Epoxide 5 was then reacted with amine 6 in ethanol or with Cs_2CO_3 in DMF or DMA at 0 °C to 80 °C to give the final compound I. Compound I can further be modified (e.g. $R^3=COOC_{1-6}$ alkyl) by hydrolysis with LiOH in THF/ethanol to I (e.g. $R^3=COO^- Li^+$) or reduction with $NaBH_4$ in EtOH or $NaBH_4$ in THF to I (e.g. $R^3=CH_2OH$). The amines HNR^1R^2 6 are commercial available or can be synthesized by methods known in the art. The R^4 -substitution can be introduced or manipulated on the appropriate protected amine NR^1R^2 . Hydroxy groups can be synthesized from ketones, both can be transformed either to mono or di -halogenides. The ketone group in the protected NR^1R^2 can be reacted with the metal reagent of C_{1-6} alkyl, phenyl, phenyl C_{1-3} alkyl, heteroaryl, heteroaryl C_{1-3} alkyl and heterocyclyl which are optionally substituted to give the tertiary alcohol. The tertiary alcohol can optionally be eliminated and the double bond hydrogenated to give the corresponding substituted protected NR^1R^2 . Alternatively, the ketone group in the protected NR^1R^2 can be converted to an allylic alcohol via a two step sequence of Wittig reaction to the exomethylene and subsequent allylic oxidation using a suitable reagent e.g. SeO_2 to afford the allylic alcohol (as described in J.Org. Chem. 2001, 66, 2487). The resulting allylic alcohol can then be cyclopropanated (e.g with

Et₂Zn/CH₂ClI) to afford the cyclopropanated derivatives, which in turn can be reduced catalytically (e.g. Pt₂O and hydrogen) to afford gem-dimethyl piperidines. Alternatively the cyclopropyl can be introduced directly by double alkylation of the alpha-position of the ketone group in the protected NR¹R² by deprotonation with a suitable base e.g. tBuOK, and reaction with a double nucleophile as described in Tet. Lett. 1984, 25, 5501. Subsequent reduction of the ketone with e.g. NaBH₄ affords the alcohol derivatives. Additionally, spirocyclic derivatives can be prepared from such a suitably protected ketone bearing NR¹R² as described in J. Org. Chem. 1996, 61, 22, 7650-7651 and J. Med. Chem. 1995, 38, 3772-3779. Substitution on the C₁₋₆ alkyl, phenyl, phenyl C₁₋₃ alkyl, heteroaryl, heteroaryl C₁₋₃ alkyl and heterocyclyl can be further manipulated as discussed below. Cyano groups can be synthesized from amides. R^aR^b in the NR^aR^b-substituent can be introduced through orthogonal protection strategy. C₁₋₆ alkyl, halo C₁₋₆ alkyl, hydroxy C₁₋₆ alkyl, acyl can be introduced through enolate alkylation of keton or esters followed by optionally reduction of the ketone to the corresponding methylene group. C(O)NR^aR^b groups are synthesized from acids and amines HNR^aR^b, -NR^a-C(O)-R^b from amines and acids HOOC-R^b, -NR^a-C(O)-OR^b from amines and chloro-formates Cl-C(O)-OR^b, -NR^a-C(O)-NR^b from amines and isocyanates OCN-R^b (which can also be used to generate cyclic ureas as described in WO2005/101989 (A2) where R^b bears a leaving group), -NR^a-SO₂-R^b from amines and sulfonyl chlorides ClSO₂-R^b, -NR^a-SO₂-NR^bR^c from amines and sulfamoyl chlorides which can be synthesized in acetonitrile with R^bR^cNH and sulfuryl chloride at 0 °C to 65 °C. In case R^a is an alkyl side chain, this group may be introduced with NaH, R^a halide in DMF at 0 °C to room temperature. The R^d-substitution can also be introduced or transformed on the appropriate protected amine NR¹R² with hydroxy groups: the hydroxy group and isocyanates OCN-R^b gives -OC(O)NR^aR^b, the hydroxy group and chloro-formates Cl-C(O)-OR^b gives -OC(O)OR^b, the hydroxy group can be alkylated. The hydroxy group can be mesylated and reacted with C₁₋₆ alkylthiol, which can optionally be oxidized to C₁₋₆ alkylsulfonyl- or C₁₋₆ alkylsulfinyl-substituents. The mesylate in NR¹R² can also be reacted with amines HNR^aR^b, with NH of heteroaryls or heterocyclyl in the presence of a base. Alternatively, the R^d-substitution can also be introduced or transformed on the appropriate protected amine NR¹R² bearing an ester group, which on reaction with hydrazine at reflux in EtOH affords the corresponding hydrazide which can be then condensed with alkoxyamidines to afford 1,2,4-triazoloyl derivatives. Esters can also be reacted with N-hydroxy-amidines in THF with e.g. NaH as base to [1,2,4]oxadiazols. Acids can be reacted with hydrazides to di acylated hydrazides which can be cyclised with phosphoroxo chloride in acetonitrile to [1,3,4]oxadiazol. Nitriles can be transformed to the corresponding N-hydroxy-amidines and then transformed to the [1,2,4]oxadiazols. Additionally, the appropriately protected amine NR¹R² derivatives can be prepared from the corresponding pyridine derivatives by reduction to the piperidine under catalytic hydrogenation conditions e.g. Pt₂O or Pd/C and hydrogen as described in WO2004/094371(A2) or by partial reduction of the corresponding pyridinium compounds

(prepared by alkylation of the pyridine with a suitable alkylating reagent e.g. benzylbromide) with a suitable reducing agent e.g. NaBH_4 . The resulting olefins can then be hydroborated e.g. with borane and subsequent oxidative work up to introduce hydroxy groups stereospecifically as described in Tet. Lett. 2000, 41, 5817. Piperidines can also be prepared via condensation of benzylamine, with formaldehyde and the required ketone as described in WO 01/00577A2. The resulting ketopiperidines can be further derivatised as described previously.

Scheme 4



The compounds I with $X = -\text{N}(\text{R}^1)(\text{R}^2)$ can optionally be converted to $X = -\text{N}^+(\text{R}^1)(\text{R}^2)(\text{R}^3)$ with R^3 -halogenide in a solvent like methanol as described in scheme 5 shown below.

In Scheme 4, PG means protecting group, such as BOC(tert-butyloxy carbonyl), Z(benzyloxy carbonyl). X is Cl and A, R^1 , R^2 , R^3 , R^4 , R^5 and R^6 , m and n are as defined before. The same reactions described in scheme 4 can be performed with 1 being substituted with R^5 , R^6 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} , as defined before.

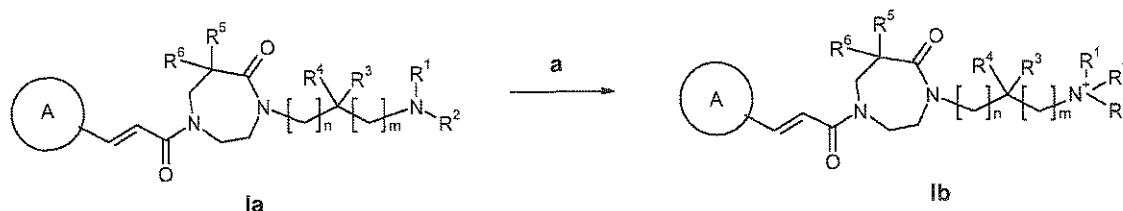
An alternative method for the preparation of 5-oxo-[1,4]diazepanes I in which R^2 and R^4 are attached to form a heterocyclyl starts from a suitably protected ethylene diamine 1 (e.g. tert-butylcarbonyl), which after reductive amination with aldehyde of the type 2 under standard conditions (CH_2Cl_2 , AcOH, $\text{NaBH}(\text{OAc})_3$) will generate amine 3 (step a in Scheme 4). In case of $n = 0$, ketone 2 (e.g. benzylpiperidone) can be reductively aminated as described before or the intermediate imine can be treated with a metallo- R^3 , to introduce R^3 . Coupling of this amine 3 with an acryloyl chloride derivative 4 (Schotten-Baumann conditions) affords acrylamide derivative 5 (step b) which can then be cyclised to the diazepan 6 by treatment with

a base in a polar solvent e.g. tBuOK in DMF (step c). For the introduction of R^6 , **6** ($R^6=H$), can be deprotonated at low temperature and then be alkylated or fluorinated, to give the corresponding **6**. This can then be elaborated as described earlier (e.g. scheme 1, compound **3** to **I**) to the desired final compounds **I** (step e and f).

This reaction sequence can also be used with amines **2**, where R^4 and R^2 do not form a heterocyclyl ring.

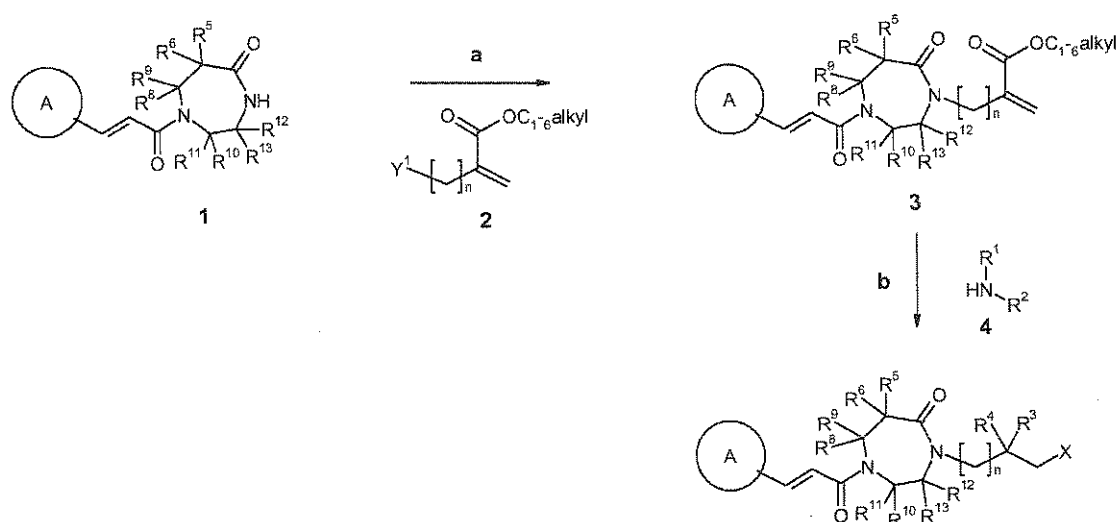
The compounds **I** with $X = -N(R^1)(R^2)$ can optionally be converted to $X = -N^+(R^1)(R^2)(R^3)$ with R^3 -halogenide in a solvent like methanol as described in scheme 5 shown below.

Scheme 5



In Scheme 5, A, R^1 , R^2 , R^3 , R^4 , R^5 and R^6 , m and n are as defined before. The same reactions described in scheme 5 can be performed with **1** being substituted with R^5 , R^6 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} , as defined before.

Scheme 6

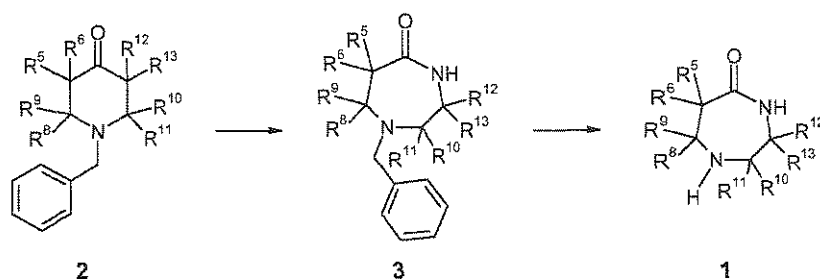


In Scheme 6, Y^1 is bromide, iodide, mesylate, tosylate or triflate, A, X, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} and n are as defined before.

In case $R^3 = \text{COOC}_{1-6}$ alkyl, $m=1$, building block 2 can be an acrylate which reacts with 5-oxo-[1,4]diazepane 1 in the presence of NaH in DMF or DMA at 0 °C to RT to give intermediate 3. Reaction with amine 4 in acetonitrile with Cs_2CO_3 at RT gives the final compound I, which optionally can be separated on a chiral column in the enantiomers. Amines 4 are commercial available or can be synthesized as described above. R^4 can be introduced at low temperatures via deprotonation and alkylation with a R^4 -halide. Compound I can further be modified (e.g. $R^3 = \text{COOC}_{1-6}$ alkyl) by hydrolysis with LiOH in THF/ethanol to I (e.g. $R^3 = \text{COO}^- \text{Li}^+$) or reduction with NaBH_4 in EtOH or LiBH_4 in THF to I (e.g. $R^3 = \text{CH}_2\text{OH}$).

[1,4]-Diazepan-5-ones intermediates of general formula 1 can be synthesized from 1-benzylpiperidin-4-ones of formula 2, as illustrated in Scheme 7. Compounds of formula 2 are either commercially available or can be synthesized according to methods described in the art (e. g., *Heterocycles* 1987, 26, 2165). Schmidt rearrangement or Beckmann rearrangement of 2 (*J. Org. Chem.* 1949, 14, 530) leads to 1-benzyl-[1,4]-diazepan-5-one 3. In the case of unsymmetrically substituted piperidin-4-ones 2, the rearrangement reaction may lead to a mixture of regioisomeric products, which can be separated e. g., by crystallization or chromatography. Finally, 1 is obtained from 3 through hydrogenation at pressures of 1–10 bar, preferably at room temperature, in a solvent such as methanol or ethanol, in the presence of a suitable catalyst such as palladium on activated charcoal.

Scheme 7

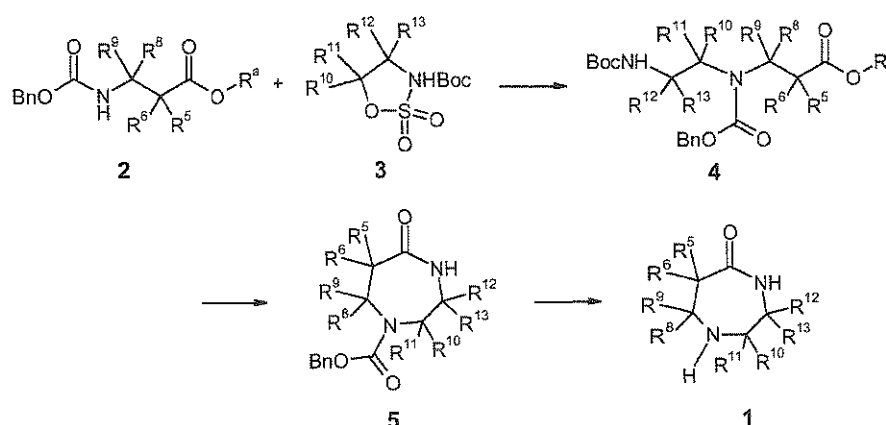


In Scheme 7, R^5 , R^6 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} are as defined before.

[1,4]-diazepan-5-ones of general formula 1 can also be synthesized as described in Scheme 8 from N-(benzyloxycarbonyl)- β -amino acid esters 2 (R^a = methyl or ethyl). Compounds of general formula 2 are either commercially available or may be synthesized according to literature methods (e. g., *Tetrahedron* 2005, 61, 8372). Reaction of 2 with appropriately substituted 2,2-dioxo[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl esters 3 (*Bioorg. Med.*

Chem. Lett. 2006, 16, 1207) in the presence of a base, e. g., potassium tert-butyrate or sodium hydride, in a solvent such as 2,2-dimethylpropan-1-ol or N,N-dimethylformamide, at temperatures between 0°C and 60°C, produces intermediate 4. Cleavage of the Boc protective group (e. g., with hydrogen chloride in 1,4-dioxane or trifluoroacetic acid in dichloromethane), followed by intramolecular ring closure (in the presence of a base such as potassium carbonate, in a solvent such as methanol or ethanol, at temperatures between 0°C and the boiling point of the solvent), furnishes the [1,4]-diazepan-5-one-1-carboxylic acid benzyl ester 5. The benzyl carbamate group of 5 is removed by hydrogenation at pressures of 1–10 bar, preferably at room temperature, in the presence of a suitable catalyst such as palladium on activated charcoal, thereby leading to 1.

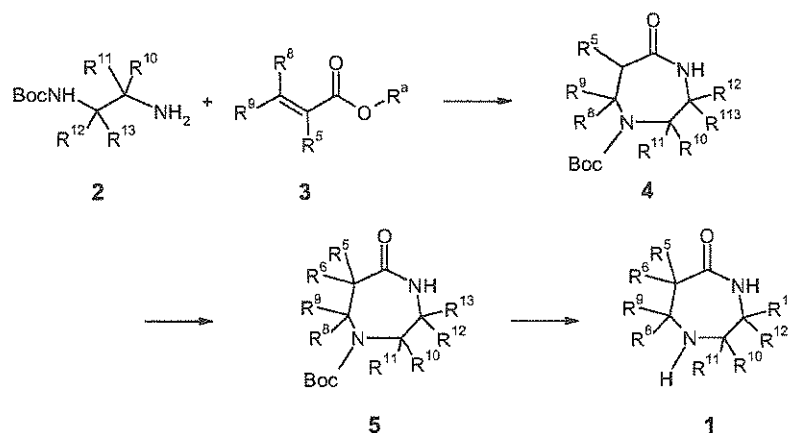
Scheme 8



In Scheme 8, R^5 , R^6 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} are as defined before.

[1,4]-diazepan-5-ones of general formula 1 can also be synthesized as described in Scheme 9 from Boc-protected 1,2-diaminoethane derivative 2. Reaction of 2 with 2-propenoic acid ester derivative 3 (R^a = methyl or ethyl) in the presence of a base, e. g., sodium hydride or potassium tert-butyrate, in a solvent such as N,N-dimethylformamide, leads to [1,4]-diazepan-5-one-1-tert-butyl ester 4. Substituents R^6 can be introduced as described in Scheme 1, leading to 5. Finally, cleavage of the tert-butyl carbamate moiety in 5 (e. g., with hydrogen chloride in 1,4-dioxane or trifluoroacetic acid in dichloromethane) leads to 1.

Scheme 9



In Scheme 8, R^5 , R^6 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} are as defined before.

Compounds of formula I can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbants or eluent). The invention embraces all of these forms.

As described above, the compounds of formula (I) are CCR-2 receptor antagonists, with some antagonist activity also at CCR-3 and CCR-5. These compounds consequently prevent migration of various leukocyte populations through the blockade of CCR-2 stimulation. They therefore can be used for the treatment and/or prevention of inflammatory and/or allergic diseases, such as peripheral arterial occlusive disease, critical limb ischemia, vulnerable atherosclerotic plaque patients, unstable angina, congestive heart failure, left ventricular hypertrophy, ischemia reperfusion injury, stroke, cardiomyopathy, restenosis, rheumatoid arthritis, diabetic nephropathy, irritable Bowel Disease, Crohns' disease, multiple sclerosis, neuropathic pain, atherothrombosis and/or burns/ulcers in Diabetes/CLI, and asthma.

Prevention and/or treatment of inflammatory diseases, particularly peripheral arterial occlusive diseases or atherothrombosis is the preferred indication.

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable excipient.

The invention likewise embraces compounds as described above for use as therapeutically active substances, especially as therapeutically active substances for the treatment and/or

prophylaxis of inflammatory and/or allergic diseases, particularly as therapeutically active substances for the treatment and/or prophylaxis of peripheral arterial occlusive disease, critical limb ischemia, vulnerable atherosclerotic plaque patients, unstable angina, congestive heart failure, left ventricular hypertrophy, ischemia reperfusion injury, stroke, cardiomyopathy, restenosis, rheumatoid arthritis, diabetic nephropathy, irritable Bowel Disease, Crohns' disease, multiple sclerosis, neuropathic pain, atherothrombosis, burns/ulcers in Diabetes/CLI, and allergy, asthma.

The invention also relates to the use of compounds as described above for the preparation of medicaments for the therapeutic and/or prophylactic treatment of inflammatory and/or allergic diseases, particularly for the therapeutic and/or prophylactic treatment of peripheral arterial occlusive disease, critical limb ischemia, vulnerable atherosclerotic plaque patients, unstable angina, congestive heart failure, left ventricular hypertrophy, ischemia reperfusion injury, stroke, cardiomyopathy, restenosis, rheumatoid arthritis, diabetic nephropathy, irritable Bowel Disease, Crohns' disease, multiple sclerosis, neuropathic pain, atherothrombosis, burns/ulcers in Diabetes/CLI, and asthma. Such medicaments comprise a compound as described above.

The invention also relates to the process and the intermediates for manufacturing the compounds of formula (I) as well as the process for manufacturing the intermediates.

CCR-2 receptor antagonistic activity by the compounds of the present invention can be demonstrated by the following assays.

Receptor binding assays

Binding assays were done with membranes from CHOK1-CCR2B-A5 cells (Euroscreen) stably overexpressing the human CCR2B.

Membranes were prepared by homogenizing the cells in 10mM Tris pH 7.4, 1mM EDTA, 0.05mM benzamidine, leupeptin 6mg/L and separating the debris at 1000g. The membranes were then isolated at 100000g in 50mM Tris pH 7.4, MgCl₂ 10mM, EGTA 1mM, glycerol 10%, benzamidine 0.05mM, leupeptine 6mg/L.

For binding, CCR2 antagonist compounds were added in various concentrations in 50mM HEPES pH 7.2, 1mM CaCl₂, 5mM MgCl₂, 0.5% BSA, 0.01% NaN₃, together with 100pM ¹²⁵I-MCP-1 (PerkinElmer, 2200Ci/mmol) to about 5 fMol CCR2 membranes and incubated for 1 hour at room temperature. For unspecific control 57.7 nM MCP-1 (R&D Systems or prepared at Roche) was added. Membranes were harvested through GF/B (glass fiber filter; PerkinElmer) plates, equilibrated with 0.3% polyethylenimine, 0.2% BSA, air dried and binding was determined by counting in a topcounter (NXT Packard). Specific

binding was defined as total binding minus nonspecific binding and typically represents about 90-95% of the total binding. Antagonist activity is indicated as inhibitor concentration required for 50% inhibition (IC_{50}) of specific binding.

Calcium mobilization assay

CHOK1-CCR2B-A5 cells (from Euroscreen) stably overexpressing the human chemokine receptor 2 isoform B were cultured in Nutrient Hams F12 medium supplemented with 5% FBS, 100U/ml penicillin, 100 µg/ml streptomycin, 400 µg/ml G418 and 5 µg/ml puromycin.

For the assay cells were grown overnight in 384-well black clear flat bottom polystyrene plates (Costar) at 37 °C at 5% CO₂. After washing with DMEM, 20mM Hepes, 2.5mM probenecid, 0.1% BSA (DMEM assay buffer) cells were loaded with 4 µM Fluo-4 in the same DMEM assay buffer for 2 hours at 30 °C. Excess dye was removed and cells were washed with DMEM assay buffer. 384-well compound plates were prepared with DMEM assay buffer / 0.5% DMSO with or without various concentrations of test compounds. Usually compounds were tested for agonist and antagonist activity.

Test compounds were added to the assay plate and agonist activity was monitored as fluorescence for 80 seconds with a FLIPR (488 nm excitation; 510-570 nm emission; Molecular Devices). After 20-30 min. of incubation at 30 °C, 20 nM MCP-1 (R&D; Roche) was added and fluorescence was monitored again for 80 seconds. Increases in intracellular calcium are reported as maximum fluorescence after agonist exposure minus basal fluorescence before exposure. Antagonist activity is indicated as inhibitor concentration required for 50% inhibition of specific calcium increases.

The compounds I of the present invention exhibit IC_{50} values in the Ca mobilisation assay of 1 nM to 10 µM, preferably 1 nM to 1.5 µM for CCR2. The following table shows measured values for some selected compounds of the present invention.

Example Number	IC50(μ M)
1	0.681
3	1.245
4	0.15
6	1.311
7	1.289
9	0.14
10	0.073
11	0.363
13	0.727
17	0.756
25	1.017
27	0.248
32	1.466
33	0.343
34	1.394
36	0.725
37	0.265
38	0.121

39	0.538
40	0.611
41	1.184
44	0.646
45	0.013
46	0.333
47	0.193
48	0.064
49	0.51
50	0.055
51	0.046
53	0.441
54	0.747
55	0.098
56	1.077
57	0.217
58	0.546
59	0.014
60	0.023

62	0.165
63	0.503
64	0.391
65	0.197
67	0.241
69	0.185
70	0.146
71	0.566
72	0.312
74	0.175
75	0.267
76	0.219
77	0.326
78	0.444
79	0.706
80	0.263
81	0.204
82	0.297
84	0.223
85	1.17
86	1.084

87	0.315
88	0.757
91	0.148
92	0.189
96	1.136
97	1.207
99	1.216
101	1.229
102	1.025
103	0.388
104	0.598
105	0.806
106	0.523
108	1.199
109	0.521
110	0.641
111	0.335
117	0.459
120	1.143
124	0.667
134	0.6

136	0.688
138	1.261
153	0.446
154	0.373
155	0.37
157	0.703
159	0.258
160	0.232
161	0.047
162	0.319
163	0.56
164	0.544
165	0.345
166	0.212
167	0.028
169	0.255
170	0.448
171	0.995
172	0.105
175	0.096
177	0.954

178	0.201
179	0.003
180	0.319
181	0.003
183	1.227
186	0.038
187	0.385
188	1.338
189	0.008
190	0.118
191	0.025
192	0.015
193	0.644
194	0.494
195	0.453
196	0.864
198	0.739
199	1.336
201	0.656
205	0.325
208	0.78

209	1.392
210	1.136
211	0.363
212	0.437
213	0.421
214	0.592
215	0.356
216	0.726
217	1.212
219	0.045
220	0.169
221	0.478
223	0.013
224	0.014
225	0.243
226	0.464
227	0.409
228	0.149
229	0.154
230	0.215
231	0.218

232	0.091
233	0.359
235	0.112
236	0.565
238	0.054
240	0.105
241	0.765
242	0.124
243	0.133
244	0.66
246	0.421
247	0.613
248	0.226
249	1.253
250	0.812
251	0.008
252	0.12
253	0.132
254	0.108
255	0.561
256	1.074

257	0.182
258	0.375
259	0.057
260	0.009
261	0.009
262	0.004
266	0.077
267	0.214
268	0.215
269	0.619
270	0.01
271	0.055
272	0.191
273	0.313
274	0.004
275	1.093
277	1.292
278	0.54
279	0.005
280	0.021
281	0.129

282	0.212
283	0.311
284	0.717
285	0.644
287	0.848
288	0.206
289	0.296
290	0.199
291	0.404
293	1.118
296	0.298
298	0.281
300	0.981
301	0.977
303	0.257
305	0.192
306	0.391
307	0.437
309	0.016
315	0.717
316	0.755

317	0.528
318	0.707
319	0.265
320	1.489
322	1.199
324	0.215
325	0.741
326	0.999
327	0.002
328	0.028
329	0.137
330	0.006
331	0.059
332	0.002
333	0.301
334	0.004
335	0.013
336	0.003
337	0.071
338	0.553
339	1.358

340	0.019
342	0.003
343	0.011
344	0.026
347	0.864
348	0.765
355	0.982
356	0.552
357	0.385
358	0.873
359	0.807
360	0.179
361	0.226
362	0.504
363	0.073
364	0.531
370	0.341
372	1.234
374	0.58
375	0.274
376	0.416

377	0.697
378	1.239
379	1.498
381	0.236
382	0.246
383	0.198
384	0.334
385	0.31
386	0.38
387	0.584
388	0.381
389	0.323
390	1.102
392	0.054
393	0.878
394	0.551
395	0.996
397	0.944
398	1.065
399	0.72
400	0.264

401	0.092
402	0.291
404	0.095
405	0.807
407	0.264
409	0.382
411	0.199
412	0.342
413	0.077
414	0.065
415	0.027
416	0.011
418	1.473
419	0.25
420	0.052
421	0.064
422	0.07
423	0.016
424	0.119
425	0.089
426	0.07

427	0.259
428	0.113
429	0.086
430	0.352
431	0.448
432	0.016
433	0.244
434	0.14
435	0.281
436	0.746
437	0.463
438	0.369
439	0.263
440	0.103
441	0.022
442	0.085
444	0.032
445	0.354
446	0.626
447	0.092
448	0.181

450	0.243
451	0.682
453	0.033
454	0.23
455	0.106
456	0.016
457	0.283
458	0.148
459	0.267
460	0.832
461	0.614
462	0.041
463	0.348
464	0.226
465	0.376
466	0.389
467	1.16
468	0.347
469	0.061
470	0.085
471	0.043

472	0.418
473	0.051
474	0.106
475	0.02
476	0.018
477	0.313
478	0.998
479	0.232
480	0.053
481	0.009
482	0.013
485	0.075
486	0.205
487	0.014
488	0.618
490	0.026
491	0.216
492	0.026
493	0.015
494	0.006
495	0.019

496	0.007
497	0.026
498	0.011
499	0.084
500	0.451
501	0.155
502	0.253
503	0.051
504	0.316

Chemotaxis assay

The chemotaxis assay was performed with THP1-4x cells (Mirzadegan et al. 2000, The Journal of Biological Chemistry 275, 33, 25562-25571) similar as described earlier (Kruszynski et al. 2005, Journal of Peptide Science, in press.).

- 5 THP1-4x were cultured in RPMI1640, 2mM L-glutamine, 0.15% Na-bicarbonat, 0.25% D-glucose, 10mM Hepes, 100mM Na-pyruvate, 50mM β -mercaptoethanol, 10% FBS. Isolated cells were labelled in culture medium with 2.5 μ g/ml calcein-AM (Molecular Probes) for 60 minutes at 37 °C. Excess calcein was removed and cells were washed in D-PBS⁺⁺, 2% FBS.
- 10 Cells (1×10^5) with or without various concentrations of test compounds were loaded on the top of 8- μ m polycarbonate filter in a 96-well-modified Boyden chamber (NeuroProbe). Beneath the filter 10 nM MCP-1 (R&D Systems; Roche) with or without test compounds or D-PBS⁺⁺, 2% FBS was placed in the corresponding well. The closed chambers were incubated for 1 hour at 37 °C, 5% CO₂. Remaining cells in
15 the top compartment were wiped off and migrated cells were measured as fluorescence in the bottom compartment in a FLUOstar (Galaxy BMG) at 485 nm excitation and 530 nm emission. Specific migration is defined as total migration towards MCP-1 minus the background migration towards D-PBS⁺⁺, 2% FBS. The ability of test compounds to antagonize CCR2-chemotaxis is reported as
20 concentration required to inhibit 50% of specific migration (IC₅₀) towards MCP-1.

The compounds I of the present invention exhibit IC₅₀ values in the chemotaxis assay of 1 nM to 10 μ M, preferably 1 nM to 250 nM for CCR2. The following table shows measured values for some selected compounds of the present invention.

Example	IC ₅₀ (nM)
Example 48	13
Example 59	77
Example 81	71
Example 160	101

25

The compounds of formula (I) and/or their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or suspensions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils. Oral administration is preferred.

The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and/or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers might, however, be required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula (I) can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in

each particular case. For adult patients a daily dosage of about 1 to 1000 mg, especially about 1 to 300 mg, comes into consideration. Depending on severity of the disease and the precise pharmacokinetic profile the compound could be administered with one or several daily dosage units, e.g. in 1 to 3 dosage units.

- 5 The pharmaceutical preparations conveniently contain about 1-500 mg, preferably 1-100 mg, of a compound of formula (I).

The following Examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

10

Examples

Abbreviations:

- AcOH = Acetic acid, BOC = t-Butyloxycarbonyl, BuLi = Butyllithium, CDI = 1,1-carbonyldiimidazole, CH₂Cl₂ = dichloromethane, DCE = 1,2-dichloroethane, DIBALH =
15 Di-*i*-butylaluminium hydride, DCC = N,N'-Dicyclohexylcarbodiimide, DMA = N,N-Dimethylacetamide, DMAP = 4-Dimethylaminopyridine, DMF = N,N-Dimethylformamide, EDCI = N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, EtOAc = Ethylacetate, EtOH = Ethanol, Et₂O = Diethylether, Et₃N = Triethylamine, eq = Equivalents, HATU = O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, HOBT = 1-Hydroxybenzo-triazole, Huenig's
20 base = *i*Pr₂NEt = N-Ethyl diisopropylamine, LAH = Lithium aluminium hydride, LDA = Lithium diisopropylamide, LiBH₄ = Lithium borohydride, MeOH = Methanol, NaI = Sodium iodide, Red-Al = Sodium bis(2-methoxyethoxy) aluminium hydride, TBDMSCl = t-Butyldimethylsilyl chloride, TFA = Trifluoroacetic acid, THF = Tetrahydrofurane,
25 quant = quantitative.

General remarks

All reactions were performed under argon.

Intermediate 1

{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-acetaldehyde

A) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one

A solution of 9.77 g (43.65 mmol) of (E)-3,4-dichlorocinnamic acid in 250 ml of CH₂Cl₂ was treated at RT with 3 drops of DMF. 4.15 ml (48.02 mmol, 1.1 eq) of oxalyl chloride in 30 ml CH₂Cl₂ were added dropwise and stirring was continued for 3 h. The solution was evaporated, redissolved in 170 ml of CH₂Cl₂, cooled (0 °C) and treated with a solution of 4.48 g (39.29 mmol, 0.9 eq) of 2,3,6,7-tetrahydro-(1H)-1,4-diazepin-5(4H)-one and 12.17 ml (87.30 mmol, 2 eq) of triethylamine in 80 ml of CH₂Cl₂. The reaction was warmed up over night to RT, then partitioned between CH₂Cl₂/MeOH 9:1 (x3)/aqueous 10 % KHSO₄, the organic phases were washed with aqueous saturated NaHCO₃ and aqueous 10% NaCl, dried over Na₂SO₄ and evaporated. The residue was dissolved and evaporated with toluene and crystallized with CH₂Cl₂/Et₂O to give 7.99 g (58%) of the title compound as white solid. MS: 312.8 (MH⁺, 2Cl).

15 B) 2-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-N-methoxy-N-methyl-acetamide

A suspension of 5.01 g (16.00 mmol) of 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one and 3.20 g (17.60 mmol) of 2-bromo-N-methoxy-N-methyl-acetamide (intermediate 1D) in 110 ml of THF was treated at 0 °C with 0.84 g (19.20 mmol) of NaH (55 % in oil) in two portions. The reaction was warmed up to RT over night and stirred for 2.5 h at 75 °C. The reaction was cooled and neutralized with cold aqueous 10 % KHSO₄ and extracted with EtOAc (3x). The organic phases were washed with aqueous saturated NaHCO₃, aqueous 10 % NaCl, dried over Na₂SO₄ evaporated and purified by flash silica gel column (CH₂Cl₂/ MeOH 99:1 to 97.5:2.5) to yield 3.49 g (53 %) of the light yellow crystalline title compound. MS: 414.1 (MH⁺, 2Cl).

25 C) {4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-acetaldehyde

7.92 ml (7.92 mmol) of a LAH-solution (1.0 M in THF) was dropped to a cooled (-30 °C) suspension of 3.28 g (7.92 mmol) of 2-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-N-methoxy-N-methyl-acetamide in 260 ml of THF. The reaction was stirred for 5 min at -30 °C and then cooled to -78 °C. The reaction was stopped by adding first 12.8 ml (174.24 mmol) of acetone and afterwards 0.9 mL (15.84 mmol) of

acetic acid. The reaction was then powered to an aqueous 10% KHSO₄ solution and extracted with ether (3x), the organic phase was dried over Na₂SO₄ evaporated dissolved in toluene and evaporated (3x) to yield 2.12 g (75%) of the title compound as light yellow foam. MS: 355.0 (MH⁺, 2Cl).

- 5 2-Bromo-N-methoxy-N-methyl-acetamide used in intermediate 1B was synthesized as follows:

D) 2-Bromo-N-methoxy-N-methyl-acetamide

- A solution of 13.90 g (100 mmol) of bromoacetic acid in 1.3 l CH₂Cl₂ was treated with 15.61 g (160 mmol) of N,O-dimethyl-hydroxylamine hydrochloride, 17.63 ml (160
10 mmol) of N-methylmorpholine and at 0 °C with 24.92 g (130 mmol) of EDCI and 3.07 g (20 mmol) of HOBT. The cooling bath was allowed to come to RT and after 3.5 h the reaction was extracted with aqueous 10 % KHSO₄/Et₂O (3x). The organic phases were washed with aqueous saturated NaHCO₃, 10 % NaCl and dried over Na₂SO₄ to yield after careful evaporation of the solvent 11.85 g (65%) of the title compound as a light yellow
15 liquid. MS: 181.1 (M⁺, 1Br).

Intermediate 2

3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propionaldehyde

A) 3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-N-methoxy-N-methyl-propionamide

- 20 A suspension of 10.02 g (32.00 mmol) of 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 1A)) and 6.27 g (32.00 mmol) of 3-bromo-N-methoxy-N-methyl-propionamide (intermediate 2C)) in 225 ml of THF was treated at 0 °C with 1.54 g (35.20 mmol) of NaH (55 % in oil) in two portions. The suspension was stirred 4 h at RT, cooled and treated again at 0 °C with 1.54 g (35.20 mmol) of NaH (55
25 % in oil) in two portions. The reaction was warmed up to RT over night, treated a third time at 0 °C with 1.54 g (35.20 mmol) of NaH (55 % in oil) in two portions and stirred for 30 min at 50 °C. After 20h at RT, the reaction was neutralized with cold aqueous 10 % KHSO₄ and extracted with EtOAc (3x). The organic phases were washed with aqueous saturated NaHCO₃, aqueous 10 % NaCl, dried over Na₂SO₄ evaporated and purified by
30 flash silica gel column (CH₂Cl₂/ MeOH 99:1 to 97.5:2.5) to yield 8.97 g (65 %) of the title compound as an off-white foam. MS: 428.2 (MH⁺, 2Cl).

B) 3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propionaldehyde

In analogy to the procedure described in intermediate 1C, 3-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-N-methoxy-N-methyl-propionamide gave
5 the title compound as white solid. MS: 368.9 (MH⁺, 2Cl).

3-Bromo-N-methoxy-N-methyl-propionamide used in intermediate 2A] was synthesized as follows:

C) 3-Bromo-N-methoxy-N-methyl-propionamide

In analogy to the procedure described in intermediate 1D, 3-bromopropionic acid gave
10 the title compound as a light yellow liquid. MS: 195.9 (MH⁺, 1Br).

Intermediate 3

{4-[(E)-3-(3-Chloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-acetaldehyde

A) 1-[(E)-3-(3-Chloro-phenyl)-acryloyl]-[1,4]diazepan-5-one

In analogy to the procedure described in intermediate 1A, (E)- 3-chlorocinnamic acid
15 and 2,3,6,7-tetrahydro-(1H)-1,4-diazepin-5(4H)-one gave the title compound as a white solid. MS: 278.9 (MH⁺, 1Cl).

B) 1-[(E)-3-(3-Chloro-phenyl)-acryloyl]-4-(2,2-diethoxy-ethyl)-[1,4]diazepan-5-one

A solution of 5.02 g (18.00 mmol) of 1-[(E)-3-(3-chloro-phenyl)-acryloyl]-
[1,4]diazepan-5-one in 140 ml of DMA was treated at RT with 0.86 g (19.80 mmol) of
20 NaH (55 % in oil) in four portions. After 1 h 3.72 ml (21.60 mmol) of 2-bromo-1,1-diethoxy-ethane were added over 30 min. The reaction was stirred over night and heated for 1 h at 75 °C. The reaction was cooled and neutralized with cold aqueous saturated NaHCO₃ and extracted with Et₂O (3x). The organic phases were washed with aqueous saturated NaHCO₃, aqueous 10 % NaCl, dried over Na₂SO₄ evaporated and purified by
25 flash silica gel column (CH₂Cl₂/ MeOH 99:1 to 98:2) to yield 1.87 g (26%) of the title compound as a yellow viscous oil. MS: 395.4 (MH⁺, Cl).

C) 4-[(E)-3-(3-Chloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl]-acetaldehyde

A solution of 1.00 g (2.53 mmol) of 1-[(E)-3-(3-chloro-phenyl)-acryloyl]-4-(2,2-diethoxy-ethyl)-[1,4]diazepan-5-one in 10 ml of toluene was treated at RT with 5.22 ml formic acid and 1.5 ml water. The reaction was stirred for 1.5 h, evaporated and
5 neutralized with aqueous saturated NaHCO_3 and extracted with Et_2O (3x). The organic phases were washed with aqueous 10 % NaCl, dried over Na_2SO_4 evaporated and purified by flash silica gel column (EtOAc) to yield 0.37 g (45%) of the title compound as off-white foam. MS: 321.3 (MH^+ , Cl).

Intermediate 4

10 4-(3-Piperidin-1-yl-propyl)-[1,4]diazepan-5-one-dihydrochloride

A) 5-Oxo-4-(3-piperidin-1-yl-propyl)-[1,4]diazepane-1-carboxylic acid tert-butyl ester

A solution of 8.52 g (39.75 mmol) of 5-oxo-[1,4]diazepane-1-carboxylic acid tert-butyl ester in 200 ml of DMA was treated at 0 °C with 2.60 g (59.62 mmol) of NaH (55 % in
15 oil) in small portions. The reaction was stirred 1 h at this temperature, then the free 1-(3-chloropropyl)piperidine in 200 ml toluene was dropped in (49.62 g (250.42 mmol, 6.3 eq.) 1-(3-chloropropyl)piperidine hydrochloride were dissolved in 262 ml of 1N NaOH and extracted with toluene (200 ml). The organic phase was dried over Na_2SO_4 . The reaction was warmed up to RT and stirred over night. After 2 h at 50 °C and cooling to
20 RT, the reaction was neutralized with water (50ml), evaporated and then dissolved in aqueous saturated $\text{NaHCO}_3/\text{Et}_2\text{O}$. After reextraction with Et_2O , the organic phase was dried (Na_2SO_4), evaporated and crystallized from pentane to yield 12.08 g (90 %) of the title compound as white crystals. MS: 340.2 (MH^+).

B) 4-(3-Piperidin-1-yl-propyl)-[1,4]diazepan-5-one-dihydrochloride

25 A solution of 7.3 g (21.50 mmol) of 5-oxo-4-(3-piperidin-1-yl-propyl)-[1,4]diazepane-1-carboxylic acid tert-butyl ester was dissolved in 140 ml CH_2Cl_2 , cooled to 0 °C and treated with 54 ml (215.03 mmol) of 4M HCl in dioxane, then warmed to RT. After 3h, 40 ml of MeOH were added to dissolve the precipitation and stirring was continued over night. The solution was evaporated, dissolved in toluene and evaporated (2x) to yield 7.71 g
30 (quantitative) of the title compound as a white solid. MS: 240.1 (MH^+).

Intermediate 5

4-(2-Pyrrolidin-1-yl-ethyl)-[1,4]di-azepan-5-one-dihydrochloride

A) 5-Oxo-4-(2-pyrrolidin-1-yl-ethyl)-[1,4]diazepane-1-carboxylic acid tert-butyl ester

In analogy to the procedure described in intermediate 4A, 5-oxo-[1,4]diazepane-1-carboxylic acid tert-butyl ester and 1-(2-chloro-ethyl)-pyrrolidine gave the title compound as light yellow solid. MS: 312.0 (MH⁺).

B) 4-(2-Pyrrolidin-1-yl-ethyl)-[1,4]di-azepan-5-one-dihydrochloride

In analogy to the procedure described in intermediate 4B, 5-oxo-4-(2-pyrrolidin-1-yl-ethyl)-[1,4]diazepane-1-carboxylic acid tert-butyl ester gave the title compound as off-white powder.

MS: 212.1 (MH⁺).

Intermediate 6

6-Fluoro-3-piperidin-4-yl-1H-indole

Prepared following the protocol published in Eur. J. Med. Chem. 1987, 22, 33-43.

Intermediate 7

1-Piperidin-4-yl-imidazolidin-2-one

Prepared following the protocol published in WO2005/101989 (A2)

Intermediate 8

4-(5-Methyl-4H-[1,2,4]triazol-3-yl)-piperidine hydrochloride

A) 4-(5-Methyl-4H-[1,2,4]triazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester

4-Hydrazinocarbonyl-piperidine-1-carboxylic acid tert-butyl ester (1.19 g, 5 mmol) was mixed with ethylacetimidate hydrochloride (0.91 g, 7 mmol) in DMF (5 ml) and Et₃N (2 ml, 15 mmol) was added. The reaction was stirred for 1h after which time the DMF was evaporated, the residue redissolved in AcOH and 0.5 g of ammonium acetate added and the reaction heated to 100 °C for a further 3h. The reaction was then concentrated, redissolved in CH₂Cl₂, washed with NaHCO₃, dried (Na₂SO₄) and concentrated. The

residue was purified by flash column chromatography (CH₂Cl₂:MeOH 1:0-9:1) to afford the title product (0.14g, 10%) as a colourless gum. MS: 267.4 (MH⁺)

B) 4-(5-Methyl-4H-[1,2,4]triazol-3-yl)-piperidine hydrochloride

- 4-(5-Methyl-4H-[1,2,4]triazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester (0.12g, 0.5 mmol) was dissolved in a solution of HCl in 1,4-dioxane (5 ml, 4 M), stirred for 2h and then concentrated to afford the title product (0.1g, quant) as a yellow solid. ¹H NMR (300 MHz, MeOD) δ 2.09–2.20 (2H, m), 2.36–2.40 (2H, m), 2.74 (3H, s), 3.22–3.33 (2H, m), 3.41–3.60 (3H, m).

Intermediate 9

- 10 1,3,8-Triaza-spiro[4.5]decan-4-one

Prepared following the protocol published in J. Med. Chem. 1998, 41, 25, 5084-5093.

Intermediate 10

4-Hydroxy-piperidine-4-carboxylic acid amide

Prepared following the protocol published in WO2005/110416 (A2).

- 15 Intermediate 11

1,3,8-Triaza-spiro[4.5]decane-2,4-dione

Prepared according to the procedure published in J. Org. Chem. 1996, 61, 22, 7650-7651.

Intermediate 12

4-(1H-Pyrazol-3-yl)-piperidine

- 20 Prepared according to the procedure published in WO2004/094371(A2).

Intermediate 13

trans-4-Amino-1-pyridin-2-yl-cyclohexanol

Prepared according to the procedure published in WO2005/060665(A2).

Intermediate 14

1-Oxa-3,8-diaza-spiro[4.5]decan-2-one

Prepared according to the procedure published in J. Med. Chem. 1995, 38, 3772-3779.

Intermediate 15

5 4-Oxazol-2-yl-piperidin-4-ol hydrochloride

A) 4-Hydroxy-4-oxazol-2-yl-piperidine-1-carboxylic acid tert-butyl ester

To a solution of oxazole (1g, 14 mmol) in anhydrous THF (10 ml) was added borane.
THF complex (14 ml, 1M in THF, 14 mmol) and the mixture stirred for 1h, after which
time the reaction was cooled to -78°C and nBuLi (9 ml, 1.6 M in hexanes, 14 mmol)
10 added dropwise and the reaction stirred for a further 1h. A solution of Boc-piperidone
(3.2g, 16 mmol) in THF (10 ml) is then added, the reaction stirred for a further 4h at -78
°C before allowing the reaction to reach room temperature overnight. The solvent is then
evaporated, the residue redissolved in EtOAc, washed with saturated ammonium chloride
solution, dried (Na₂SO₄) and concentrated. Purification by flash column
15 chromatography (EtOAc:Heptane 3:7) affords the title product (1.9g, 44%) as a
colourless gum, contaminated with an unknown byproduct. MS: 269.2 (MH⁺)

B) 4-Hydroxy-4-oxazol-2-yl-piperidine-1-carboxylic acid tert-butyl ester (0.1g, 0.4
mmol) was dissolved in a solution of HCl in dioxane (5 ml, 4 M in dioxane) and stirred
for 1h. The reaction was then concentrated to dryness to afford the title product (0.08g,
20 quant) as white solid. MS: 169.1 (MH⁺)

Intermediate 16

4-Methyl-piperidin-4-ol

Prepared according to the procedure published in J. Med. Chem. 1965, 8, 766-776.

Intermediate 17

2,8-Diaza-spiro[4.5]decane-1,3-dione

Prepared according to the procedure published in J. Med. Chem. 1995, 38, 3772-3779.

Intermediate 18

5 2,8-Diaza-spiro[4.5]decan-3-one

Prepared according to the procedure published in J. Med. Chem. 1995, 38, 3772-3779.

Intermediate 19

4-Hydroxy-piperidine-4-carboxylic acid amide

Prepared according to the procedure published in WO2004/043925(A2)

10

Intermediate 20

(±)-cis-(3-Methoxy-tetrahydro-pyran-4-yl) -amine

A slurry of 3-methoxy-tetrahydro-pyran-4-one (0.4g, 3 mmol-described in WO03/093266(A1)), ammonium formate (1.9g, 30 mmol), 10% palladium on charcoal (1g) in water:MeOH (1:5, 6 ml) was stirred overnight after which time it was filtered
15 through Hyflo, the mixture concentrated to remove the MeOH, the residue taken up in Et₂O, dried (Na₂SO₄) and concentrated to afford the title product (0.2 g, 49%) as a yellow oil (contaminated by 10-20% of the trans isomer). ¹H NMR (300 MHz, CDCl₃) (cis isomer) δ 1.60-1.80 (2H, m), 2.95-3.00 (1H, m), 3.22-3.43 (5H, m), 3.82-3.95 (1H, m), 4.01-4.13 (1H, m).

20

Intermediate 21

(2S,4R)-4-hydroxy-2-hydroxymethyl-pyrrolidine

Prepared according to the procedure published in WO92/03464.

Intermediate 22

5 (2S,4S)-4-hydroxy-2-hydroxymethyl-pyrrolidine

Prepared analogously to intermediate 21 from cis-4-hydroxy-L-proline.

Intermediate 23

(2S,3S)-3-Hydroxy-pyrrolidine-2-carboxylic acid methyl ester

Prepared from trans-3-hydroxy-L-proline (Tetrahedron Letters 2001, 42, 49, 8571-8574).

10

Intermediate 24

(2R,3S)-3-Hydroxy-2-hydroxymethyl-pyrrolidine

Prepared analogously to intermediate 21 from trans-3-hydroxy-L-proline.

Intermediate 25

(cis)-(rac)-3,4-Bis-(tert-butyl-dimethyl-silanyloxy)-piperidine

15 Prepared via (cis)-(rac)-3,4-dihydroxy-piperidine-1-carboxylic acid benzyl ester (Tetrahedron 2006, 62, 3284-3291), followed by silylation (tert-Butyl-chloro-dimethyl-silane /imidazol in DMF) and hydrogenation (10% Pd/C, H₂ in ethanol).

Intermediate 26

(trans)-(rac)-3,4-Bis-(tert-butyl-dimethyl-silanyloxy)-piperidine

20 Prepared via (trans)-(rac)-3,4-dihydroxy-piperidine-1-carboxylic acid benzyl ester (Tetrahedron 2006, 62, 3284-3291), followed by silylation (tert-Butyl-chloro-dimethyl-silane /imidazol in DMF) and hydrogenation (10% Pd/C, H₂ in ethanol).

Intermediate 27

1-Oxa-8-aza-spiro[4.5]decane trifluoroacetate

Prepared analogously to Bioorganic & Medicinal Chemistry Letters (2002), 12(13), 1759-1762.

5

Intermediate 28

4-[1,2,4]Triazol-1-yl-piperidine hydrochloride

Prepared according to the procedure published in WO2004094371.

Intermediate 29

N-Piperidin-4-yl-methanesulfonamide hydrochloride

10 Prepared according to the procedure published in US2005043298

Intermediate 30

(rac)-(3-Methyl-piperidin-3-yl)-methanol hydrochloride

A) (rac)-3-Methyl-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester

15 A solution of 2.42 ml (2.0 M in THF/n-heptane/ethylbenzene, 5.55 mmol) LDA in 10 ml THF was treated slowly at -78 °C with 2.00 g (7.77 mmol) ethyl 1-BOC-3-piperidinecarboxylate in 7 ml THF. After 30 min at -78 °C, a solution of 2.42 ml (38.86 mmol) iodomethane was added. Over night, the solution was naturally warmed to RT, poured on aqueous 10% KHSO₄ solution and extracted with ether (3x). The organic phase was dried (Na₂SO₄) and evaporated to give 2.81 g of a mixture containing 40% of
20 the desired compound and 60% of starting material.

Repetition of the procedure above gave 2.81 g (quant.) of crude title compound containing ca 10% of starting material. MS: 272.3 (MH⁺).

B) (rac)-3-Hydroxymethyl-3-methyl-piperidine-1-carboxylic acid tert-butyl ester

25 6.14 ml (1.2 M in toluene, 7.37 mmol) of DIBALH was dropped to a dry ice cooled (-30 °C) solution of 1.00 g (3.69 mmol) crude 3-methyl-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester in 2 ml of THF. The reaction was warmed up (0 °C for 1 h), continued for 3h, cooled (-15 °C) and treated again with 0.61 ml (1.2 M in toluene, 0.74

mmol) of DIBALH. After 1h the reaction was warmed up to 0 °C and neutralized with aqueous 10% KHSO₄ solution. The mixture was extracted with ether (3x), the organic phases were washed with a aqueous 10% NaCl solution, dried (Na₂SO₄) and evaporated to give after flash silica gel column (n-heptane/EtOAc 9:1) 0.61 g (73%) of the title
5 compound as yellow oil. MS: 230.0 (MH⁺).

C) (rac)-(3-Methyl-piperidin-3-yl)-methanol hydrochloride

A solution of 0.20 g (0.87 mmol) of (rac)-3-hydroxymethyl-3-methyl-piperidine-1-carboxylic acid tert-butyl ester was dissolved in 5 ml of CH₂Cl₂, treated at 0 °C with a solution of HCl in dioxane (2.18 ml, 4 M in dioxane) and stirred for 2h at RT. The
10 reaction was then concentrated to dryness and re-evaporated with toluene to afford the title product (0.17 g, quant.) as white solid. MS: 130.1 (MH⁺)

Intermediate 31

(rac)-3-Methoxymethyl-3-methyl-piperidine hydrochloride

A) (rac)-3-Methoxymethyl-3-methyl-piperidine-1-carboxylic acid tert-butyl ester

15 A solution of 0.37 g (1.60 mmol) of (rac)-3-hydroxymethyl-3-methyl-piperidine-1-carboxylic acid tert-butyl ester (intermediate 30B) and 0.20 ml (3.20 mmol) of iodomethane in 15 ml of DMF was treated at 0 °C with 0.08 g (1.92 mmol) of NaH (55 % in oil). The reaction was stirred for 2 h at 0 °C, neutralized with cold aqueous 10 % KHSO₄ and extracted with Et₂O (3x). The organic phases were washed with aqueous
20 saturated NaHCO₃, aqueous 10 % NaCl, dried over Na₂SO₄ evaporated and purified by flash silica gel column (n- heptane/EtOAc 95:5) to yield 0.25 g (64%) of the title compound as colorless liquid. MS: 244.1 (MH⁺).

B) (rac)-3-Methoxymethyl-3-methyl-piperidine hydrochloride

In analogy to the procedure described for intermediate 30C, (rac)-3-methoxymethyl-3-methyl-piperidine-1-carboxylic acid tert-butyl ester gave the title compound as white
25 powder. MS: 144.0 (MH⁺).

Intermediate 32

(4-Methyl-piperidin-4-yl)-methanol trifluoro-acetate

In analogy to the procedure described for intermediate 30A to 30C, ethyl 1-BOC-4-piperidinecarboxylate gave after TFA deprotection (instead of HCl in dioxane) the title compound as colorless oil.

Intermediate 33

4-Methoxymethyl-4-methyl-piperidine hydrochloride

In analogy to the procedure described for intermediate 31A to 31B, 4-hydroxymethyl-4-methyl-piperidine-1-carboxylic acid tert-butyl ester gave the title compound as white solid.

Intermediate 34

(rac)-(2-Methyl-piperidin-2-yl)-methanol hydrochloride

In analogy to the procedure described for intermediate 30A to 30C, ethyl 1-BOC-2-piperidinecarboxylate gave the title compound as light yellow powder.

Intermediate 35

(rac)-3-Hydroxymethyl-piperidin-4-ol hydrochloride 1:1 diast. Mixture

A) (rac)-3-Hydroxymethyl-piperidin-4-ol hydrochloride 1:1 diast. Mixture

A solution of 1 g (4.52 mmol) (rac)-1-benzyl-3-hydroxymethyl-piperidin-4-ol (ca 1:1 diast mixture, Synthesis (1999), 11, 1937-1943) in 25 ml of MeOH was treated with a solution of HCl in dioxane (1.24 ml, 4 M in dioxane, 4.97 mmol) and 95 mg of Pd(OH)₂/C (20 %) and was stirred over H₂-atmosphere for 16h. After filtration, new catalyst was added (95 mg of Pd(OH)₂/C (20 %)) and stirred over H₂-atmosphere for 2 days. After filtration, the solution was evaporated under reduced pressure to yield 0.66 g (86%) of the title compound as a ca 1:1 cis/trans mixture, MS: 132.3 (MH⁺).

Intermediate 36(rac)-3-Methoxymethyl-piperidin-4-ol hydrochlorideA) (rac)-4-Methoxy-3-methoxymethyl-piperidine-1-carboxylic acid tert-butyl ester and 4-Hydroxy-3-methoxymethyl-piperidine-1-carboxylic acid tert-butyl ester

- 5 A solution of 0.61 g (2.62 mmol) of (rac)-4-hydroxy-3-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester (Bioorganic & Medicinal Chemistry Letters (2005), 15(5), 1375-1378) in 25 ml of DMF was treated at 0 °C with 0.13 g (2.88 mmol) of NaH (55 % in oil) and after 30 min slowly with 0.18 ml (2.88 mmol) of iodomethane in 14 ml of THF. The reaction was stirred for 3 h at 0 °C, neutralized with cold aqueous 10 %
- 10 KHSO₄ and extracted with Et₂O (3x). The organic phases were washed with aqueous 10 % NaCl, dried over Na₂SO₄ evaporated and purified by flash silica gel column (n-heptane/EtOAc 95:5 to 1:1) to yield 0.073 g (11%) of 4-methoxy-3-methoxymethyl-piperidine-1-carboxylic acid tert-butyl ester as light yellow oil, MS: 260.0 (MH⁺) and 0.46 g (71%) of (rac)-4-hydroxy-3-methoxymethyl-piperidine-1-carboxylic acid tert-
- 15 butyl ester as a light yellow oil containing ca 25% of (rac)-3-hydroxymethyl-4-methoxy-piperidine-1-carboxylic acid tert-butyl ester. MS: 246.1 (MH⁺).

B) (rac)-3-Methoxymethyl-piperidin-4-ol hydrochloride

- In analogy to the procedure described for intermediate 30C, (rac)-4-hydroxy-3-methoxymethyl-piperidine-1-carboxylic acid tert-butyl ester gave the title compound as
- 20 light yellow gum, containing 25% of (rac)-(4-methoxy-piperidin-3-yl)-methanol hydrochloride. MS: 146.3 (MH⁺).

Intermediate 37(rac)-4-Methoxy-3-methoxymethyl-piperidine hydrochloride

- 25 In analogy to the procedure described for intermediate 30C, (rac)-4-methoxy-3-methoxymethyl-piperidine-1-carboxylic acid tert-butyl ester (intermediate 36A) gave the title compound as light yellow gum. MS: 160.2 (MH⁺).

Intermediate 38

Piperidin-4-yl-carbamic acid methyl ester hydrochloride

A) 4-Methoxycarbonylamino-piperidine-1-carboxylic acid tert-butyl ester

A solution of 4.00 g (2.00 mmol) of 4-amino-1-BOC-piperidine and 4.18 ml (3.00 mmol) of Et₃N in 50 ml of CH₂Cl₂ was treated at 0 °C with 1.62 ml (2.10 mmol) of methyl chloroformate. The reaction was stirred for 16 h at RT, neutralized with aqueous 10 % KHSO₄ and extracted with CH₂Cl₂ (3x). The organic phases were washed with aqueous 10 % NaCl, dried over Na₂SO₄ evaporated and purified by flash silica gel column (n-heptane/EtOAc 1:1 to 1:2) to yield 3.30 g (64%) of the title compound as white solid. MS: 259.2 (MH⁺).

B) Piperidin-4-yl-carbamic acid methyl ester hydrochloride

In analogy to the procedure described for intermediate 30C, 4-methoxycarbonylamino-piperidine-1-carboxylic acid tert-butyl ester gave the title compound as white solid. MS: 158.3 (M⁺).

Intermediate 39

Methyl-piperidin-4-yl-carbamic acid methyl ester hydrochloride

A) 4-(Methoxycarbonyl-methyl-amino)-piperidine-1-carboxylic acid tert-butyl ester

A solution of 1.01 g (3.91 mmol) of 4-methoxycarbonylamino-piperidine-1-carboxylic acid tert-butyl ester (intermediate 38A) in 15 ml of DMF was treated at 0 °C with 0.26 g (5.86 mmol) of NaH (55 % in oil) and after 30 min with 1.95 ml (31.28 mmol) of iodomethane. The reaction was stirred for 16 h at RT, neutralized with cold aqueous 10 % KHSO₄ and extracted with Et₂O (3x). The organic phases were washed with aqueous 10 % NaCl, dried over Na₂SO₄ evaporated and purified by flash silica gel column (n-heptane/EtOAc 1:1) to yield 0.99 g (93%) of the title compound as colorless oil. MS: 273.1 (MH⁺).

B) Methyl-piperidin-4-yl-carbamic acid methyl ester hydrochloride

In analogy to the procedure described for intermediate 30C, 3-methoxymethyl-3-methyl-piperidine-1-carboxylic acid tert-butyl ester gave the title compound as white solid. MS: 173.0 (MH⁺).

Intermediate 40

(rac)-Piperidin-3-yl-carbamic acid methyl ester hydrochloride

A) (rac)-3-Methoxycarbonylamino-piperidine-1-carboxylic acid tert-butyl ester

5 In analogy to the procedure described for intermediate 38A, (rac)-3-amino-1-BOC-piperidine gave the title compound as off-white gum. MS: 258.9 (MH⁺).

B) (rac)-Piperidin-3-yl-carbamic acid methyl ester hydrochloride

In analogy to the procedure described for intermediate 30C, (rac)-3-methoxycarbonylamino-piperidine-1-carboxylic acid tert-butyl ester gave the title compound as off-white solid. MS: 159.2 (MH⁺).

10

Intermediate 41

Ethyl-carbamic acid piperidin-4-yl ester hydrochloride

A) 4-Ethylcarbamoxyloxy-piperidine-1-carboxylic acid tert-butyl ester

15 A solution of 1.50 g (7.45 mmol) of N-BOC-4-hydroxypiperidine in 20 ml of DMF was treated at RT with 0.74 g (7.45 mmol) of copper(I) chloride and 0.59 ml (7.45 mmol) of ethyl isocyanate. The reaction was stirred for 4 h at 0 °C and the partitioned between aqueous 10 % NaCl and Et₂O (3x). The organic phases were washed with aqueous 10 % NaCl, dried over Na₂SO₄ evaporated and purified by flash silica gel column (n-heptane/EtOAc 4:1 to 2:1) to yield 1.66 g (82%) of the title compound as light yellow oil.
20 MS: 273.1 (MH⁺).

B) Ethyl-carbamic acid piperidin-4-yl ester hydrochloride

In analogy to the procedure described for intermediate 30C, 4-ethylcarbamoxyloxy-piperidine-1-carboxylic acid tert-butyl ester gave the title compound as white powder. MS: 173.0 (MH⁺).

Intermediate 42

4-(5-Methyl-[1,3,4]oxadiazol-2-yl)-piperidine

A) 4-(N'-Acetyl-hydrazinocarbonyl)-piperidine-1-carboxylic acid benzyl ester

- A suspension of 0.80 g (3.04 mmol) of 1-[(benzyloxy)carbonyl]-4-piperidinecarboxylic acid and 0.25 g (3.34 mmol) in 28 ml CH₂Cl₂ of N-acetyl hydrazine was treated at 0 °C with 0.73 g (3.80 mmol) of EDCI. Over night, the suspension was naturally warmed to RT, poured on aqueous 10% KHSO₄ solution and extracted with CH₂Cl₂ (3x). The organic phases were washed with aqueous saturated NaHCO₃ and aqueous 10 % NaCl, dried (Na₂SO₄) and evaporated to give 0.84 g (87%) of the title compound as white solid.
- MS: 320.2 (MH⁺).

B) 4-(5-Methyl-[1,3,4]oxadiazol-2-yl)-piperidine-1-carboxylic acid benzyl ester

- A suspension of 2.00 g (6.26 mmol) of 4-(N'-acetyl-hydrazinocarbonyl)-piperidine-1-carboxylic acid benzyl ester in 30 ml acetonitril was treated at RT with 0.69 ml (7.51 mmol) of phosphoroxchloride. The suspension was stirred 1 h at RT and the refluxed for 2 h, evaporated, dissolved in CH₂Cl₂ and neutralized with aqueous saturated NaHCO₃ solution. The aqueous phase was extracted with CH₂Cl₂ (2x). The organic phase was dried (Na₂SO₄) and and evaporated to give after flash silica gel column (EtOAc) 1.69 g (89%) of the title compound as light yellow oil. MS: 302.1 (MH⁺).

C) 4-(5-Methyl-[1,3,4]oxadiazol-2-yl)-piperidine

- A suspension of 100 mg (0.33 mmol) of 4-(5-methyl-[1,3,4]oxadiazol-2-yl)-piperidine-1-carboxylic acid benzyl ester in 5 ml EtOAc and 10 mg Pd/C 10% was hydrogenated (1 atm) for 1 h. The reaction was filtered (Celite) and evaporated to give 55.4 mg (99 %) of the title compound as white solid. MS: 167.9 (MH⁺).

Intermediate 43

- 4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidine hydrochloride

A) 4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidine-1-carboxylic acid tert-butyl ester

- A solution 1.30 g (17.49 mmol) of acetamide oxime in 55 ml THF was treated with 0.76 g (17.49 mmol) of NaH (55 % in oil) and the corresponding suspension stirred for 45 min at RT. 3.00 g (11.66 mmol) of ethyl 1-tert-butoxycarbonylpiperidine-4-carboxylate dissolved in 15 ml of THF was added and heated at 65 °C for 2 h. The solution was

cooled to RT, poured on aqueous saturated NH_4Cl solution and extracted with Et_2O (3x). The organic phases were washed with aqueous saturated NaHCO_3 and aqueous 10 % KHSO_4 , dried (Na_2SO_4) and evaporated to give 2.19 g (70%) of the title compound as orange liquid. MS: 268.2 (MH^+).

5 B) 4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-piperidine hydrochloride

In analogy to the procedure described for intermediate 30C, 4-(3-methyl-[1,2,4]oxadiazol-5-yl)-piperidine-1-carboxylic acid tert-butyl ester gave the title compound as off-white solid. MS: 168.1 (MH^+).

Intermediate 44

10 (rac, cis)-2-Hydroxymethyl-piperidin-4-ol hydrochloride

A) (rac, cis)-4-Hydroxy-piperidine-2-carboxylic acid methyl ester hydrochloride

A solution of 1.09 g (5.00 mmol) (1RS,5SR)-2-benzyl-6-oxa-2-aza-bicyclo[3.2.1]octan-7-one (Journal of Organic Chemistry (1996), 61(6), 2226-31) in 25 ml of MeOH was treated with a solution of HCl in dioxane (1.38 ml, 4 M in dioxane, 5.50 mmol) and 109
15 mg of $\text{Pd}(\text{OH})_2/\text{C}$ (20 %) and was stirred over H_2 -atmosphere for 2.5h. After filtration, the solution was evaporated under reduced pressure and precipitated from $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ to yield 0.81 g (83%) of the title compound as an off-white powder, MS: 160.2 (MH^+).

B) (rac, cis)-4-Hydroxy-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester

A solution of 0.70 g (4.40 mmol) (rac, cis)-4-hydroxy-piperidine-2-carboxylic acid
20 methyl ester hydrochloride and 1.01 g (4.62 mmol) di-tert-butyl-dicarbonate in 10 ml CH_2Cl_2 was slowly treated with 0.77 ml (5.50 mmol) Et_3N . The reaction was stirred for 30 min at RT, poured on ice cold aqueous 10% KHSO_4 solution and extracted with Et_2O (3x). The organic phases were washed with aqueous 10% KHSO_4 and aqueous 10 % NaCl , dried (Na_2SO_4) and evaporated to give 1.09 g (96%) of the title compound as light
25 yellow oil. MS: 259.9 (MH^+).

C) (rac, cis)-4-(tert-Butyl-dimethyl-silanyloxy)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester

A solution of 1.00 g (3.88 mmol) (rac, cis)-4-hydroxy-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester and 0.87 g (12.79 mmol) imidazole in 2.5 ml DMF was
30 cooled to 0 °C and treated with 0.64 g (7.7 mmol, 1.1 eq) TBDMSCl. After 30 min, the solution was stirred at RT for 1h. Additional 0.12 g (0.78 mmol, 1.1 eq) TBDMSCl were

added and stirred for additional 3 h. The solution was added to ice water and extracted with Et₂O (3x). The organic phases were washed with water and aqueous 10 % NaCl, dried (Na₂SO₄) and evaporated to give after flash silica gel column (n-heptane/EtOAc 1:9 to 1:4) 1.04 g (72%) of the title compound as colorless oil. MS: 374.3 (MH⁺).

5 D) (rac, cis)-4-(tert-Butyl-dimethyl-silanyloxy)-2-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester

4.46 ml (1.2 M in toluene, 5.35 mmol) of DIBALH was dropped to a dry ice cooled (-30 °C) solution of 1.00 g (2.68 mmol) (rac, cis)-4-(tert-butyl-dimethyl-silanyloxy)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester in 15 ml of THF. The
10 reaction was warmed up (0 °C for 1 h), continued for 1.5h, cooled (-15 °C) and treated again with 0.45 ml (1.2 M in toluene, 0.54 mmol) of DIBALH. After 2h at 0 °C, the reaction was neutralized with aqueous 10% KHSO₄ solution. The mixture was extracted with ether (3x), the organic phases were washed with a aqueous 10% NaCl solution, dried (Na₂SO₄) and evaporated to give 0.98 g (quantitative) of the title compound as light
15 yellow waxy solid. MS: 346.2 (MH⁺).

E) (rac, cis)-2-Hydroxymethyl-piperidin-4-ol hydrochloride

A solution of 0.16 g (0.45 mmol) of (rac, cis)-4-(tert-butyl-dimethyl-silanyloxy)-2-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester dissolved in 1 ml of MeOH was treated at 0 °C with a solution of HCl in dioxane (1.12 ml, 4 M in dioxane) and
20 stirred for 30 min at 0 °C. The reaction was then concentrated to dryness, re-evaporated with toluene and precipitated with CH₂Cl₂/Et₂O to give 0.05 g (68%) of the title product as white solid. MS: 132.3 (MH⁺)

Intermediate 45

(rac, cis)-2-Methoxymethyl-piperidin-4-ol hydrochloride

25 A) (rac, cis)-4-(tert-Butyl-dimethyl-silanyloxy)-2-methoxymethyl-piperidine-1-carboxylic acid tert-butyl ester

In analogy to the procedure described for intermediate 31A, (rac, cis)-4-(tert-butyl-dimethyl-silanyloxy)-2-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester (intermediate 44D) gave the title compound as colorless oil. MS: 360.3 (MH⁺).

30 B) (rac, cis)-2-Methoxymethyl-piperidin-4-ol hydrochloride

In analogy to the procedure described for intermediate 44E, (rac)-cis-4-(tert-butyl-dimethyl-silanyloxy)-2-methoxymethyl-piperidine-1-carboxylic acid tert-butyl ester gave after precipitation with MeOH/Et₂O the title compound as white solid. MS: 146.0 (MH⁺).

Intermediate 46

5 (rac, trans)-2-Hydroxymethyl-piperidin-4-ol hydrochloride.

A) (rac, cis)-1-Benzyl-4-hydroxy-piperidine-2-carboxylic acid methyl ester

A solution of 4.35 g (20.00 mmol) (1R,5SR)-2-benzyl-6-oxa-2-aza-bicyclo[3.2.1]octan-7-one (Journal of Organic Chemistry (1996), 61(6), 2226-31) in 100 ml of MeOH was treated at 0 °C with a solution of HCl in dioxane (5.50 ml, 4 M in dioxane, 220 mmol) and was stirred for 24h at RT. The solution was evaporated under reduced pressure, partitioned in water acidified with 0.1 N HCl / Et₂O and washed with Et₂O (2x). The aqueous phase was basified with aqueous saturated NaHCO₃ and extracted with Et₂O (3x). These organic phases were washed with 10% NaCl, dried over Na₂SO₄ and evaporated to give 4.25 g (85%) of the title compound as a viscous yellow oil, MS: 250.0 (MH⁺).

B) (rac, trans)-1-Benzyl-4-formyloxy-piperidine-2-carboxylic acid methyl ester

A solution of 1.84 ml (8.00 mmol) of di-tert-butyl azodicarboxylate in 3.1 ml of THF was slowly added (during 10 min, exothermic!) to a solution of 1.00 g (4.00 mmol) (rac, cis)-1-benzyl-4-hydroxy-piperidine-2-carboxylic acid methyl ester, 2.10 g (8.00 mmol) triphenylphosphine and 0.30 (8.00 mmol) formic acid in 11 ml THF. During the addition, the reaction was cooled to RT with a water bath. The resulting suspension was stirred at RT for 16h, then added to diluted aqueous 10% KHSO₄ and washed with Et₂O (3x). The aqueous phase was basified with NaHCO₃ and extracted with Et₂O (3x). The organic phases were washed with aqueous 10% NaCl dried over Na₂SO₄ and evaporated to give 0.93 g of crude product. Flash silica gel column (n-heptane/EtOAc 95/5) gave 0.53 g (47%) of the title compound as light yellow oil. MS: 278.0 (MH⁺).

C) (rac, trans)-1-Benzyl-2-hydroxymethyl-piperidin-4-ol

7.51 ml (1.2 M in toluene, 9.01 mmol) of DIBALH was dropped to a dry ice cooled (-30 °C) solution of 0.50 g (1.80 mmol) (rac, trans)-1-benzyl-4-formyloxy-piperidine-2-carboxylic acid methyl ester in 9 ml of THF. The reaction was warmed up (0 °C for 1 h), and stirred for 1h at this temperature, then added to diluted aqueous 10% KHSO₄ and washed with Et₂O (3x). The aqueous phase was basified with NaHCO₃, saturated with

NaCl and extracted with EtOAc (3x). The organic phase was dried over Na₂SO₄ and evaporated to give 0.34 g (85%) of the title compound as off-white solid. MS: 222.0 (MH⁺).

D) (rac, trans)-2-Hydroxymethyl-piperidin-4-ol hydrochloride

- 5 In analogy to the procedure described for intermediate 35A, (rac, trans)-1-benzyl-2-hydroxymethyl-piperidin-4-ol gave after precipitation with CH₂Cl₂/Et₂O the title compound as white powder. MS: 132.3 (MH⁺).

Intermediate 47

(rac, cis)-4-Hydroxymethyl-piperidin-3-ol hydrochloride

- 10 A) (rac, cis)-4-Hydroxymethyl-piperidin-3-ol hydrochloride

In analogy to the procedure described for intermediate 35A, (rac, cis)-1-benzyl-4-hydroxymethyl-piperidin-3-ol (Helvetica Chimica Acta, Volume 87, Number 10, 2629-2661) gave the title compound as light brown solid. MS: 132.3 (MH⁺).

Intermediate 48

- 15 (rac, trans)-4-Hydroxymethyl-piperidin-3-ol hydrochloride

A) (rac, trans)-4-Hydroxymethyl-piperidin-3-ol hydrochloride

In analogy to the procedure described for intermediate 35A, (rac, trans)-1-benzyl-4-hydroxymethyl-piperidin-3-ol (Helvetica Chimica Acta, Volume 87, Number 10, 2629-2661) gave the title compound as orange solid. MS: 132.16 (MH⁺).

- 20 Intermediate 49

(rac, cis)-4-Methoxymethyl-piperidin-3-ol hydrochloride

A) (rac, cis)-1-Benzyl-4-methoxymethyl-piperidin-3-ol, (rac, cis)-1-Benzyl-3-methoxy-piperidin-4-yl)-methanol and ((rac, cis)-1-Benzyl-3-methoxy-4-methoxymethyl-piperidine

- 25 A solution of 0.80 g (3.63 mmol) of (rac, cis)-1-benzyl-4-hydroxymethyl-piperidin-3-ol (Helvetica Chimica Acta, Volume 87, Number 10, 2629-2661) in 40 ml of THF was treated at 0 °C with 0.45 g (3.99 mmol) of potassium tert-butyrate and after 10 min with slowly with 0.25 ml (3.99 mmol) of iodomethane in 20 ml of THF. Over night, the

solution was naturally warmed to RT, partitioned between Et₂O / aqueous saturated NaHCO₃ and extracted again with Et₂O (2x). The organic phases were washed with aqueous saturated NaHCO₃, dried over Na₂SO₄ evaporated and gave after purification on a flash isolate NH₂-column (n-heptane/EtOAc 95:5 to 4:1) 0.33 g (39%) of (rac, cis)-1-benzyl-4-methoxymethyl-piperidin-3-ol as light yellow oil, MS: 236.1 (MH⁺), R_f = 0.39 on silicagel with n-heptane/EtOAc 1:1;

0.17 g (20%) of (rac, cis)-1-benzyl-3-methoxy-piperidin-4-yl)-methanol as light yellow oil, MS: 236.1 (MH⁺), R_f = 0.19 on silicagel with n-heptane/EtOAc 1:1;

and 0.09 g (10%) (rac, cis)-1-benzyl-3-methoxy-4-methoxymethyl-piperidine as light yellow oil, MS: 250.2 (MH⁺), R_f = 0.02 on silicagel with n-heptane/EtOAc 1:1.

B) (rac, cis)-4-Methoxymethyl-piperidin-3-ol hydrochloride

A solution of 0.31 g (1.39 mmol) (rac, cis)-1-benzyl-4-methoxymethyl-piperidin-3-ol in 6 ml of EtOH was treated with a solution of 1.43 ml of aqueous 1N HCl and 30 mg of Pd/C (10 %) and was stirred over H₂-atmosphere for 2 day. After filtration, the solution was evaporated, suspended in acetonitrile and evaporated again under reduced pressure to yield 0.25 g (quantitative) of the title compound as a white solid. MS: 146.3 (MH⁺).

Intermediate 50

(rac, cis)-(3-Methoxy-piperidin-4-yl)-methanol hydrochloride

A) (rac, cis)-(3-Methoxy-piperidin-4-yl)-methanol hydrochloride

In analogy to the procedure described for intermediate 49B, (rac, cis)-1-benzyl-3-methoxy-piperidin-4-yl)-methanol (intermediate 49A) gave the title compound as light yellow oil. MS: 146.3 (MH⁺).

Intermediate 51

(rac, cis)-3-Methoxy-4-methoxymethyl-piperidine hydrochloride

A) (rac, cis)-3-Methoxy-4-methoxymethyl-piperidine hydrochloride

In analogy to the procedure described for intermediate 49B, (rac, cis)-1-benzyl-3-methoxy-piperidin-4-yl)-methanol (intermediate 49A) gave the title compound as light brown oil. MS: 160.2 (MH⁺).

Intermediate 52

(rac, cis)-4-Hydroxymethyl-4-methyl-piperidin-3-ol hydrochloride

A) (rac)-1-Benzyl-4-methyl-3-oxo-piperidine-4-carboxylic acid ethyl ester

A milky solution of 7.75 g (69.02 mmol) of potassium tert-butyrate in 125 ml of THF was
5 cooled (0 °C) and treated portion wise with 10.44 g (34.00 mmol) of ethyl-N-benzyl-3-oxo-4-piperidin-carboxylate hydrochloride so the temperature did not rise over 5 °C. After 1 h at RT, the reaction was cooled (0 °C) and ad treated slowly with 5.07 ml (35.70 mmol) of iodomethane in 4 ml of THF. After 4.5 h at RT, the reaction was cooled (0 °C) and neutralized with 40 ml of aqueous saturated NH₄Cl solution. The aqueous phase was
10 extracted with Et₂O (3x). The organic phases were washed with aqueous saturated NaCl, dried over Na₂SO₄ and evaporated to give 4.97 g (53%) of the title compound as orange oil. MS: 276.1 (MH⁺).

B) (rac, cis)-1-Benzyl-4-hydroxymethyl-4-methyl-piperidin-3-ol and (rac, trans)-1-Benzyl-4-hydroxymethyl-4-methyl-piperidin-3-ol

15 24.33 ml (1.2 M in toluene, 29.20 mmol) of DIBALH was dropped to a dry ice cooled (-30 °C) solution of 2.01 g (7.30 mmol) (rac)-1-benzyl-4-methyl-3-oxo-piperidine-4-carboxylic acid ethyl ester in 37 ml of THF. Over night, the solution was naturally warmed to RT, cooled (0 °C) and treated again with 6.08 ml (1.2 M in toluene, 7.30 mmol) of DIBALH. After 4 h at RT, the reaction was neutralized with ice cooled aqueous
20 10% KHSO₄ solution. The mixture was extracted with ether (3x), the organic phases were washed with aqueous 10% KHSO₄ and aqueous 10% NaCl solution, dried (Na₂SO₄) and evaporated to give after flash silica gel column (CH₂Cl₂/MeOH 99:1 to 95:5) 0.28 g (16%) of (rac, cis)-1-benzyl-4-hydroxymethyl-4-methyl-piperidin-3-ol as a viscous orange oil, MS: 236.1 (MH⁺),

25 0.20 g (12%) of a cis/trans mixture of (rac)-1-benzyl-4-hydroxymethyl-4-methyl-piperidin-3-ol

and 0.19 g (11%) (rac, trans)-1-benzyl-4-hydroxymethyl-4-methyl-piperidin-3-ol as a viscous orange oil. MS: 236.3 (MH⁺)

C) (rac, cis)-4-Hydroxymethyl-4-methyl-piperidin-3-ol hydrochloride

In analogy to the procedure described for intermediate 49B, hydrogenation of (rac, cis)-1-benzyl-4-hydroxymethyl-4-methyl-piperidin-3-ol (intermediate 52B) in MeOH gave after 2.5 days the title compound as light yellow solid. MS: 146.1 (MH⁺).

Intermediate 53

- 5 (rac, trans)-4-Hydroxymethyl-4-methyl-piperidin-3-ol hydrochloride

A) (rac, trans)-4-Hydroxymethyl-4-methyl-piperidin-3-ol hydrochloride

In analogy to the procedure described for intermediate 35A, hydrogenation of (rac, trans)-1-benzyl-4-hydroxymethyl-4-methyl-piperidin-3-ol (intermediate 52B) in MeOH gave after 3 days the title compound as light yellow waxy solid. MS: 146.1 (MH⁺).

10

Intermediate 54

- 1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-[1,4]diazepan-5-one

A) 1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-[1,4]diazepan-5-one

- 15 In analogy to the procedure described for intermediate 1A, (E)-3-chloro-4-fluorocinnamic acid and 2,3,6,7-tetrahydro-(1H)-1,4-diazepin-5(4H)-one gave the title compound as white solid. MS: 297.2 (MH⁺, 1Cl).

Intermediate 55

- 1-[(E)-3-(3,4-Difluoro-phenyl)-acryloyl]-[1,4]diazepan-5-one

A) 1-[(E)-3-(3,4-Difluoro-phenyl)-acryloyl]-[1,4]diazepan-5-one

- 20 In analogy to the procedure described for intermediate 1A, (E)-4,4-difluorocinnamic acid and 2,3,6,7-tetrahydro-(1H)-1,4-diazepin-5(4H)-one gave the title compound as white solid. MS: 281.2 (MH⁺).

Intermediate 56

1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-((R)-2-oxiranyl-ethyl)-[1,4]diazepan-5-one

A) 1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-((R)-2-oxiranyl-ethyl)-[1,4]diazepan-5-one

In analogy to the procedure described for example 172A to 172C, 1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 54) and methanesulfonic acid 2-((R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester gave the title compound as pink oil. MS: 367.0 (MH⁺, 1Cl).

Intermediate 57

1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-(4-iodo-butyl)-[1,4]diazepan-5-one

A) 1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-[1,4]diazepan-5-one

In analogy to the procedure described for intermediate 1A, (E)-4-chloro-3-fluorocinnamic acid and 2,3,6,7-tetrahydro-(1H)-1,4-diazepin-5(4H)-one gave the title compound as white solid. MS: 297.3 (MH⁺).

B) 1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-(4-iodo-butyl)-[1,4]diazepan-5-one

In analogy to the procedure described for example 9A and 9B, 1-[(E)-3-(4-chloro-3-fluoro-phenyl)-acryloyl]-[1,4]diazepan-5-one gave the title compound as light yellow solid. MS: 478.8 (MH⁺, 1Cl).

Intermediate 58

(rac)-1-[(E)-3-(3,4-Difluoro-phenyl)-acryloyl]-4-(2-oxiranyl-ethyl)-[1,4]diazepan-5-one

A) (rac)-1-[(E)-3-(3,4-Difluoro-phenyl)-acryloyl]-4-(2-oxiranyl-ethyl)-[1,4]diazepan-5-one

In analogy to the procedure described for example 170A, 1-[(E)-3-(3,4-difluoro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 55) and (rac)-2-(2-bromo-ethyl)-oxirane (Journal of Organic Chemistry (1969), 34(12), 4060-5) gave the title compound as light yellow viscous oil. MS: 351.3 (MH⁺).

Intermediate 59

3-{4-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propionaldehyde

- 5 A) 3-{4-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propionaldehyde

In analogy to the procedure described for intermediate 2A and 2B, 1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 54) gave the title compound as colorless gum. MS: 353.2 (MH⁺, 1Cl).

Intermediate 60

- 10 3-{4-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propionaldehyde

A) 3-{4-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propionaldehyde

- 15 In analogy to the procedure described for intermediate 2A and 2B, 1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 57A) gave the title compound as white solid. MS: 353.1 (MH⁺, 1Cl).

Intermediate 61

5-Oxo-4-(3-oxo-propyl)-[1,4]diazepane-1-carboxylic acid tert-butyl ester

A) 5-Oxo-4-(3-oxo-propyl)-[1,4]diazepane-1-carboxylic acid tert-butyl ester

- 20 In analogy to the procedure described for intermediate 2A and 2B, 5-oxo-[1,4]diazepane-1-carboxylic acid tert-butyl ester gave the title compound as colorless oil. MS: 215.3 (M⁺-tert-butyl).

Intermediate 62

(rac, cis)-2-Hydroxymethyl-piperidin-3-ol

- 25 A) (rac)-3-Hydroxy-2-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester

A suspension of 5 g (31.00 mmol) of 2-hydroxymethyl-pyridin-3-ol hydrochlorid and 2.50 g 5% Rh/Alox in 100 ml AcOEt was stirred under hydrogen atmosphere 20h at 25°C

and 8 bar. The suspension was filtered and evaporated to give an yellow oil. The crude product was treated with 8.78 g (40.00 mmol) BOC₂O and 12 ml (93.00 mmol) Hunig's base in 30 ml DMF under ice cooling for 25h. An extraction (water / brine / AcOEt) and two crystallizations (AcOEt, MeCN/ CH₂Cl₂) gave 1.77 g (25%) of the title compound as a white solid. MS: 232.0 (MH⁺).

B) (rac, cis)-2-Hydroxymethyl-piperidin-3-ol hydrochlorid

0.80 g (3.46 mmol) of (rac)-3-hydroxy-2-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester in 10 ml dioxane was treated with 4M HCl / dioxane for 18h at RT to give the title compound as white solid 0.15 g (100%). MS: 132.2 (MH⁺).

10

Intermediate 63

(rac, cis)-6-Methoxymethyl-piperidin-3-ol

A) 5-Benzyloxy-4-chloro-2-methoxymethyl-pyridine

A solution of 9.30 g (172 mmol) of sodium methylate in 132 ml methanol was added drop wise to a solution of 5-benzyloxy-4-chloro-2-chloromethyl-pyridine (Australian Journal of chemistry, 1977, 30, 649) in 130 ml DMSO. The suspension was heated at 100 °C for 6 h, poured on ice, extracted with four portions of CH₃Cl. The organic phases were dried (Na₂SO₄), evaporated and distilled (Kp 0.2mm Hg, 150-152 °C) to give 12.80 g (91%) of the title compound. MS: 264.0 (MH⁺).

B) (rac, cis)-6-Methoxymethyl-piperidin-3-ol

A suspension of 1.00 g (3.79 mmol) of 5-benzyloxy-4-chloro-2-methoxymethyl-pyridine and 0.20 g 5% Rh/Alox in 25 ml methanol was stirred under hydrogen atmosphere 20h at 50 °C and 8 bar. The suspension was filtered, evaporated and purified by silica gel column (AcOEt) to give 0.55 g (99%, 84% cis- and 16% trans-isomer) of the titled compound as a light yellow oil MS: 146.3 (MH⁺).

25

Intermediate 64

(rac, cis)-2-Methoxymethyl-6-methyl-piperidin-3-ol

A) [3-(4-Methoxy-benzyloxy)-6-methyl-pyridin-2-yl]-methanol

1.39 g (10 mmol) of the commercial 3-hydroxy-6-methyl-2-pyridinemethanol in 15 ml DMF was cooled (0 °C), treated with 0.52 g (13.00 mmol) of NaH (55 % in oil) and after

30 min, with 1.35 mL (10.00 mmol) p-methoxybenzylchlorid. The suspension was stirred 1h at 0 °C and 2h at RT. The reaction mixture was diluted with CH₂Cl₂ and washed with 1M NaOH and brine. The organic layers were dried over magnesium sulfate, evaporated, purified by silica gel column (AcOEt) and crystallized (AcOEt/n-n-heptane) to give 1.55 g (60%) of the title compound as a white solid. MS: 260.0 (MH⁺).

B) 3-(4-Methoxy-benzyloxy)-2-methoxymethyl-6-methyl-pyridine

1.55 g (6.00 mmol) of [3-(4-Methoxy-benzyloxy)-6-methyl-pyridin-2-yl]-methanol in cold 10 ml THF (0 °C) was treated 30 min with 0.41 g (10.30 mmol) of NaH (55 % in oil), then 0.43 ml (6.90 mmol) of iodomethane was added and the yellow suspension stirred 1h. An extraction (water / CH₂Cl₂) and a chromatography (silica gel, AcOEt/n-n-heptane) delivered 1.41 g (86%) of the title compound as a yellow oil. MS: 274.3 (MH⁺).

C) (rac, cis)-2-Methoxymethyl-6-methyl-piperidin-3-ol

3-(4-Methoxy-benzyloxy)-2-methoxymethyl-6-methyl-pyridine was hydrogenated using the method described in intermediate 63B to give the title compound as a white solid. MS: 160.2 (MH⁺).

Intermediate 65

(rac, cis)- 6-Hydroxymethyl-piperidin-3-ol

A) (rac)-5-Hydroxy-2-methyl-piperidine-1-carboxylic acid tert-butyl ester and

(rac, cis)-5-Hydroxy-2-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester

1.50 g (9.28 mmol) of 6-Hydroxymethyl-pyridin-3-ol hydrochlorid was hydrogenated under the conditions described in intermediate 63B. The crude product was dissolved in 5 ml DMF, 5.60 ml (32.00 mmol) of Hunig's base and 3.56 g (16.00 mmol) of BOC₂O were added and the yellow solution was stirred 18h at RT. Evaporation, extraction (AcOEt / water / brine) and chromatography (silica gel, AcOEt / MeOH) gave 0.35 g (15%) (rac)-5-hydroxy-2-methyl-piperidine-1-carboxylic acid tert-butyl ester; MS: 216.4 (MH⁺)

and 0.24 g (10%) (rac, cis)-5-hydroxy-2-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester of the title compound as a light yellow oil. MS: 232.1 (MH⁺).

B) (rac, cis)- 6-Hydroxymethyl-piperidin-3-ol hydrochlorid

In analogy to intermediate 62B, (rac, cis)-5-hydroxy-2-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester gave the title compound as a light brown solid. MS: 132.0 (MH⁺).

5 Intermediate 66(rac)-6-Methyl-piperidin-3-ol

In analogy to intermediate 62B, 5-hydroxy-2-methyl-piperidine-1-carboxylic acid tert-butyl ester (intermediate 65A) gave title compound as a light brown solid. MS: 116.3 (MH⁺).

10 Intermediate 67(rac)-5-Methoxy-piperidin-2-yl)-methanol

In analogy to the procedure described for intermediate 63B, (5-methoxy-pyridin-2-yl)-methanol gave the title compound as a light yellow oil. MS: 146.3 (MH⁺).

Intermediate 6815 4-Methoxy-6-methoxymethyl-piperidin-3-ol; hydrochloride

4-Methoxy-6-methoxymethyl-pyridin-3-ol [prepared from 5-benzyloxy-4-chloro-2-methoxymethyl-pyridine (intermediate 63A) by reaction with 1) NaOMe, 2) MCPBA, 3) PdC/H₂] was hydrogenated in analogy to intermediate 63B to give the title compound as a white solid MS: 176.2 (MH⁺).

20 Intermediate 69N-(2R,4S,5R)-(5-Methoxy-2-methoxymethyl-piperidin-4-yl)-acetamide and N-(2S,4R,5S)-(5-Methoxy-2-methoxymethyl-piperidin-4-yl)-acetamide

0.60 g (2.93 mmol) of 5-Methoxy-2-methoxymethyl-pyridin-4-ylamine (prepared by treatment of the 5-methoxy-2-methoxymethyl-pyran-4-one with aqueous 25% ammonia at 100 °C) in 10 mL CH₂Cl₂ was treated at 0 °C with 0.26 mL (3.65 mmol) acetyl chloride and 1.25 mL (7.30 mmol) Hunig's base. After 20 min, the suspension was diluted with CH₂Cl₂ and washed with aqueous 10% Na₂CO₃ and brine. The organic layers were dried over magnesium sulfate and evaporated to give 0.71 g of the title compound as a yellow gum. The crude product was hydrogenated in analogy to intermediate 63B. A

chromatography (silica gel, AcOEt / MeOH) and crystallization (AcOEt/n-n-heptane) gave 0.09 g (11%) of the title compound as a white solid. MS: 217.2 (MH⁺).

Intermediate 70

(rac, trans)-6-Methyl-piperidin-3-ol

- 5 1.00 g (9.16 mmol) of 6-Methyl-pyridin-3-ol was hydrogenated under the conditions described in intermediate 63B, then chromatographed (silica gel, AcOEt / MeOH) to give 161 mg (15%) of the title compound as a white solid. MS: 116.2 (MH⁺).

Intermediate 71

(rac)-2,6-Bis-methoxymethyl-piperidin-3-ol

- 10 2.00 g (8.15 mmol) of (5-benzyloxy-6-hydroxymethyl-pyridin-2-yl)-methanol (prepared from 2,6-bis-hydroxymethyl-pyridin-3-ol by treatment with benzylbromide, K₂CO₃ in MeCN, WO 2006100305) was reacted in analogy to intermediate 64B and intermediate 64C to give 0.83 g (74%) of the title compound as a yellow oil. MS: 190.4 (MH⁺).

Intermediate 72

- 15 (rac)-2-(6-Hydroxymethyl-piperidin-3-yloxy)-acetamide

A) 2-(6-Hydroxymethyl-pyridin-3-yloxy)-acetamide

- 1.25 g (6.35 mmol) of (6-Hydroxymethyl-pyridin-3-yloxy)-acetic acid methyl ester (prepared from 6-methyl-pyridin-3-ol by reaction with: 1) Chloro-acetic acid methyl ester, 2) m-Cl-perbenzoic acid and 3) trifluoroacetic acid anhydride) was treated with 31
20 ml 7M NH₃ in MeOH for 2.5h at RT. The suspension was evaporated to give 1.19 g (100%) of the title compound as a white solid. MS: 183.3 (MH⁺).

B) (rac)-2-(6-Hydroxymethyl-piperidin-3-yloxy)-acetamide

2-(6-Hydroxymethyl-pyridin-3-yloxy)-acetamide was hydrogenated as described in intermediate 63B, to give the title compound as a yellow gum. MS: 189.4 (MH⁺).

Intermediate 73

(rac)-2-Methoxymethyl-piperidin-3-ol

In analogy to the procedure described for intermediate 64, 2-hydroxymethyl-pyridin-3-ol gave the title compound as yellow oil. MS: 146.4 (MH⁺).

5

Intermediate 74

(rac, trans)-6-Methoxymethyl-piperidin-3-ol

A) (rac, cis)-5-hydroxy-2-methoxymethyl-piperidine-1-carboxylic acid tert-butyl ester and

(rac, trans)-5-hydroxy-2-methoxymethyl-piperidine-1-carboxylic acid tert-butyl ester

- 10 In analogy to the procedure described for intermediate 65A, crude (rac)-6-methoxymethyl-piperidin-3-ol (intermediate 63B) gave after separation by silica gel column (AcOEt) 34% of the (rac, cis)-5-hydroxy-2-methoxymethyl-piperidine-1-carboxylic acid tert-butyl ester and 6% of the (rac, trans)-5-hydroxy-2-methoxymethyl-piperidine-1-carboxylic acid tert-butyl ester as a light yellow liquid. MS: 246.3 (MH⁺).

- 15 B) (rac, trans)-6-Methoxymethyl-piperidin-3-ol hydrochlorid

In analogy to the procedure described for intermediate 62B, (rac, trans)-5-hydroxy-2-methoxymethyl-piperidine-1-carboxylic acid tert-butyl ester gave the title compound as a white solid. MS: 146.4 (MH⁺).

Intermediate 75

- 20 (rac, cis)-5-Methyl-piperidin-3-ol hydrochloride

A) (rac, cis)-3-Hydroxy-5-methyl-piperidine-1-carboxylic acid tert-butyl ester and

(rac, cis)-3-Hydroxy-5-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester

- 25 A solution of 1.20 g (9.59 mmol) of 5-hydroxymethyl-pyridin-3-ol (Jensen, Henrik Helligso; Lyngbye, Laila; Jensen, Astrid; Bols, Mikael. Chemistry--A European Journal (2002), 8(5), 1218-1226) in 1.3 ml of aqueous 25% HCl and 10 ml of MeOH was hydrogenated with 0.60 g 10% Pd/C at 50 bar and 120 °C for 20h. Filtration and reaction with new catalyst with the same conditions gave crude product which was reacted with di-tert-butyl-dicarbonate in analogy to intermediate 44B. Purification by silica gel

column (n-n-heptane/iso-propanol 95:5 to 1:1) gave 0.50 g (27%) of (rac, cis)-3-hydroxy-5-methyl-piperidine-1-carboxylic acid tert-butyl ester as light yellow oil, MS: 216.2 (MH⁺)

and 0.15 g (8%) of rac-3-hydroxy-5-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester as light yellow oil. MS: 232.0 (MH⁺).

B) (rac, cis)-5-Methyl-piperidin-3-ol hydrochloride

In analogy to the procedure described for intermediate 62B, (rac, cis)-3-hydroxy-5-methyl-piperidine-1-carboxylic acid tert-butyl ester gave the title compound as a white solid. MS: 116.3 (MH⁺).

10 Intermediate 76

(rac)-5-Hydroxymethyl-piperidin-3-ol hydrochloride

A) (rac)-5-Hydroxymethyl-piperidin-3-ol hydrochloride

In analogy to the procedure described for intermediate 62B, rac-3-hydroxy-5-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester gave the title compound as orange gum. MS: 132.2 (MH⁺).

Intermediate 77

(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-3-methyl-[1,4]diazepan-5-one

A) (rac)-1-Benzyl-3-methyl-[1,4]diazepan-5-one

Sodium azide (1.58 g, 24.4 mmol) was added portionwise over 6 h to a solution of 1-benzyl-3-methylpiperidin-4-one (5.00 g, 24.4 mmol) at 0 °C, then the reaction mixture was allowed to reach room temperature over 16 h. The reaction mixture was then poured upon ice/40% aq. sodium hydroxide solution/ethyl acetate, the organic layer was washed with brine, dried (MgSO₄), and evaporated. Recrystallization in n-heptane/ethyl acetate 2:1 (60 ml) produced the title compound (2.59 g, 49%). White solid, MS: 219.3 (MH⁺).

25 B) (rac)-3-Methyl-[1,4]diazepan-5-one

A mixture of 1-benzyl-3-methyl-[1,4]diazepan-5-one (1.88 g, 8.62 mmol) and palladium (10% on activated charcoal, 188 mg) in ethanol (50 ml) was stirred at room temperature under a hydrogen atmosphere (3 bar). After 18 h, the catalyst was removed by filtration

and the filtrate evaporated to afford the title compound (1.12 g, 99%). White solid, MS: $m/e = 128$ (M^+).

C) (rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-3-methyl-[1,4]diazepan-5-one

- 5 In analogy to the procedure described in intermediate 1A, (E)-3,4-dichlorocinnamic acid and 3-methyl-[1,4]diazepan-5-one gave the title compound as a white solid. MS: 327.2 (MH^+).

Intermediate 78

(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-methyl-[1,4]diazepan-5-one

A) (rac)-7-Methyl-5-oxo-[1,4]diazepane-1-carboxylic acid benzyl ester

- 10 2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester (WO2002072584; 454 mg, 2.03 mmol) was added to a solution of 3-benzyloxycarbonylamino-butyric acid ethyl ester (450 mg, 1.69 mmol) and potassium tert-butyrate (228 mg, 2.03 mmol). The reaction mixture was stirred for 72 h at room temperature and heated at 50 °C for another 24 h. After cooling, the reaction mixture was partitioned between 10% aq. citric acid solution and ethyl acetate, the organic layer was washed with brine, dried ($MgSO_4$),
15 and evaporated. The residue was taken up in dichloromethane (10 ml), treated with trifluoroacetic acid (2.5 ml), stirred at room temperature for 45 min, then evaporated. The residue was dissolved in methanol (10 ml), then potassium carbonate (3.08 g, 22.3 mmol) was added and the reaction mixture was stirred at room temperature for 16 h.
20 After evaporation, the residue was partitioned between ethyl acetate and 1 M aq. sodium hydroxide solution. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. Chromatography (SiO_2 ; $CH_2Cl_2/MeOH/NH_4OH$ 95:5:0.25) produced the title compound (205 mg, 46%). Colorless gum, MS: 263.2 (MH^+).

B) (rac)-7-Methyl-[1,4]diazepan-5-one

- 25 A mixture of 7-methyl-5-oxo-[1,4]diazepane-1-carboxylic acid benzyl ester (201 mg, 0.77 mmol) and palladium (10% on activated charcoal, 80 mg) in ethanol (2 ml) was stirred at room temperature under a hydrogen atmosphere (3 bar). After 20 h, the catalyst was removed by filtration and the filtrate evaporated to afford the title compound (81 mg, 82%). White solid, MS: 128 (M^+).

- 30 C) (rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-methyl-[1,4]diazepan-5-one

- O-(7-Azobenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (343 mg, 0.90 mmol) was added to a solution of 3,4-dichlorocinnamic acid (130 mg, 0.60 mmol), 7-methyl-[1,4]diazepan-5-one (77 mg, 0.60 mmol), and 4-methylmorpholine (304 mg, 3.01 mmol) in N,N-dimethylformamide (1 ml). The reaction mixture was stirred for 3 h at room temperature, then partitioned between n-heptane/ethyl acetate 1:1 and water. The organic layer was washed with brine, dried (MgSO₄), and evaporated. Chromatography (SiO₂; CH₂Cl₂/MeOH/NH₄OH 95:5:0.25) produced the title compound (193 mg 98%). Colorless gum, MS: 327.1 (MH⁺).

Intermediate 79

- 10 (R)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-2-methyl-[1,4]diazepan-5-one

A) (R)-2-methyl-5-oxo-[1,4]diazepane-1-carboxylic acid benzyl ester

- In analogy to the procedure described in intermediate 78A, 3-benzyloxycarbonylamino-propanoic acid methyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester (*Bioorg. Med. Chem. Lett.* 2006, 16, 1207) gave the title compound. Colorless gum, MS: m/e = 263.1 (MH⁺).

B) (R)-2-Methyl-[1,4]diazepan-5-one

In analogy to the procedure described in intermediate 78B, (R)-2-methyl-5-oxo-[1,4]diazepane-1-carboxylic acid benzyl ester gave the title compound. Colorless gum, MS: m/e = 128 (M⁺).

- 20 C) (R)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-2-methyl-[1,4]diazepan-5-one

In analogy to the procedure described in intermediate 78C, (E)-3,4-dichlorocinnamic acid and (R)-2-methyl-[1,4]diazepan-5-one gave the title compound as a colorless gum, MS: m/e = 327.3 (MH⁺).

Intermediate 80

- 25 (rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-6-methyl-[1,4]diazepan-5-one

A) (rac)-6-Methyl-5-oxo-[1,4]diazepane-1-carboxylic acid tert-butyl ester

Sodium hydride (60% dispersion in mineral oil, 275 mg, 6.88 mmol) was added at room temperature to a solution of tert-butyl N-(2-aminoethyl)carbamate (1.00 g, 6.24 mmol), then after 30 min ethyl methacrylate (712 mg, 6.24 mmol) was added. The reaction

mixture was stirred at room temperature over 16 h, then partitioned between ethyl acetate/n-heptane 1:1 and water. The organic layer was washed with brine, dried (MgSO₄), and evaporated. Chromatography (SiO₂; ethyl acetate, then CH₂Cl₂/MeOH/NH₄OH 95:5:0.25) produced the title compound (51 mg, 4%). White solid, MS: m/e = 229.4 (MH⁺).

B) (rac)-6-Methyl-[1,4]diazepan-5-one hydrochloride

6-Methyl-5-oxo-[1,4]diazepane-1-carboxylic acid tert-butyl ester (42 mg, 0.18 mmol) was suspended in hydrogen chloride solution (4 M in 1,4-dioxane, 0.5 ml) and stirred at room temperature for 4 h, then volatile material was removed by distillation, to afford the title compound (29 mg, 96%). Colorless gum, MS: 129.1 ([M-Cl]⁺).

C) (rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-6-methyl-[1,4]diazepan-5-one

In analogy to the procedure described in intermediate 78C, (E)-3,4-dichlorocinnamic acid and 6-methyl-[1,4]diazepan-5-one hydrochloride gave the title compound as a colorless gum, MS: 327.1 (MH⁺).

15

Intermediate 81

(rac)-6-Aza-spiro[2.5]octan-4-ol hydrochloride

A) (rac)-6-Aza-spiro[2.5]octane-6-carboxylic acid tert-butyl ester

To a solution of Et₂Zn (37.5 ml, 1.1M solution in toluene, 0.04 mmol) in DCE (80 ml) at 0 °C was added chloriodomethane (5.99 ml, 0.08 mmol) under Ar. This mixture was stirred for 15 minutes before a solution of 3-hydroxy-4-methylene-piperidine-1-carboxylic acid tert-butyl ester (J.Org. Chem. 2001, 66, 2487) (4.19 g, 0.02 mmol) in DCE (10 ml) was added, after which time the reaction was stirred for 0.5h at 0 °C and then allowed to reach room temperature, stirring for a further 1h. The reaction was then quenched by addition of saturated NH₄Cl, separated, and the organic dried (Na₂SO₄) and concentrated. Purification by flash column chromatography (EtOAc:n-heptane 2:8-1:1) afforded the title product (2.4 g, 54%) as a crystalline solid. MS: 228.2 (MH⁺).

B) (rac)-6-Aza-spiro[2.5]octan-4-ol hydrochloride

Intermediate 81A (0.52 g, 2 mmol) was dissolved in 10 ml of HCl in dioxane (4M), stirred for ten minutes. The reaction was then concentrated to afford the title product (0.38 g, quant.) as a white powder. MS: 128.1 (MH⁺).

Intermediate 82**(+)-6-Aza-spiro[2.5]octan-4-ol hydrochloride**

The title compound was prepared by chiral separation of Intermediate 81A on a Chiralpak AD column (Isopropanol:n-heptane 5:95) and subsequent analogous
5 deprotection with HCl in dioxane. MS: 128.1 (MH⁺).

Intermediate 83**(-)-6-Aza-spiro[2.5]octan-4-ol hydrochloride**

The title compound was prepared by chiral separation of Intermediate 81A on a Chiralpak AD column (Isopropanol:n-heptane 5:95) and subsequent analogous
10 deprotection with HCl in dioxane. MS: 128.1 (MH⁺).

Intermediate 84**(rac)-3-Hydroxy-4,4-dimethyl-piperidine hydrochloride**A) (rac)-3-Hydroxy-4,4-dimethyl-piperidine-1-carboxylic acid tert-butyl ester

Intermediate 81A (0.43 g, 1.9 mmol) was dissolved in AcOH (7 ml) with platinum oxide
15 (0.4 g, 1.9 mmol) and stirred under hydrogen atmosphere (balloon) for 2d. The reaction was then filtered through Hyflo and concentrated to afford the title product (0.41 g, 94%) as oil. MS: 230.2 (MH⁺).

B) (rac)-3-Hydroxy-4,4-dimethyl-piperidine hydrochloride

Intermediate 84A was deprotected with HCl in dioxane to afford the title product as a
20 white powder. MS: 130.1 (MH⁺).

Intermediate 85**(+, cis)-4-Methyl-piperidin-3-ol hydrochloride**A) (rac, trans)-3-Hydroxy-4-methyl-piperidine-1-carboxylic acid tert-butyl ester

(rac, trans)-1-Benzyl-4-methyl-piperidin-3-ol (Tet. Lett. 2000, 5817) (13.0 g, 63 mmol)
25 was dissolved in MeOH with Pd(OH)₂/C (4 g) and stirred under a hydrogen atmosphere (balloon) for 16h after which time Boc₂O (13.8 g, 63 mmol) was added, the reaction

stirred for 1h, filtered through Hyflo and concentrated to afford the title product (13.3 g, 98%) as a crystalline solid. MS: 216.2 (MH⁺).

B) (rac, cis)-4-Methyl-3-(4-nitro-benzoyloxy)-piperidine-1-carboxylic acid tert-butyl ester

- 5 Intermediate 85A (6.0 g, 28 mmol) was dissolved in THF (40 ml) with PPh₃ (8.9 g, 34 mmol), 4-nitrobenzoic acid (5.7 g, 34 mmol) and cooled to 0 °C before dropwise addition of diisopropyl diazadicarboxylate (6.9 g, 34 mmol). The ice bath was removed and the reaction allowed coming to room temperature, stirring for 16h. The reaction was then directly absorbed onto silica gel and purified by flash column chromatography (EtOAc: n-heptane 2:8) to afford the title product (4.0 g, 40%) as a white solid. MS: 365.2 (MH⁺).
- 10

C) (rac, cis)-3-Hydroxy-4-methyl-piperidine-1-carboxylic acid tert-butyl ester

- Intermediate 85B (5.0 g, 14 mmol) was dissolved in MeOH (70 ml) and NaOH (4.5 ml, 6N in water, 27 mmol) was added. The reaction was stirred for 1h after which time the solvent removed under vacuum, the residue portioned between water and CH₂Cl₂ and the organic collected, dried (Na₂SO₄) and concentrated to afford the title product (2.6 g, 87%) as a crystalline solid. MS: 216.1 (MH⁺).
- 15

D) (+, cis)-3-hydroxy-4-methyl-piperidine-1-carboxylic acid tert-butyl ester

Intermediate 85C was separated on a Chiralpak AD column (Isopropanol: n-heptane 5:95) to afford the title compound. MS: 216.1 (MH⁺).

- 20 E) (+, cis)-4-Methyl-piperidin-3-ol hydrochloride

Intermediate 85D was deprotected with HCl in dioxane to afford the title compounds as a white powder. MS: 116.2 (MH⁺).

Intermediate 86

(-, cis)-4-Methyl-piperidin-3-ol hydrochloride

- 25 The title compound was prepared in analogy to Intermediate 85D and subsequently deprotected with HCl in dioxane to afford the title product as a white powder. MS: 116.2 (MH⁺).

Intermediate 87

(rac, trans)-2-Methyl-piperidin-3-ol hydrochloride

(rac, trans)-3-Hydroxy-2-methyl-piperidine-1-carboxylic acid tert-butyl ester

3-Hydroxy-2-methylpyridine (2.0 g, 18 mmol) was dissolved in MeOH (40 ml) with 5% Rh on alumina (0.27 g) and heated to 30 °C at 90 bar of hydrogen atmosphere for 22h. The reaction was then filtered through Hyflo, Boc₂O (4.0 g, 18 mmol) added and the
5 reaction stirred for 1h before removing the solvent under vacuum. The residue was redissolved in CH₂Cl₂, washed with 10% citric acid solution, dried (Na₂SO₄) and concentrated. Purification by flash column chromatography (EtOAc:n-heptane 3:7-1:1) afforded the title product (0.7 g, 18%) of the title product as a light yellow liquid. MS: 216.1 (MH⁺). A small quantity of (rac, cis)-3-hydroxy-2-methyl-piperidine-1-carboxylic
10 acid tert-butyl ester (0.06 g, 2%) was also obtained from the column. MS: 216.1 (MH⁺).

B) (rac, trans)-2-Methyl-piperidin-3-ol hydrochloride

Intermediate 87A (0.7 g, 3 mmol) was deprotected using HCl in dioxane affording the title product (0.45 g, 91%) as a white powder. MS: 116.1 (MH⁺).

Intermediate 88

15 (rac, cis)-2-Methyl-piperidin-3-ol hydrochloride

The byproduct (rac, cis)-3-hydroxy-2-methyl-piperidine-1-carboxylic acid tert-butyl ester from the reaction to make intermediate 87A was deprotected with HCl in dioxane to afford the title compound. MS: 116.1 (MH⁺).

Intermediate 89

20 (rac, trans)-4-Fluoro-piperidin-3-ol hydrochloride

A) (rac, trans)-4-Fluoro-piperidin-3-ol-1-carboxylic acid tert-butyl ester

(rac)-7-Oxa-3-aza-bicyclo[4.1.0]heptane-3-carboxylic acid tert-butyl ester (Heter. 1994, 39, 163) (2.0 g, 10 mmol) was dissolved in a mixture of DCE (1.5 ml) and trisHF.Et₃N (1.6 g, 10 mmol) and heated to 80 °C for 12h after which time the reaction was diluted
25 with CH₂Cl₂, washed with sat. NaHCO₃, then sat. NH₄Cl, dried (Na₂SO₄) and concentrated. Purification by flash column chromatography (EtOAc:n-heptane 3:7) afforded the title compound (1.5 g, 66%) as a yellow liquid. MS: 220.1 (MH⁺). Also obtained was the regioisomer (rac, trans)-3-fluoro-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (0.26 g, 12%) as a yellow oil. MS: 220.1 (MH⁺).

30 B) (rac, trans)-4-Fluoro-piperidin-3-ol hydrochloride

Intermediate 89A (0.5 g, 2 mmol) was deprotected with HCl in dioxane affording the title product (0.34 g, 95%) as a white powder. MS: 120.1 (MH⁺).

Intermediate 90

(rac, trans)-3-Fluoro-piperidin-4-ol hydrochloride

- 5 The byproduct (rac, trans)-3-fluoro-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester from the reaction to make intermediate 89A was deprotected with HCl in dioxane to afford the title compound. MS: 120.1 (MH⁺).

Intermediate 91

(rac)-4-Methyl-piperidin-3-ol hydrochloride

- 10 A) 3-Hydroxy-4-methyl-piperidine-1-carboxylic acid tert-butyl ester

3-Hydroxy-4-methylpyridine (0.98 g, 9 mmol) was dissolved in a AcOH (50 ml) and Pt₂O (0.10 g) added. The mixture was heated to 100 °C under 100 bar of hydrogen pressure for 20h. The reaction was then filtered through Hyflo and concentrated. The residue was dissolved in CH₂Cl₂ (30 ml) and Et₃N (2.75 ml, 20 mmol) and Boc₂O (2.2 g, 10 mmol) added and the mixture stirred for 1h. The reaction was then washed with 10% citric acid solution, dried (Na₂SO₄) and concentrated. Purification by flash column chromatography (EtOAc:n-heptane 3:7) afforded the title product (0.63 g, 33%), a 3:1 mixture of diastereomers (cis:trans) as a colourless oil. MS: 216.1 (MH⁺).

B) (rac)-4-Methyl-piperidin-3-ol hydrochloride

- 20 Intermediate 91A was deprotected with HCl in dioxane to afford the title product as a white powder. MS: 116.1 (MH⁺).

Intermediate 92

4-[3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one dihydrochloride

- 25 A) 4-[3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-5-oxo-[1,4]diazepane-1-carboxylic acid tert-butyl ester

5-Oxo-4-(3-oxo-propyl)-[1,4]diazepane-1-carboxylic acid tert-butyl ester (intermediate 61) (0.19 g, 0.7 mmol) was reacted with (-)-6-Aza-spiro[2.5]octan-4-ol hydrochloride (intermediate 83) (0.12 g, 0.7 mmol) in DCE:EtOH (1:1, 6 ml), AcOH (0.18 ml) and

pyridine-borane complex (0.18 ml, 8M in pyridine, 1.4 mmol) for 20 minutes. The reaction was then concentrated, redissolved in CH₂Cl₂ and washed with sat. NaHCO₃, dried (Na₂SO₄) and concentrated. The residue was purified by flash column chromatography (CH₂Cl₂:MeOH 8:2) to afford the title product (0.25 g, 91%) as a gum.

5 MS: 382.4 (MH⁺).

B) 4-[3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one dihydrochloride

Intermediate 92A was deprotected with HCl in dioxane to afford the title product as a white powder. MS: 282.3 (MH⁺).

10

Intermediate 93

(rac, cis)-3-Fluoro-piperidin-4-ol hydrochloride

A) 3-Fluoro-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester

3-Fluoro-4-oxo-piperidine-1-carboxylic acid tert-butyl ester (Chem. Europ. J. 2005, 5, 1579) (1.0 g, 5 mmol) was dissolved in MeOH (5 ml), cooled to 0 °C and sodium borohydride (0.2 g, 5 mmol) was added portionwise. The reaction was allowed to reach room temperature and stirred overnight after which time the solvent was removed under vacuum, the residue redissolved in CH₂Cl₂, washed with water, dried (Na₂SO₄) and concentrated. The product was purified by flash column chromatography (EtOAc:n-heptane 3:7-1:1) to afford the title compound (0.67 g, 67%) as a white solid. ¹H NMR (400 MHz, DMSO) δ 1.19-1.68 (11H, m), 2.80-3.0 (1H, m), 3.06-3.17 (1H, m), 3.59-3.70 (2H, m), 3.90-3.97 (1H, m), 4.55 (1H, dt, J 52, 4 Hz).

20

B) (rac, cis)-3-Fluoro-piperidin-4-ol hydrochloride

Intermediate 93A was deprotected with HCl in dioxane to afford the title compound as a white powder. MS: 120.1 (MH⁺).

25

Intermediate 94

(rac)-3-Methyl-piperidin-4-ol

A) (rac)-1-Benzyl-3-methyl-piperidin-4-ol

1-Benzyl-3-methyl-piperidin-4-one (2.0 g, 10mmol) was dissolved in MeOH (10 ml), cooled to 0 °C and sodium borohydride (0.2 g, 5 mmol) was added portionwise. The

reaction was allowed to reach room temperature and stirred overnight after which time the solvent was removed under vacuum, the residue redissolved in CH_2Cl_2 , washed with water, dried (Na_2SO_4) and concentrated to afford the title compound (2.1 g, quant), a 3:1 mixture of diastereomers (trans:cis) as gum. MS: 206.2 (MH^+).

5 B) (rac)-3-Methyl-piperidin-4-ol

Intermediate 94A (0.93 g) was dissolved in EtOH (10 ml) and $\text{Pd}(\text{OH})_2/\text{C}$ (0.2 g) and cyclohexen (2 ml) added. The reaction was heated to reflux for 16 h after which time it was filtered through Hyflo and concentrated, affording the title product (0.52 g, quant) a brown oil. MS: 116.1 (MH^+).

10

Intermediate 95

(rac,trans)- 3-Methyl-piperidin-4-ol hydrochloride

A) (rac,trans)-4-Hydroxy-3-methyl-piperidine-1-carboxylic acid tert-butyl ester

- 1-Benzyl-5-methyl-1,2,3,6-tetrahydro-pyridine (Tet. Lett. 1998, 39, 5417) (7.7 g, 41 mmol) was dissolved in THF (100 ml) and sodium borohydride (2.6 g, 69 mmol) added.
- 15 The mixture was cooled to 0 °C and borontrifluoride etherate (6.2 ml, 49 mmol) added, the reaction allowed to reach room temperature and subsequently stirred for 1h. The reaction was recooled to 0 °C, a small quantity of water added to quench any remaining borane, and then a suspension of Oxone (42.6 g, 69 mmol) in water (100 ml) was added and the reaction again allowed to reach room temperature (1h). The reaction was
- 20 filtered, extracted with EtOAc, the aqueous phase made basic by addition of solid NaOH, and then reextracted with CH_2Cl_2 , dried (Na_2SO_4) and concentrated. The crude residue (5.2 g) was redissolved in MeOH, $\text{Pd}(\text{OH})_2/\text{C}$ added and the reaction stirred under an atmosphere of hydrogen (balloon) for 16h after which time Boc_2O (5.5 g, 25 mmol) was added, the reaction stirred for 1h, and then filtered through Hyflo and concentrated.
- 25 Purification by flash column chromatography (EtOAc: n-heptane 4:6) afforded the title product (2.1 g, 39%) as a colourless gum. MS: 216.2 (MH^+).

B) (rac,trans)- 3-Methyl-piperidin-4-ol hydrochloride

Intermediate 95A was deprotected with HCl in dioxane to afford the title product as a white powder. MS: 116.2 (MH^+).

30

Intermediate 96

(rac,cis)- 3-Methyl-piperidin-4-ol hydrochloride

A) (rac, cis)-3-Methyl-4-(4-nitro-benzoyloxy)-piperidine-1-carboxylic acid tert-butyl ester

Intermediate 95A (0.6 g, 3 mmol) was converted to the 4-nitrobenzoic ester analogously to Intermediate 85B affording the titled product (0.9 g, 90%) as a white solid. MS: 365.2 (MH⁺).

B) (rac, cis)-4-Hydroxy-3-methyl-piperidine-1-carboxylic acid tert-butyl ester

Intermediate 96A (0.86 g, 2 mmol) was saponified analogously to intermediate 85C affording the title product (0.5 g, 98%) as a colourless oil. MS: 216.4 (MH⁺).

C) (rac, cis)-3-Methyl-piperidin-4-ol hydrochloride

Intermediate 96B was deprotected with HCl in dioxane to afford the title product as a white powder. MS: 116.1 (MH⁺).

Intermediate 97

(rac)-3,3-Dimethyl-piperidin-4-ol

A) (rac)-1-Benzyl-3,3-dimethyl-piperidin-4-ol

1-Benzyl-3,3-dimethyl-piperidin-4-one (WO 01/00577 A2) (5.0 g, 23 mmol) was dissolved in MeOH (25 ml), cooled to 0 °C and sodium borohydride (1.0 g, 25 mmol) was added portionwise. The reaction was allowed to reach room temperature and stirred overnight after which time the solvent was removed under vacuum, the residue redissolved in CH₂Cl₂, washed with water, dried (Na₂SO₄) and concentrated to afford the title compound (4.9 g, 97%). MS: 220.4 (MH⁺).

B) (rac)-3,3-Dimethyl-piperidin-4-ol

Intermediate 97A (4.9 g) was dissolved in EtOH (50 ml) and Pd(OH)₂/C (0.3 g) and cyclohexene (6 ml) added. The reaction was heated to reflux for 16 h after which time it was filtered through Hyflo and concentrated, affording the title product (0.5 g, quant) a white crystalline solid. MS: 130.1 (MH⁺).

Intermediate 98

(rac)-5-Aza-spiro[2.5]octan-8-ol

A) 8-Oxo-5-aza-spiro[2.5]octane-5-carboxylic acid tert-butyl ester

- 4-Oxo-piperidine-1-carboxylic acid tert-butyl ester (1.0 g, 5 mmol) was dissolved in tBuOH (10 ml) with tBuOK (1.1 g, 10 mmol) and stirred for 15 minutes before portionwise addition of (2-chloro-ethyl)-dimethyl-sulfonium iodide (Tet. Lett. 1984, 25, 5501) (1.1 g, 5 mmol) over 1h. The reaction was stirred for 16h after which time it was
- 5 partitioned between water and CH₂Cl₂, the organic collected, dried (Na₂SO₄) and concentrated. Flash column chromatography (EtOAc:n-heptane 1:9-3:7) afforded the titled product (0.2 g, 19%) as a colourless oil. MS: 130.1 (MH⁺).

B) (rac)-8-Hydroxy-5-aza-spiro[2.5]octane-5-carboxylic acid tert-butyl ester

- Intermediate 98A (0.2 g, 1 mmol) was dissolved in MeOH (5 ml) and sodium
- 10 borohydride (0.04 g, 1 mmol) added. The reaction was stirred for 1h, concentrated, partitioned between CH₂Cl₂ and water, the organic collected, dried (Na₂SO₄) and concentrated. Flash column chromatography (EtOAc:n-heptane 3:7-1:1) afforded the titled prouduct (0.15 g, 68%) as colourless gum. MS: 228.1 (MH⁺).

C) (rac)-5-Aza-spiro[2.5]octan-8-ol

- 15 Intermediate 98B was deprotected with HCl in dioxane to afford the titled product as a white powder. MS: 128.1 (MH⁺).

Intermediate 99

1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-(4-iodo-butyl)-[1,4]diazepan-5-one

A) 1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-(4-iodo-butyl)-[1,4]diazepan-5-one

- 20 In analogy to the procedure described for example 9A and 9B, 1-[(E)-3-(3-chloro-4-fluoro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 54) gave the title compound as yellow foam. MS: 478.9 (MH⁺).

Intermediate 100

(rac, trans)-4-Methyl-piperidin-3-ol hydrochloride

- 25 The title compound was prepared from intermediate 85B, (rac, trans)-3-Hydroxy-4-methyl-piperidine-1-carboxylic acid tert-butyl ester, by deprotection with HCl in dioxane. MS:116.2 (MH⁺).

Intermediate 101

(rac)-3-Methyl-piperidin-3-ol hydrochloride

The title compound was prepared in analogy to intermediate 16. MS:116.2 (MH⁺).

Intermediate 102

1-Oxa-4,9-diaza-spiro[5.5]undecan-3-one

The title compound was prepared as described in J. Med. Chem. 1983, 26, 6, 855.

5

Example 1

1-[(E)-3-(3-Chloro-phenyl)-acryloyl]-4-(2-pyrrolidin-1-yl-ethyl)-[1,4]diazepan-5-one

10 A) 1-[(E)-3-(3-Chloro-phenyl)-acryloyl]-4-(2-pyrrolidin-1-yl-ethyl)-[1,4]diazepan-5-one

In analogy to the procedure described in intermediate 4A, 1-[(E)-3-(3-chloro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 3A) and 1-(2-chloro-ethyl)-pyrrolidine gave the title compound as off-white powder. MS: 376.5 (MH⁺, Cl).

Example 2

15 4-[2-(4-Acetyl-piperazin-1-yl)-ethyl]-1-[(E)-3-(3-chloro-phenyl)-acryloyl]-[1,4]diazepan-5-one

A) 4-[2-(4-Acetyl-piperazin-1-yl)-ethyl]-1-[(E)-3-(3-chloro-phenyl)-acryloyl]-[1,4]diazepan-5-one

20 In analogy to the procedure described in intermediate 4A, 1-[(E)-3-(3-chloro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 3A) and 1-[4-(2-chloro-ethyl)-piperazin-1-yl]-ethanone gave the title compound as off-white foam. MS: 433.2 (MH⁺, Cl).

Example 3

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(2-piperidin-1-yl-ethyl)-[1,4]diazepan-5-one

A) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(2-piperidin-1-yl-ethyl)-[1,4]diazepan-5-one

- 5 In analogy to the procedure described in intermediate 4A, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 1A) and 1-(2-chloro-ethyl)-piperidine gave the title compound as white solid. MS: 424.1 (MH⁺, 2Cl).

Example 4

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

A) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

- In analogy to the procedure described in intermediate 4A, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 1A) and 1-(3-chloro-propyl)-piperidine gave the title compound as light yellow solid. MS: 438.1 (MH⁺, 2Cl).

Example 5

1-[(E)-3-(3-Chloro-phenyl)-acryloyl]-4-(2-morpholin-4-yl-ethyl)-[1,4]diazepan-5-one

A) {4-[(E)-3-(3-Chloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-acetic acid ethyl ester

- 20 A solution of 4.33 g (15.53 mmol) of 1-[(E)-3-(3-chloro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 3A) in 80 ml of DMF was treated at 0 °C with 0.75 g (17.09 mmol) of NaH (55 % in oil) in two portions and after 30 min with 1.89 ml (17.09 mmol) of bromo-acetic acid ethyl ester in 1 ml of DMF. The reaction was stirred for 5 h at RT, cooled (0 °C) and treated again with 0.20 g (4.66 mmol) of NaH (55 % in oil) and
- 25 after 20 min with 0.34 ml (3.11 mmol) of bromo-acetic acid ethyl ester. The reaction was warmed up to RT over night, cooled and neutralized with cold aqueous 10 % KHSO₄ and extracted with Et₂O (3x). The organic phases were washed with aqueous saturated NaHCO₃, aqueous 10 % NaCl, dried over Na₂SO₄ evaporated and purified by flash silica gel column (EtOAc/n-heptane 1:1 to 9:1) to yield 2.92 g (52 %) of the title compound as
- 30 light yellow viscous oil. MS: 365.0 (MH⁺, Cl).

B) 1-[(E)-3-(3-Chloro-phenyl)-acryloyl]-4-(2-hydroxy-ethyl)-[1,4]diazepan-5-one

A solution of 2.16 g (5.91 mmol) of {4-[(E)-3-(3-chloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-acetic acid ethyl ester in 30 ml of ethanol was treated at 0 °C with 0.45 g (11.81 mmol) of sodium borohydride in 30 ml of ethanol during 20 min. The reaction was stirred for 21 h at RT, cooled (0 °C) and treated again with 0.45 g (11.81 mmol) of sodium borohydride. After 22 h at RT the reaction neutralized with cold aqueous 10 % KHSO₄ and extracted with EtOAc (3x). The organic phases were washed with aqueous 10 % NaCl, dried over Na₂SO₄ evaporated and purified by flash silica gel column (EtOAc and then EtOAc/EtOH 1 to 7.5%) to yield 1.50 g (79 %) of the title compound as light white foam. MS: 323.1 (MH⁺, Cl).

C) 4-(2-Chloro-ethyl)-1-[(E)-3-(3-chloro-phenyl)-acryloyl]-[1,4]diazepan-5-one

To an ice-cooled solution of 2.13 g (3.50 mmol) of 1-[(E)-3-(3-chloro-phenyl)-acryloyl]-4-(2-hydroxy-ethyl)-[1,4]diazepan-5-one and 0.73 ml (5.25 mmol) of Et₃N in 35 ml of dichloromethane were added 0.29 ml (3.68 mmol) of methanesulfonyl chloride under stirring within 5 min keeping the temperature at 0 °C. The reaction was stirred at room temperature for 1 h 45 min. Water was added and after 5 min, the reaction was then partitioned between ether and aqueous saturated NaHCO₃. The water phase was extracted again with ether (2x), the organic phases were washed with aqueous 10% NaCl, dried (Na₂SO₄) and concentrated to yield 1.22 g (87 %) of the title compound as yellow viscous oil. MS: 341.0 (MH⁺, 2Cl).

D) 1-[(E)-3-(3-Chloro-phenyl)-acryloyl]-4-(2-morpholin-4-yl-ethyl)-[1,4]diazepan-5-one

A solution of 0.085 g (0.25 mmol) of 4-(2-chloro-ethyl)-1-[(E)-3-(3-chloro-phenyl)-acryloyl]-[1,4]diazepan-5-one in 1.3 ml of DMA was treated with 0.04 ml (0.50 mmol) of morpholine and stirred for 8 h at RT, a crystal of NaI was added and stirring was continued for 40 h. The reaction was extracted with aqueous saturated NaHCO₃/EtOAc (3x). The organic phases were washed with aqueous 10% NaCl, dried (Na₂SO₄), concentrated and evaporated. Purification by catridges, Si-Amine, 70 ml, 20g (EtOAc) gave 0.008 g (8 %) of the title compound as off-white viscous oil. MS: 392.0 (MH⁺, Cl).

Example 6

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(3-morpholin-4-yl-propyl)-[1,4]diazepan-5-one

A) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(tetrahydro-pyran-2-yloxy)-propyl]-[1,4]diazepan-5-one

In analogy to the procedure described in example 5A, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 1A)) and 2-(3-bromo-propoxy)-tetrahydro-pyran gave the title compound as white solid. MS: 455.3 (MH⁺, 2Cl).

B) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(3-hydroxy-propyl)-[1,4]diazepan-5-one

A solution of 1.30 g (2.85 mmol) of 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-[3-(tetrahydro-pyran-2-yloxy)-propyl]-[1,4]diazepan-5-one in 6 ml of methanol was treated with 0.22 g (0.86 mmol) of pyridinium toluene-4-sulfonate and stirred at 55 °C for 30 min. The reaction was cooled and extracted with aqueous 10 % KHSO₄/Et₂O (3x). The organic phases were washed with aqueous saturated NaHCO₃, aqueous 10% NaCl, dried (Na₂SO₄) and evaporated to give after crystallization (Et₂O) 0.98 g (92 %) of the title compound as white solid. MS: 371.0 (MH⁺, 2Cl).

C) Methanesulfonic acid 3-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl ester

In analogy to the procedure described in example 5C, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-(3-hydroxy-propyl)-[1,4]diazepan-5-one and methanesulfonyl chloride gave the crude title compound as white foam and as a mixture of mainly mesylate and some chloride. MS: 448.2 (M⁺, 2Cl).

D) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(3-iodo-propyl)-[1,4]diazepan-5-one

A solution of 0.50 g (1.11 mmol) of crude methanesulfonic acid 3-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl ester in 20 ml of 2-butanone was treated with 0.33 g (2.23 mmol) of sodium iodide and stirred at 95 °C for 30 min. The reaction was cooled, evaporated, suspended in 60 ml dichloromethane/Et₂O (1:3), filtered and the organic solvent discarded. The residue was then washed again with dichloromethane to give after evaporation 0.27 g (51 %) of the title compound as white solid. MS: 481.0 (MH⁺, 2Cl).

E) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(3-morpholin-4-yl-propyl)-[1,4]diazepan-5-one

In analogy to the procedure described in example 5D, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-(3-iodo-propyl)-[1,4]diazepan-5-one and morpholine (with no additional sodium iodide) gave after flash silica gel column purification (CH₂Cl₂/EtOAc 99:1 to 96:4) the title compound as a light yellow viscous oil. MS: 440.2 (MH⁺, 2Cl).

Example 7

1-[(E)-3-(3,4-Difluoro-phenyl)-acryloyl]-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

10 A) 1-[(E)-3-(3,4-Difluoro-phenyl)-acryloyl]-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

In analogy to the procedure described in intermediate 1A, (E)-3,4-difluorocinnamic acid and 4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one-dihydrochloride (intermediate 4B, suspended in CH₂Cl₂ with 4 equivalent of Et₃N) gave after purification on catridges, Si-
15 Amine, 70 ml, 20g (EtOAc) the title compound as a white powder. MS: 406.2 (MH⁺).

Example 8

4-(3-Piperidin-1-yl-propyl)-1-[(E)-3-(3-trifluoromethyl-phenyl)-acryloyl]-[1,4]diazepan-5-one

20 A) 4-(3-Piperidin-1-yl-propyl)-1-[(E)-3-(3-trifluoromethyl-phenyl)-acryloyl]-[1,4]diazepan-5-one

In analogy to the procedure described in intermediate 1A, (E)-3-(trifluoromethyl)cinnamic acid and 4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one-dihydrochloride (intermediate 4B, suspended in CH₂Cl₂ with 4 equivalent of Et₃N) gave after purification on catridges, Si-Amine, 70 mL, 20g (EtOAc) the title compound as a
25 light yellow viscous oil. MS: 438.4 (MH⁺).

Example 9

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(4-piperidin-1-yl-butyl)-[1,4]diazepan-5-one

A) 4-(4-Chloro-butyl)-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one

- 5 In analogy to the procedure described in example 5A, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 1A) and 1-chloro-4-iodobutane gave the title compound as orange solid. MS: 403.2 (MH⁺, 3Cl).

B) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(4-iodo-butyl)-[1,4]diazepan-5-one

- 10 In analogy to the procedure described in example 6D, 4-(4-chloro-butyl)-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one and sodium iodide were stirred at 90 °C for 26 h to give the title compound as orange foam. MS: 495.0 (MH⁺, 2Cl).

C) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(4-piperidin-1-yl-butyl)-[1,4]diazepan-5-one

- 15 In analogy to the procedure described in example 5D, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-(4-iodo-butyl)-[1,4]diazepan-5-one and piperidine (with no additional sodium iodide) gave the title compound as white powder. MS: 452.2 (MH⁺, 2Cl).

Example 10

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{4-[methyl-(tetrahydro-pyran-4-yl)-amino]-butyl}-[1,4]diazepan-5-one

- 20 A) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{4-[methyl-(tetrahydro-pyran-4-yl)-amino]-butyl}-[1,4]diazepan-5-one

- A solution of 0.100 g (0.20 mmol) of 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-(4-iodo-butyl)-[1,4]diazepan-5-one (example 9B) in 3.1 ml of DMA was treated with free methyl-(tetrahydro-pyran-4-yl)-amine in 1 ml of toluene [0.035 g (0.22 mmol) methyl-(tetrahydro-pyran-4-yl)-amine hydrochloride were dissolved in 0.8 ml of 0.5 N NaOH was extracted with toluene (2 ml). The organic phase was dried over Na₂SO₄] and stirred for 22 h at RT, 0.06 ml (0.40 mmol) of Et₃N was added and stirring was continued for 18 h at 50 °C. Again methyl-(tetrahydro-pyran-4-yl)-amine in 1 ml of CH₂Cl₂ [0.035 g (0.22 mmol) methyl-(tetrahydro-pyran-4-yl)-amine hydrochloride were dissolved in 0.5 ml aqueous 10% NaCl solution/0.4 ml of 1 N NaOH was extracted with CH₂Cl₂ (1 ml). The
- 25
- 30

organic phase was dried over Na_2SO_4] was added and heated for 9 h at 50 °C. The reaction was extracted with aqueous saturated $\text{NaHCO}_3/\text{Et}_2\text{O}$ (3x). The organic phases were washed with aqueous 10% NaCl, dried (Na_2SO_4), concentrated and evaporated. Purification by catridges, Si-Amine, 70 ml, 20g (n-heptane/EtOAc 1:4 to 1:9) gave 0.004 g (4 %) of the title compound as a light yellow semisolid. MS: 482.3 (MH^+ , 2Cl).

Example 11

1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

10 A) 1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

A suspension of 0.099 g (0.32 mmol) 4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one-dihydrochloride (intermediate 4B) and 0.077 g (0.38 mmol) of (E)-3-chloro-4-fluorocinnamic acid in 3 ml of CH_2Cl_2 was treated with 0.09 ml (0.64 mmol) of Et_3N at RT, cooled (0 °C) and treated with a 0.085 g (0.41 mmol) of N,N'-dicyclohexylcarbodiimide. The reaction was warmed up over night to RT, then partitioned between EtOAc (x3)/ saturated NaHCO_3 . The organic phases were washed with aqueous 10% NaCl, dried over Na_2SO_4 and evaporated to give after purification on catridges, Si-Amine, 70 ml, 20g (EtOAc/n-heptane 9:1) 0.075 g (64 %) of the title compound as a white solid. MS: 422.1 (MH^+ , Cl).

Example 12

1-[(E)-3-(5,6-Dichloro-pyridin-3-yl)-acryloyl]-4-(3-piperidin-1-yl-propyl)-
[1,4]diazepan-5-one

5

A) (E)-3-(5,6-Dichloro-pyridin-3-yl)-acrylic acid methyl ester

To a solution of (5,6-Dichloro-pyridin-3-yl)-methanol (1.8 g, 10 mmol) in CH₂Cl₂ (20 ml) was added manganese dioxide (4.4g, 50 mmol). The reaction was stirred for 16h after which time it was filtered through a pad of Hyflo and a fresh portion of manganese
10 dioxide (1.8g, 20 mmol) added and the reaction stirred for a further 4h. The manganese dioxide was removed by filtration through Hyflo and the reaction concentrated affording crude 5,6-dichloro-pyridine-3-carbaldehyde (1.4g, 81%). This was then dissolved in toluene (20 ml) and (methoxycarbonylmethylene)triphenylphosphorane (4.1g, 12 mmol) added and the mixture heated to reflux for 1h after which time the mixture was diluted
15 with CH₂Cl₂, silica gel added and the mixture concentrated to dryness. The absorbed product was then purified by flash column chromatography (EtOAc:Heptane 1:1) furnishing the title compound (1.5g, 81%) as a white solid.
MS: 232.0 (MH⁺, 2Cl).

20 B) (E)-3-(5,6-Dichloro-pyridin-3-yl)-acrylic acid

(E)-3-(5,6-Dichloro-pyridin-3-yl)-acrylic acid methyl ester (1.54g, 7 mmol) was suspended in MeOH (20 ml) and aqueous sodium hydroxide (1.1 ml, 6M, 7 mmol) added. The mixture was heated to reflux for 20 min after which time the reaction was concentrated, the residue taken up in water and the pH adjusted to 1 by addition of 1M
25 HCl. The product could then be isolated by filtration affording the title compound (1.11g, 77%) as a white solid. MS: 216.0 (M-H⁻ 2Cl).

C) (E)-3-(5,6-Dichloro-pyridin-3-yl)-acryloyl]-4-(3-piperidin-1-yl-propyl)-
[1,4]diazepan-5-one

To a suspension of (E)-3-(5,6-Dichloro-pyridin-3-yl)-acrylic acid (26 mg, 0.12 mmol), 4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one-dihydrochloride (intermediate 4) (24 mg, 0.1 mmol), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (46 mg, 0.12 mmol) in DMF (1 ml) was added Et₃N (21 ul, 0.15 mmol) and the mixture shaken for 1h. The reaction was then directly purified by preparative HPLC affording the title product (14 mg, 32%) as a white powder. MS: 439.4 (MH⁺, 2Cl).

Example 13

10 1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

A) 1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

In analogy to the procedure described in intermediate 1A, 4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one-dihydrochloride (intermediate 4B) and (E)-4-chloro-3-fluorocinnamic acid gave after work up with EtOAc (x3)/saturated NaHCO₃ and precipitation (n-pentane) the title compound as off-white solid. MS: 422.2 (MH⁺, Cl).

Examples 14-26

20 General procedure for examples 14-26

A solution CDI (0.016g, 0.1 mmol) in DMF (0.5 ml) was added to the appropriate cinnamic acid (0.1 mmol) and the solution shaken for 1h after which time a solution of 4-(2-pyrrolidin-1-yl-ethyl)-[1,4]diazepan-5-one-dihydrochloride (intermediate 5) (0.027g, 0.1 mmol), Et₃N (28 ul, 0.2 mmol) in DMF (0.5 ml) was added and the shaking continued for 16h. The reactions were then directly purified by preparative HPLC.

Table 1.

Example No.	Compound Name	Cinnamic Acid	MS: (MH ⁺)
14	4-(2-Pyrrolidin-1-yl-ethyl)-1-[(E)-3-(4-trifluoromethyl-phenyl)-acryloyl]-	4-Trifluoromethylcinnamic	410.5

	[1,4]diazepan-5-one	acid	
15	4-(2-Pyrrolidin-1-yl-ethyl)-1-[(E)-3-(4-methoxy-phenyl)-acryloyl]-[1,4]diazepan-5-one	4-Methoxycinnamic acid	372.5
16	4-(2-Pyrrolidin-1-yl-ethyl)-1-[(E)-3-(2,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	2,4-Dichlorocinnamic acid	410.5
17	1-[(E)-3-(4-Benzyloxy-phenyl)-acryloyl]-4-(2-pyrrolidin-1-yl-ethyl)-[1,4]diazepan-5-one	4-Benzyloxycinnamic acid	448.6
18	1-(E)-(3-Benzo[1,3]dioxol-5-yl-acryloyl)-4-(2-pyrrolidin-1-yl-ethyl)-[1,4]diazepan-5-one	3,4-Methylenedioxcinnamic acid	386.5
19	4-(2-Pyrrolidin-1-yl-ethyl)-1-[(E)-3-(2,4-difluoro-phenyl)-acryloyl]-[1,4]diazepan-5-one	2,4-Difluorocinnamic acid	378.5
20	1-[(E)-3-(3,5-Difluoro-phenyl)-acryloyl]-4-(2-pyrrolidin-1-yl-ethyl)-[1,4]diazepan-5-one	3,5-Difluorocinnamic acid	378.5
21	4-(2-Pyrrolidin-1-yl-ethyl)-1-[(E)-3-phenyl-acryloyl]-[1,4]diazepan-5-one	Cinnamic acid	342.5
22	4-(2-Pyrrolidin-1-yl-ethyl)-1-[(E)-3-(2-methoxy-phenyl)-acryloyl]-[1,4]diazepan-5-one	2-Methoxycinnamic acid	372.5
23	4-(2-Pyrrolidin-1-yl-ethyl)-1-[(E)-3-(4-fluoro-phenyl)-acryloyl]-[1,4]diazepan-5-one	4-Fluorocinnamic acid	360.5
24	4-(2-Pyrrolidin-1-yl-ethyl)-1-[(E)-3-(3-fluoro-phenyl)-acryloyl]-[1,4]diazepan-5-one	3-Fluorocinnamic acid	360.5

	[1,4]diazepan-5-one		
25	1-(E)-(3-Naphthalen-2-yl-acryloyl)-4-(2-pyrrolidin-1-yl-ethyl)-[1,4]diazepan-5-one	2-Naphthyacrylic acid	392.5
26	4-(2-Pyrrolidin-1-yl-ethyl)-1-[(E)-3-(4-chloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	4-Chlorocinnamic acid	376.2

Examples 27-34

General Procedure for Examples 27-34

- 5 A solution of {4-[(E)-3-(3-chloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-acetaldehyde (intermediate 3) (0.031 g, 0.1 mmol) in DCE (0.5 ml) was added to the appropriate amine (0.1 mmol) followed by a freshly prepared solution of pyridine-borane complex (25 ul, 8M in pyridine, 0.2 mmol) and acetic acid (25 ul) in EtOH (0.5 ml). The reaction was then shaken overnight, concentrated and the residue purified by preparative
- 10 HPLC.

Table 2.

Example No.	Compound Name	Amine	MS: (MH ⁺)
27	1-[(E)-3-(3-Chloro-phenyl)-acryloyl]-4-{3-[4-(6-fluoro-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-[1,4]diazepan-5-one	6-Fluoro-3-piperidin-4-yl-1H-indole (intermediate 6)	522.8
28	1-[(E)-3-(3-chloro-phenyl)-acryloyl]-4-{3-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-ethyl}-[1,4]diazepan-5-one	1-Piperidin-4-yl-imidazolidin-2-one (intermediate 7)	473.8

29	1-[(E)-3-(3-Chloro-phenyl)-acryloyl]-4-{3-[4-(5-methyl-1H-[1,2,4]triazol-3-yl)-piperidin-1-yl]-ethyl}-[1,4]diazepan-5-one	4-(5-Methyl-4H-[1,2,4]triazol-3-yl)-piperidine hydrochloride (intermediate 8)	470.8
30	4-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-1-[(E)-3-(3-chloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	4-Benzylpiperidine	479.8
31	1-[(E)-3-(3-Chloro-phenyl)-acryloyl]-4-[3-(4-hydroxy-4-phenyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	4-Hydroxy-4-phenyl-piperidine	481.8
32	1-[(E)-3-Chloro-phenyl-acryloyl]-4-[2-[4-phenyl-piperidin-1-yl]-ethyl]-[1,4]diazepan-5-one	4-Phenylpiperidine	465.8
33	1-[(E)-3-(3-Chloro-phenyl)-acryloyl]-4-[3-(4-(4-fluoro-phenyl)-piperidin-1-yl)-ethyl]-[1,4]diazepan-5-one	4-(4-Fluoro-phenyl)-piperidine	483.8
34	1-[(E)-3-(3-Chloro-phenyl)-acryloyl]-4-[2-[4-(3-chloro-phenyl)-piperidin-1-yl]-ethyl]-[1,4]diazepan-5-one	4-(3-Chloro-phenyl)-piperidine	499.8

Examples 35-92

General Procedure for Examples 35-92

- 5 A solution of 3-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propionaldehyde (intermediate 2) (0.037 g, 0.1 mmol) in DCE (0.5 ml) was added to the appropriate amine (0.1 mmol) followed by a freshly prepared solution of pyridine-borane

complex (25 ul, 8M in pyridine, 0.2 mmol) and acetic acid (25 ul) in EtOH (0.5 ml). The reaction was then shaken overnight, concentrated and the residue purified by preparative HPLC.

Table 3.

Example No.	Compound Name	Amine	MS: (MH ⁺)
35	4-[3-(4-Cyclopropanecarbonyl-piperazin-1-yl)-propyl]-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	Cyclopropyl-piperazin-1-yl-methanone	507.2
36	4-[3-(Cyclopentyl-amino)-propyl]-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	Cyclopentylamine	438.2
37	4-[3-(Cyclopentyl-methyl-amino)-propyl]-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	Cyclopentyl-methyl-amine	452.2
38	(+/-)-4-[3-(Bicyclo[2.2.1]hept-2-ylamino)-propyl]-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	(+/-)-endo-2-Norbonylamine hydrochloride	464.2
39	4-[3-(Cyclohexyl-methyl-amino)-propyl]-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	Cyclohexyl-methyl-amine	466.2
40	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(1,1-dioxo-thiomorpholin-4-yl)-propyl]-[1,4]diazepan-5-one	Thiomorpholine-1,1-dioxide	488.1
41	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-[(2-methoxy-ethyl)-methyl-amino]-propyl]-	(2-Methoxy-ethyl)-methyl-amine	442.2

	[1,4]diazepan-5-one		
42	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{3-[(2-hydroxy-ethyl)-methyl-amino]-propyl}-[1,4]diazepan-5-one	(2-Hydroxy-ethyl)-methyl-amine	428.2
43	4-{3-[Bis-(2-hydroxy-ethyl)-amino]-propyl}-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	2-(2-Hydroxy-ethylamino)-ethanol	458.2
44	(+/-)-N-[1-(E)-(3-{4-[3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4] diazepan-1-yl}-propyl)-pyrrolidin-3-yl]-acetamide	(+/-)-N-Pyrrolidin-3-yl-acetamide	481.2
45	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-phenyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	4-Phenyl-piperidine	514.2
46	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(3-pyrrolidin-1-yl-propyl)-[1,4]diazepan-5-one	Pyrollidine	424.2
47	(S)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(2-hydroxymethyl-pyrrolidin-1-yl)-propyl]-[1,4]diazepan-5-one	(S)-Prolinol	454.2
48	8-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione	1,3,8-Triaza-spiro[4.5]decane-2,4-dione (intermediate 11)	522.2
49	4-[(E)-3-(4-Benzyl-4-hydroxy-piperidin-1-yl)-propyl]-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	4-Benzyl-piperidin-4-ol	544.2

50	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	4-Methyl-piperidine	452.2
51	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(3-thiomorpholin-4-yl-propyl)-[1,4]diazepan-5-one	Thiomorpholine	456.1
52	(+/-)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-([1,4]dioxan-2-ylmethyl-methyl-amino)-propyl]-[1,4]diazepan-5-one	(1,4)-dioxan-2-yl-methylamine	484.2
53	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-hydroxy-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-yl)-propyl]-[1,4]diazepan-5-one	4-Hydroxy-4-pyrid-4-yl(piperidine)	531.2
54	cis/trans-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{3-[methyl-(4-methyl-cyclohexyl)-amino]-propyl}-[1,4]diazepan-5-one	cis/trans-Methyl-(4-methyl-cyclohexyl)-amine	480.3
55	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4,4-difluoro-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	4,4-Difluororpiperidine	474.2
56	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{3-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-propyl}-[1,4]diazepan-5-one	1-Piperidin-4-yl-imidazolidin-2-one (intermediate 7)	522.2
57	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{3-[4-(1H-pyrazol-3-yl)-piperidin-1-yl]-propyl}-[1,4]diazepan-5-one	4-(1H-Pyrazol-3-yl)-piperidine (intermediate 12)	504.2
58	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{3-[4-(5-methyl-1H-	4-(5-Methyl-4H-[1,2,4]triazol-3-yl)-piperidine	519.2

	[1,2,4]triazol-3-yl)-piperidin-1-yl]-propyl]-[1,4]diazepan-5-one	hydrochloride (intermediate 8)	
59	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-hydroxy-4-phenyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	4-Phenyl-piperidin-4-ol	530.5
60	1-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-4-phenyl-piperidine-4-carbonitrile	4-Phenyl-piperidine-4-carbonitrile	539.5
61	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-morpholin-4-yl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	4-Piperidin-4-yl-morpholine	523.5
62	(+/-)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(2-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(+/-)-2-Methylpiperidine	452.4
63	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(tetrahydro-pyran-4-ylamino)-propyl]-[1,4]diazepan-5-one	Tetrahydro-pyran-4-ylamine	454.5
64	<i>cis/trans</i> -1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(2-methyl-cyclohexylamino)-propyl]-[1,4]diazepan-5-one	<i>cis/trans</i> -2-Methylcyclohexylamine	466.4
65	<i>trans</i> -1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-hydroxy-4-pyridin-2-yl-cyclohexylamino)-propyl]-[1,4]diazepan-5-one	<i>trans</i> -4-Amino-1-pyridin-2-yl-cyclohexanol (intermediate 13)	545.5
66	<i>trans</i> -1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-(4-hydroxy-	<i>trans</i> -4-Amino-cyclohexanol	468.5

	cyclohexylamino)propyl]- [1,4]diazepan-5-one		
67	4-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)- acryloyl]-7-oxo-[1,4]diazepan-1-yl}- propylamino)-cyclohexanecarboxylic acid ethyl ester	Piperidine-4-carboxylic acid ethyl ester	510.2
68	1-[(E)-3-(3,4-Dichloro-phenyl)- acryloyl]-4-{3-[(3-hydroxy-propyl)- amino]-propyl}-[1,4]diazepan-5-one	3-Amino-propan-1-ol	428.2
69	1-[(E)-3-(3,4-Dichloro-phenyl)- acryloyl]-4-[3-(4'-hydroxy-3',4',5',6'- tetrahydro-2'H-[2,4']bipyridinyl-1'- yl)-propyl]-[1,4]diazepan-5-one	4-Hydroxy-4-pyrid-2- yl(piperidine)	531.2
70	1-[(E)-3-(3,4-Dichloro-phenyl)- acryloyl]-4-[3-(4'-hydroxy-3',4',5',6'- tetrahydro-2'H-[3,4']bipyridinyl-1'- yl)-propyl]-[1,4]diazepan-5-one	4-Hydroxy-4-pyrid-3- yl(piperidine)	531.2
71	(+/-)-1-[(E)-3-(3,4-Dichloro-phenyl)- acryloyl]-4-[3-(3-hydroxy-pyrrolidin- 1-yl)-propyl]-[1,4]diazepan-5-one	(+/-) 3-Hydroxy-pyrrolidine	440.2
72	1-[(E)-3-(3,4-Dichloro-phenyl)- acryloyl]-4-[3-(4-trifluoromethyl- piperidin-1-yl)-propyl]- [1,4]diazepan-5-one	4-Trifluoromethyl-piperidine	506.2
73	1-[(E)-3-(3,4-Dichloro-phenyl)- acryloyl]-4-[3-(4-methanesulfonyl- piperazin-1-yl)-propyl]- [1,4]diazepan-5-one	1-Methanesulfonyl- piperazine	517.2
74	1-[(E)-3-(3,4-Dichloro-phenyl)- acryloyl]-4-[3-(4-fluoro-piperidin-1- yl)-propyl]-[1,4]diazepan-5-one	4-Fluoro-piperidine	456.2

75	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-methyl-piperazin-1-yl)-propyl]-[1,4]diazepan-5-one	1-Methyl-piperazine	517.2
76	4-[3-(4-Methyl-4-hydroxy-piperidin-1-yl)-propyl]-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	4-Methyl-piperidin-4-ol	456.2
77	4-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propylamino)-cyclohexanecarboxylic acid amide	Piperidine-4-carboxylic acid amide	481.2
78	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{3-[methyl-(tetrahydro-pyran-4-yl)-amino]-propyl}-[1,4]diazepan-5-one	Methyl-(tetrahydro-pyran-4-yl)-amine	468.2
79	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-methoxy-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	4-Methoxy-piperidine	468.3
80	(+/-)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-methoxy-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	3-Methoxy-piperidine	468.1
81	(+/-)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-hydroxy-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(+/-) 3-Hydroxy-piperidine	454
82	[1-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-piperidin-4-yl]-carbamic acid ethyl ester	Ethyl piperidin-4-yl carbamate	525.1
83	N-[1-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-	N-Piperidin-4-yl-acetamide	495.1

	piperidin-4-yl]-acetamide		
84	8-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-1-oxa-3,8-diaza-spiro[4.5]decan-2-one	1-Oxa-3,8-diaza-spiro[4.5]decan-2-one (intermediate 14)	509.3
85	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-hydroxy-4-oxazol-2-yl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	4-Oxazol-2-yl-piperidin-4-ol hydrochloride (intermediate 15)	521.0
86	1-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-piperidine-4-carboxylic acid methylamide	Piperidine-4-carboxylic acid methylamide	495.0
87	8-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-2,8-diaza-spiro[4.5]decane-1,3-dione	2,8-Diaza-spiro[4.5]decane-1,3-dione (intermediate 17)	521.1
88	8-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-2,8-diaza-spiro[4.5]decan-3-one	2,8-Diaza-spiro[4.5]decan-3-one (intermediate 18)	507.4
89	8-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-1,3,8-triaza-spiro[4.5]decan-4-one	1,3,8-Triaza-spiro[4.5]decan-4-one (intermediate 9)	508.2
90	1-(3-{4-[3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-4-hydroxy-piperidine-4-carboxylic acid amide	4-Hydroxy-piperidine-4-carboxylic acid amide (intermediate 19)	497.2
91	(R)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-hydroxy-piperidin-	(R)-3-Hydroxypiperidine	454.2

	1-yl)-propyl]-[1,4]diazepan-5-one		
92	(S)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-hydroxy-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(S)-3-Hydroxypiperidine	454.2

Examples 93-151

General Procedure for Examples 93-151

- 5 A solution of 3-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4] diazepan-1-yl}-acetaldehyde (intermediate 3) (0.036 g, 0.1 mmol) in DCE (0.5 ml) was added to the appropriate amine (0.1 mmol) followed by a freshly prepared solution of pyridine-borane complex (25 ul, 8M in pyridine, 0.2 mmol) and acetic acid (25 ul) in EtOH (0.5 ml). The reaction was then shaken overnight, concentrated and the residue purified by preparative
- 10 HPLC.

Table 4.

Example No.	Compound Name	Amine	MS: (MH ⁺)
93	(S)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(2-methoxymethyl-pyrrolidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(S)-2-Methoxymethyl-pyrrolidine	454.1
94	(R)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(2-methoxymethyl-pyrrolidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(R)-2-Methoxymethyl-pyrrolidine	454.1
95	(R)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(2-hydroxymethyl-pyrrolidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(R)-Prolinol	440.1

96	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-hydroxy-4-phenyl-piperidin-1-yl)-ethyl]-[1,4]diazepan-5-one	4-Phenyl-piperidin-4-ol	516.5
97	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-(4-hydroxymethyl-piperidin-1-yl)-ethyl]-[1,4]diazepan-5-one	4-Methyl-piperidin-4-ol	454.4
98	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4'-hydroxy-3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-yl)-ethyl]-[1,4]diazepan-5-one	4-Hydroxy-4-pyrid-2-yl(piperidine)	517.5
99	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4'-hydroxy-3',4',5',6'-tetrahydro-2'H-[3,4']bipyridinyl-1'-yl)-ethyl]-[1,4]diazepan-5-one	4-Hydroxy-4-pyrid-3-yl(piperidine)	517.5
100	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-hydroxy-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-yl)-ethyl]-[1,4]diazepan-5-one	4-Hydroxy-4-pyrid-4-yl(piperidine)	517.5
101	1-(-3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-ethyl)-4-phenyl-piperidine-4-carbonitrile	4-Phenyl-piperidine-4-carbonitrile	525.5
102	(+/-)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(2-methyl-piperidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(+/-)-2-Methylpiperidine	438.4
103	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(tetrahydro-pyran-4-ylamino)-ethyl]-[1,4]diazepan-5-one	Tetrahydro-pyran-4-ylamine	440.4
104	cis/trans-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(2-methyl-cyclohexylamino)-ethyl]-[1,4]diazepan-5-one	cis/trans-2-Methylcyclohexylamine	452.4

105	trans-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-hydroxy-4-pyridin-2-yl-cyclohexylamino)-ethyl]-[1,4]diazepan-5-one	trans-4-Amino-1-pyridin-2-yl-cyclohexanol (intermediate 13)	531.5
106	trans-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-(4-hydroxy-cyclohexylamino)-ethyl]-[1,4]diazepan-5-one	trans-4-Amino-cyclohexanol	454.4
107	4-[3-(4-Cyclopropanecarbonyl-piperazin-1-yl)-ethyl]-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	Cyclopropyl-piperazin-1-yl-methanone	493.2
108	4-[3-(Cyclopentyl-amino)-ethyl]-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	Cyclopentylamine	424.2
109	4-[3-(Cyclopentyl-methyl-amino)-ethyl]-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	Cyclopentyl-methyl-amine	438.1
110	(+/-)-4-[3-(Bicyclo[2.2.1]hept-2-ylamino)ethyl]-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	(+/-)-endo-2-Norbonylamine hydrochloride	450.2
111	4-[3-(Cyclohexyl-methyl-amino)-ethyl]-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	Cyclohexyl-methyl-amine	452.1
112	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(1,1-dioxo-thiomorpholin-4-yl)-ethyl]-[1,4]diazepan-5-one	Thiomorpholine-1,1-dioxide	474.0
113	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-[(2-methoxy-ethyl)-methyl-amino]-ethyl]-[1,4]diazepan-5-one	(2-Methoxy-ethyl)-methyl-amine	428.1

114	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-[(2-hydroxy-ethyl)-methyl-amino]-ethyl]-[1,4]diazepan-5-one	(2-Hydroxy-ethyl)-methyl-amine	414.1
115	4-[3-[Bis-(2-hydroxy-ethyl)-amino]-ethyl]-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	2-(2-Hydroxy-ethylamino)-ethanol	444.2
116	(+/-)-N-[1-((E)-3-{4-[3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-ethyl)-pyrrolidin-3-yl]-acetamide	(+/-)N-Pyrrolidin-3-yl-acetamide	467.2
117	(S)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(2-hydroxymethyl-pyrrolidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(S)-Prolinol	440.1
118	8-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-ethyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione	1,3,8-Triaza-spiro[4.5]decane-2,4-dione (intermediate 11)	508.2
119	4-[(E)-3-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	4-Benzyl-piperidin-4-ol	530.1
120	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-methyl-piperidin-1-yl)-ethyl]-[1,4]diazepan-5-one	4-Methyl-piperidine	438.2
121	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(3-thiomorpholin-4-yl-ethyl)-[1,4]diazepan-5-one	Thiomorpholine	442.1
122	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(2-morpholin-4-yl-ethyl)-[1,4]diazepan-5-one	Morpholine	426.1

123	(+/-)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-([1,4]dioxan-2-ylmethyl-methyl-amino)-ethyl]-[1,4]diazepan-5-one	(1,4)-Dioxan-2-yl-methylamine	470.1
124	<i>cis/trans</i> -1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-[methyl-(4-methyl-cyclohexyl)-amino]-ethyl]-[1,4]diazepan-5-one	<i>cis/trans</i> -Methyl-(4-methyl-cyclohexyl)-amine	466.3
125	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4,4-difluoro-piperidin-1-yl)-ethyl]-[1,4]diazepan-5-one	4,4-Difluororpiperidine	460.1
126	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-[4-(2-oxo-imidazolidin-1-yl)-piperidin-1-yl]-ethyl]-[1,4]diazepan-5-one	1-Piperidin-4-yl-imidazolidin-2-one (intermediate 7)	508.1
127	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-[4-(1H-pyrazol-3-yl)-piperidin-1-yl]-ethyl]-[1,4]diazepan-5-one	4-(1H-Pyrazol-3-yl)-piperidine (intermediate 12)	490.2
128	4-(3-[4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl]-ethylamino)-cyclohexanecarboxylic acid ethyl ester	Piperidine-4-carboxylic acid ethyl ester	496.2
129	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-trifluoromethyl-piperidin-1-yl)-ethyl]-[1,4]diazepan-5-one	4-Trifluoromethyl-piperidine	492.1
130	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-fluoro-piperidin-1-yl)-ethyl]-[1,4]diazepan-5-one	4-Fluoro-piperidine	442.1
131	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-(4-methyl-piperazin-1-yl)-ethyl]-	1-Methyl-piperazine	439.2

	[1,4]diazepan-5-one		
132	4-[3-(4-Methyl-4-hydroxy-piperidin-1-yl)-ethyl]-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	4-Methyl-piperidin-4-ol	454.1
133	4-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-ethylamino)-cyclohexanecarboxylic acid amide	Piperidine-4-carboxylic acid amide	467.1
134	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{3-[methyl-(tetrahydro-pyran-4-yl)-amino]-ethyl}-[1,4]diazepan-5-one	Methyl-(tetrahydro-pyran-4-yl)-amine	454.2
135	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{3-[(3-hydroxy-propyl)-amino]-ethyl}-[1,4]diazepan-5-one	3-Amino-propan-1-ol	414.1
136	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-(1-isopropyl-piperidin-4-ylamino)-ethyl]-[1,4]diazepan-5-one	1-Isopropyl-piperidin-4-ylamine	481.2
137	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-(1-methyl-piperidin-4-ylamino)-ethyl]-[1,4]diazepan-5-one	1-Methyl-piperidin-4-ylamine	453
138	cis/trans-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{3-[(4-methyl-cyclohexyl)-amino]-ethyl}-[1,4]diazepan-5-one	Cis/trans-4-Methyl-cyclohexylamine	452.1
139	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-hydroxy-piperidin-1-yl)-ethyl]-[1,4]diazepan-5-one	Piperidin-4-ol	440.1
140	(+/-)-cis-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-[(3-methoxy-tetrahydro-pyran-4-yl)-amino]-ethyl]-[1,4]diazepan-5-one	(+/-)-cis-(3-Methoxy-tetrahydro-pyran-4-yl)-amine	470.1

		(intermediate 20)	
141	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-((R)-3-hydroxy-piperidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(R)-3-Hydroxypiperidine	440.2
142	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-((S)-3-hydroxy-piperidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(S)-3-Hydroxypiperidine	440.2
143	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-((R)-3-hydroxy-pyrrolidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(R)-3-hydroxy pyrrolidine	– 426.1
144	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-((S)-3-hydroxy-pyrrolidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(S)-3-hydroxy pyrrolidine	– 426.1
145	(S)-1-(2-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-ethyl)-pyrrolidine-2-carboxylic acid methylamide	(S)-pyrrolidine-2-carboxylic acid methylamide	467.2
146	(S)-1-(2-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-ethyl)-pyrrolidine-2-carboxylic acid amide	(S)-pyrrolidine-2-carboxylic acid amide	453.1
147	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-((S)-3-ethoxy-pyrrolidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(S)-3-ethoxy-pyrrolidine	454.2
148	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-((2S,4R)-4-hydroxy-2-hydroxymethyl-pyrrolidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(2S,4R)-4-hydroxy-2-hydroxymethyl-pyrrolidine (intermediate 21)	456.1
149	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-((2S,4S)-4-hydroxy-2-hydroxymethyl-pyrrolidin-1-yl)-ethyl]-	(2S,4S)-4-hydroxy-2-hydroxymethyl-	456.1

	[1,4]diazepan-5-one	pyrrolidine (intermediate 22)	
150	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-((2R,3S)-3-hydroxy-2-hydroxymethyl-pyrrolidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(2R,3S)-3-hydroxy-2-hydroxymethyl-pyrrolidine	456.1
151	(2S,3S)-1-(2-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-ethyl)-3-hydroxy-pyrrolidine-2-carboxylic acid methyl ester	(2S,3S)-3-hydroxy-pyrrolidine-2-carboxylic acid methyl ester	484.1

Example 152

(+/-)-cis-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{2-[(3-methoxy-tetrahydro-pyran-4-yl)-methyl-amino]-ethyl}-[1,4]diazepan-5-one

- 5 To the crude reaction mixture from (+/-)-cis-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-{2-[(3-methoxy-tetrahydro-pyran-4-yl)-amino]-ethyl}-[1,4]diazepan-5-one (example 140) was added 2 drops of 36% aqueous formaldehyde solution and the mixture shaken for 1h. The reaction was then concentrated and the residue purified by flash column chromatography (CH₂Cl₂: MeOH 1:0-8:2) affording the titled product (21 mg, 44%) as a
- 10 colourless solid. MS: 484.1 (MH⁺, 2Cl).

Example 153

8-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-8-methyl-2,4-dioxo-1,3-diaza-8-azonia-spiro[4.5]decane iodide

- 15 To a solution of 8-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione (example 48) (10 mg, 19 umol) in MeOH (0.5 ml) was added iodomethane (10 uL, 95 umol) and the reaction left for 2 days at room temperature. Concentration of the mixture affording the title product (13 mg, 98%) as a white solid. MS: 536.1 (M⁺, 2Cl).

Example 154

1-(3-{4-[3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-1-methyl-piperidinium iodide

- To a solution of 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one (example 4) (27 mg, 62 μ mol) in MeOH (0.5 ml) was added
- 5 iodomethane (40 μ L, 620 μ mol) and the reaction left for overnight at room temperature. Concentration of the mixture affording the title product (35 mg, 98%) as a white solid. MS: 452.2 (M^+ , 2Cl).

Example 155

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(4-morpholin-4-yl-butyl)-[1,4]diazepan-5-one

A) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(4-morpholin-4-yl-butyl)-

5 [1,4]diazepan-5-one

In analogy to the procedure described in example 5D, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-(4-iodo-butyl)-[1,4]diazepan-5-one (example 9C) and morpholine (10 eq, with no additional sodium iodide) gave the title compound as light yellow oil. MS: 454.2 (MH⁺, 2Cl).

Example 156

1-[(E)-(3-Phenyl-acryloyl)]-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

A) 1-[(E)-(3-Phenyl-acryloyl)]-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

In analogy to the procedure described in example 11A, 4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one-dihydrochloride (intermediate 4B) and (E)-cinnamic acid gave the
15 title compound as off-white solid. MS: 370.2 (MH⁺).

Example 157

1-((E)-3-Naphthalen-2-yl-acryloyl)-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

A) 1-((E)-3-Naphthalen-2-yl-acryloyl)-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-

20 one

In analogy to the procedure described in example 11A, 4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one-dihydrochloride (intermediate 4B) and 2-naphthylacrylic acid gave the title compound as white solid. MS: 420.2 (MH⁺)

Example 158

25 4-(1-Benzyl-piperidin-4-yl)-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one

A) {2-[Acryloyl-(1-benzyl-piperidin-4-yl)-amino]-ethyl}-carbamic acid tert-butyl ester

To a solution of benzylpiperidone (5 g, 26 mmol) and (2-amino-ethyl)-carbamic acid tert-butyl ester (4.23 g, 26 mmol) and acetic acid (2.5 ml, 53 mmol) in CH₂Cl₂ (50.0 ml) was slowly added NaBH(OAc)₃ (6.69 g, 32 mmol). On completion of the addition the reaction was stirred for 0.5 h. Saturated NaHCO₃ (30 ml) was then cautiously added until the pH was basic. A solution of acrylyl chloride (2.3 ml, 29 mmol) in CH₂Cl₂ (10.0 ml) was then added and the reaction stirred for a further 1h. The organic layer was then separated, dried (Na₂SO₄) and concentrated. The product was isolated by flash column chromatography (EtOAc) to afford the title compound as a light yellow foam (6 g, 58%). MS: 388.2 (MH⁺).

10

B) 4-(1-Benzyl-piperidin-4-yl)-5-oxo-[1,4]diazepane-1-carboxylic acid tert-butyl ester

To a solution of {2-[Acryloyl-(1-benzyl-piperidin-4-yl)-amino]-ethyl}-carbamic acid tert-butyl ester (4.6 g, 12 mmol) in DMF (40 ml) was added potassium tert-butoxide (0.1 g, 1 mmol) and the reaction stirred for 2h after which time it was concentrated, the residue dissolved in CH₂Cl₂, washed with saturated NaHCO₃, dried (Na₂SO₄), and concentrated. The product was isolated by flash column chromatography (CH₂Cl₂: MeOH 9:1) to afford the title compound (3.5 g, 75%) as a white solid. MS: 388.3 (MH⁺)

20

C) 4-(1-Benzyl-piperidin-4-yl)-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one

4-(1-Benzyl-piperidin-4-yl)-5-oxo-[1,4]diazepane-1-carboxylic acid tert-butyl ester (1.5 g, 4 mmol) was dissolved in trifluoroacetic acid (10 ml) and the reaction stirred for 1h. The reaction was concentrated to dryness, portioned between CH₂Cl₂ (20 ml) and saturated NaHCO₃ (20 ml) and a solution of (E)-3-(3,4-dichloro-phenyl)-acryloyl chloride (prepared by Vilsmeier-Heck reaction on the acid) (0.9g, 4 mmol) in CH₂Cl₂ (10 ml) was added dropwise. The reaction was stirred for 0.5h after which time the organic was collected, dried (Na₂SO₄), and concentrated to afford the title compound (1.8 g, 92%) as a white solid. MS: 486.9 (MH⁺, 2Cl).

30

Example 159

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-hydroxy-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one

In analogy to examples 35-91, 3-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-
5 [1,4]diazepan-1-yl}-propionaldehyde (intermediate 2) was reacted with piperidine-4-ol to afford the title product as a white solid. MS: 454.4 (MH⁺, 2Cl).

Example 160

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(2-pyrrolidin-1-yl-ethyl)-[1,4]diazepan-5-one

10 In analogy to examples 14-26, 4-(2-pyrrolidin-1-yl-ethyl)-[1,4]diazepan-5-one-dihydrochloride (intermediate 5) was reacted with 3, 4-dichlorocinnamic acid to afford the title compound as a white solid. MS: 410.3 (MH⁺, 2Cl).

Example 161

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-hydroxy-piperidin-1-yl)-butyl]-
15 [1,4]diazepan-5-one

A) (rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-hydroxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one

In analogy to the procedure described in example 5D, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-(3-iodo-propyl)-[1,4]diazepan-5-one and (rac)-3-hydroxy-piperidine (10
20 equivalents, with no additional sodium iodide) gave after purification on a flash isolate NH₂-column (n-heptane/EtOAc 1:4 to 1:9 and EtOAc) the title compound as a light yellow oil. MS: 468.1 (MH⁺, 2Cl).

Example 162

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(5-piperidin-1-yl-pentyl)-[1,4]diazepan-5-
25 one

A) 4-(5-Chloro-pentyl)-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one

In analogy to the procedure described in example 5A, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 1A)) and 1-chloro-5-iodopentane gave the title compound as yellow oil. MS: 416.9 (MH⁺, 3Cl).

B) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(5-iodo-pentyl)-[1,4]diazepan-5-one

In analogy to the procedure described in example 6D, 4-(5-chloro-pentyl)-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one and sodium iodide were stirred at 90 °C for 20 h to give the title compound as orange oil. MS: 509.2 (MH⁺, 2Cl).

5 C) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(5-piperidin-1-yl-pentyl)-[1,4]diazepan-5-one

In analogy to the procedure described in example 5D, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-(5-iodo-pentyl)-[1,4]diazepan-5-one and piperidine (10 equivalents, with no additional sodium iodide) gave the title compound as yellow oil. MS: 466.2 (MH⁺, 2Cl).

10

Example 163

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-((3RS,4SR)-3,4-dihydroxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one hydrochlorid

A) 4-[4-[(3RS,4SR)-3,4-Bis-(tert-butyl-dimethyl-silanyloxy)-piperidin-1-yl]-butyl]-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one

- 15 A solution of 0.279 g (0.56 mmol) of 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-(4-iodo-butyl)-[1,4]diazepan-5-one (example 9B) in 2 ml of DMA was treated with 0.195 ml (0.56 mmol) of (cis)-(rac)-3,4-Bis-(tert-butyl-dimethyl-silanyloxy)-piperidine (intermediate 25) and 0.184 g (0.56 mmol) of cesium carbonate. After 2.25 h at RT, CH₂Cl₂ was added, filtrated and evaporated. Purification by catridges, Si-Amine, 50 g, (EtOAc/n-heptane 4:1) gave 0.300 g (75%) of the title compound as light brown foam.
20 MS: 712.6 (MH⁺, 2Cl).

B) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-((3RS,4SR)-3,4-dihydroxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one hydrochlorid

- A solution of 0.100 g (0.14 mmol) of 4-[4-[(3RS,4SR)-3,4-bis-(tert-butyl-dimethyl-silanyloxy)-piperidin-1-yl]-butyl]-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-
25 [1,4]diazepan-5-one in 2 mL of MeOH was cooled (0 °C), treated with 0.35 ml (1.40 mmol) of 4M HCl in dioxane and stirred at RT for 2h. The solution was evaporated, dissolved in toluene and evaporated (2x) to yield 0.053 g (73%) of the title compound as light brown foam. MS: 484.2 (MH⁺, 2Cl).

Example 164

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-((3RS,4RS)-3,4-dihydroxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one hydrochloride

5 A) 4-{4-[(3RS,4RS)-3,4-Bis-(tert-butyl-dimethyl-silanyloxy)-piperidin-1-yl]-butyl}-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one

In analogy to the procedure described in example 163A, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-(4-iodo-butyl)-[1,4]diazepan-5-one (example 9B) and (trans)-(rac)-3,4-Bis-(tert-butyl-dimethyl-silanyloxy)-piperidine (intermediate 26) gave the title compound as colorless oil. MS: 712.5 (MH⁺, 2Cl).

10 B) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-((3RS,4RS)-3,4-dihydroxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one hydrochloride

In analogy to the procedure described in example 163B, 4-{4-[(3RS,4RS)-3,4-bis-(tert-butyl-dimethyl-silanyloxy)-piperidin-1-yl]-butyl}-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one gave the title compound as off-white solid. MS: 484.4
15 (MH⁺, 2Cl).

Example 165

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-((3RS,4RS)-3,4-dihydroxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one

20 A) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-((3RS,4RS)-3,4-dihydroxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one

A solution of 0.025 g (0.05 mmol) 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-[4-((3RS,4RS)-3,4-dihydroxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one was dissolved in EtOAc and washed with aqueous saturated NaHCO₃. The water phase was extracted with EtOAc(2x), the organic phases washed with aqueous saturated NaHCO₃, dried over
25 Na₂SO₄ and evaporated to give 0.017 g (73%) of the title compound as colorless foam. MS: 484.2 (MH⁺, 2Cl).

Example 166

(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(2-hydroxy-3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

A) (rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-oxiranylmethyl-[1,4]diazepan-5-one

5 one

A solution of 1.50 g (4.79 mmol) of 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 1A) in 30 ml of DMF, with 0.29 g (6.71 mmol) of NaH (55 % in oil) was stirred for 30 min at 0 °C and then treated slowly with 0.47 ml (5.75 mmol) of 2-bromomethyl-oxirane in 15 ml DMF. After 3.5 h at 0 °C, the reaction
10 was extracted with aqueous saturated NaHCO₃ / EtOAc (3x). The organic phases were washed with aqueous saturated NaHCO₃, dried over Na₂SO₄ and evaporated to yield 2.79 g (quantitative) of the crude title compound as off-white semisolid, which was used directly in the next steps. MS: 368.9 (MH⁺, 2Cl).

B) (rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(2-hydroxy-3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

15 propyl)-[1,4]diazepan-5-one

A solution of 0.30 g (0.81 mmol) of (rac)-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-oxiranylmethyl-[1,4]diazepan-5-one in 0.3 ml of DMA was treated with 0.19 ml (1.22 mmol) of piperidine and 0.265 g (0.81 mmol) of cesium carbonate. The reaction was stirred over night at RT, CH₂Cl₂ was added, filtrated and evaporated. Crystallization
20 (CH₂Cl₂/Et₂O) gave 0.16 g (43%) of the title compound as pink crystalline solid. MS: 454.2 (MH⁺, 2Cl).

Example 167

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-((S)-2-hydroxy-3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

25 A) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-((R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-[1,4]diazepan-5-one

A solution of 6.26 g (20.00 mmol) of 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 1A) in 200 ml of THF was treated at 0 °C with 2.47 g (22.00 mmol) of potassium tert-butyrate and after 10 min with 5.73 (20.00 mmol) of
30 toluene-4-sulfonic acid (S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester. The reaction was stirred for 14 h at RT, 28 h at reflux temperature, cooled and extracted with aqueous

saturated NaHCO_3 / Et_2O (3x). The organic phases were washed with aqueous saturated NaHCO_3 , aqueous 10 % NaCl , dried over Na_2SO_4 evaporated and purified by flash silica gel column ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 97.5/2.5) to yield 4.27 g (50 %) of the title compound as off-white powder. MS: 427.1 (MH^+ , 2Cl).

5 B) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-((R)-2,3-dihydroxy-propyl)-[1,4]diazepan-5-one

A solution of 4.16 g (9.72 mmol) of 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-((R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-[1,4]diazepan-5-one in 35 ml of methanol and 3.8 ml of water was treated with 1.95 g of Dowex 50WX8 (activated with aqueous 25% HCl and washed neutral with water). The reaction was stirred for 10 h at reflux temperature, cooled, evaporated, dissolved in CH_2Cl_2 , dried over Na_2SO_4 and evaporated to yield 3.37 g (89 %) of the title compound as light yellow foam. MS: 387.1 (MH^+ , Cl).

C) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(R)-1-oxiranylmethyl-[1,4]diazepan-5-one

15 An ice-cooled solution of 0.50 g (1.30 mmol) of 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-((R)-2,3-dihydroxy-propyl)-[1,4]diazepan-5-one and 1.72 ml (13.00 mmol) of 2,4,6-trimethyl-pyridine in 5.2 ml of DMF was treated with 0.11 ml (1.36 mmol) of methanesulfonyl chloride in 0.3 mL of DMF. The reaction was stirred 2.5 h at 0 °C and 1 h at RT. After cooling (0 °C), 0.13 g (2.86 mmol) of NaH (55 % in oil) was added and the
20 reaction was continued at this temperature for 16 h. The solution was poured on cold aqueous 10% KH_2PO_4 and extracted with Et_2O (3x). The organic phases were washed with aqueous 10% KH_2PO_4 (2x), aqueous saturated NaHCO_3 and aqueous 10% NaCl , dried (Na_2SO_4) and concentrated to yield after precipitation ($\text{CH}_2\text{Cl}_2/\text{n-pentane}$) 0.38 g (78 %) of the title compound as light yellow powder. MS: 368.9 (MH^+ , 2Cl).

25 D) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-((S)-2-hydroxy-3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

A suspension of 0.10 g (0.27 mmol) of 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-(R)-1-oxiranylmethyl-[1,4]diazepan-5-one in 0.27 ml of EtOH was treated at 0 °C with 0.04 ml (0.40 mmol) of piperidine. The reaction was stirred for 20 h at RT, then evaporated,
30 suspended in toluene and evaporated again. Precipitation ($\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}/\text{n-pentane}$) gave 0.10 g (84%) of the title compound as off-white powder with 90% ee. MS: 454.1 (MH^+ , 2Cl). (The enantiomeric purity was determined with a chiralpak-ADH column, 25cm*4.6mm, No.DL182 and 30% n-heptane + 70% ($\text{EtOH}+0.01\text{M NH}_4\text{AcOH}$) as

eluent. The purity corresponds to the purity of toluene-4-sulfonic acid (S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester).

Example 168

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-((R)-2-hydroxy-3-piperidin-1-yl-propyl)-
5 [1,4]diazepan-5-one

A) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-((R)-2-hydroxy-3-piperidin-1-yl-propyl)-
[1,4]diazepan-5-one

135 mg of (rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-((S)-2-hydroxy-3-piperidin-
1-yl-propyl)-[1,4]diazepan-5-one (example 166) were separated with a chiralpak-ADH
10 column, 5 μ M, 25cm*20mm, Daicel, Cat.-No. 19345 and 25% n-heptane + 75%
(EtOH/MeOH 25:75v/v) as eluent. 48.9 mg (36%) of 1-[(E)-3-(3,4-dichloro-phenyl)-
acryloyl]-4-((S)-2-hydroxy-3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one (99.4%ee)
(example 167D) and 50 mg (37%) of 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-((R)-2-
hydroxy-3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one (99.6%ee) was isolated as a white
15 foam. MS: 454.1 (MH⁺, 2Cl). (The enantiomeric purity was determined with a chiralpak-
ADH column, Daicel, Cat.-No. 19325, 25cm*4.6mm and 35% n-heptan + 65% EtOH as
eluent).

Example 169

(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-fluoro-piperidin-1-yl)-2-
20 hydroxy-propyl]-[1,4]diazepan-5-one

A) (rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-fluoro-piperidin-1-yl)-2-
hydroxy-propyl]-[1,4]diazepan-5-one

A solution of 0.080 g (0.22 mmol) of (rac)-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-
oxiranylmethyl-[1,4]diazepan-5-one (example 166A) in 0.5 ml of MeOH was treated with
25 0.038 (0.26 mmol) of 4-fluoropiperidine hydrochloride and 0.15 ml (1.08 mmol) of Et₃N
in 0.5 ml of MeOH. The reaction was stirred for 24 h at RT, partitioned between
aqueous saturated NaHCO₃ and extracted with Et₂O (3x). The organic phase was dried
over Na₂SO₄ and evaporated to give after flash silica gel column (CH₂Cl₂/MeOH 98:2)
0.0099 g (10%) of the title compound as white foam. MS: 471.9 (MH⁺, 2Cl).

Example 170

(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(3-hydroxy-4-piperidin-1-yl-butyl)-[1,4]diazepan-5-one

5 A) (rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(2-oxiranyl-ethyl)-[1,4]diazepan-5-one

In analogy to the procedure described for example 166A, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 1A) and (rac)-2-(2-bromo-ethyl)-oxirane (Journal of Organic Chemistry (1969), 34(12), 4060-5) gave after extraction with Et₂O instead of EtOAc the title compound as yellow oil. MS: 383.2 (MH⁺, 2Cl).

10 B) (rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(3-hydroxy-4-piperidin-1-yl-butyl)-[1,4]diazepan-5-one

In analogy to the procedure described for example 167D, (rac)-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-(2-oxiranyl-ethyl)-[1,4]diazepan-5-one and piperidine gave the title compound as yellow oil. MS: 468.1 (MH⁺, 2Cl).

15 Example 171

(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(3-hydroxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one

A) (rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(3-hydroxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one

20 In analogy to the procedure described for example 167D, (rac)-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-(2-oxiranyl-ethyl)-[1,4]diazepan-5-one and 3-hydroxypiperidine gave the title compound as yellow oil. MS: 484.2 (MH⁺, 2Cl).

Example 172

25 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-((R)-3-hydroxy-4-piperidin-1-yl-butyl)-[1,4]diazepan-5-one

A) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-((R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl]-[1,4]diazepan-5-one

In analogy to the procedure described for example 167A, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 1A)) and methanesulfonic acid 2-((R)-2,2-

dimethyl-[1,3]dioxolan-4-yl)-ethyl ester (prepared from 2-((R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-ethanol and methanesulfonyl chloride) gave after reaction at RT, the title compound as an off-white foam. MS: 441.1 (MH^+ , 2Cl).

5 B) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-((R)-3,4-dihydroxy-butyl)-[1,4]diazepan-5-one

In analogy to the procedure described for example 167B, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-[2-((R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl]-[1,4]diazepan-5-one gave after 3 h at reflux, the title compound as a white foam. MS: 401.2 (MH^+ , 2Cl).

10 C) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-((R)-2-oxiranyl-ethyl)-[1,4]diazepan-5-one

In analogy to the procedure described for example 167C, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-((R)-3,4-dihydroxy-butyl)-[1,4]diazepan-5-one gave the title compound as an off-white foam. MS: 383.0 (MH^+ , 2Cl).

15 D) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-((R)-3-hydroxy-4-piperidin-1-yl-butyl)-[1,4]diazepan-5-one

In analogy to the procedure described for example 167D, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-((R)-2-oxiranyl-ethyl)-[1,4]diazepan-5-one the title compound as a white foam with 94% ee. MS: 368.3 (MH^+ , 2Cl). (The enantiomeric purity was determined with a chiralpak-ADH column, 25cm*4.6mm, No.DL182 and 50% n-heptan + 50% (EtOH+0.01M NH_4AcOH) as eluent. The purity corresponds to the purity of 2-((R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-ethanol).

Example 173

1-((Z)-3-Naphthalen-1-yl-acryloyl)-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

A) 1-((Z)-3-Naphthalen-1-yl-acryloyl)-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

25 In analogy to the procedure described for example 11A, 4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one-dihydrochloride (intermediate 4B) and (Z)-3-naphthalen-1-yl-acrylic acid gave the title compound as light yellow foam. MS: 420.1 (MH^+).

Example 174

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(2,2-dimethyl-3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

A) 2,2-Dimethyl-3-piperidin-1-yl-propan-1-ol

- 5 A solution of 3.00 g (17.96 mmol) of 3-bromo-2,2-dimethyl-propan-1-ol, 17.78 ml (179.59 mmol) of piperidine, 2.48 g (17.96 mmol) of K_2CO_3 and 2.69 g (17.96 mmol) of potassium iodide in 20 ml of DMA were stirred at 70 °C for 20 h. After filtration and evaporation of the solvents, the crude product was dissolved in diluted aqueous HCl solution and washed with EtOAc (3x). The aqueous phase was basified with $KHCO_3$ and
10 some drops of 1N NaOH and extracted with EtOAc (3x). The organic phase was dried (Na_2SO_4) and evaporated to give 0.57 g (18%) of the title compound as yellow liquid. MS: 172.0 (MH^+).

B) Methanesulfonic acid 2,2-dimethyl-3-piperidin-1-yl-propyl ester

- A solution of 0.51 g (2.99 mmol) of 2,2-dimethyl-3-piperidin-1-yl-propan-1-ol in 7 ml of
15 dichloromethane was treated at 0 °C with 0.24 ml (179.59 mmol) of methanesulfonyl chloride and stirred at RT for 2.5 h. The reaction was extracted with aqueous saturated $NaHCO_3$ / Et_2O (3x). The organic phases were washed with aqueous saturated $NaHCO_3$, dried over Na_2SO_4 and evaporated to give 0.85 g (quantitative) of the title compound as light brown oil. MS: 249.2 (M^+).

20 C) 1-(3-Iodo-2,2-dimethyl-propyl)-piperidine

In analogy to the procedure described for example 6D, methanesulfonic acid 2,2-dimethyl-3-piperidin-1-yl-propyl ester and sodium iodide stirred at 95 °C for 3 h gave the title compound as brown oil. MS: 282.1 (MH^+).

25 D) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(2,2-dimethyl-3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

In analogy to the procedure described for intermediate 4A, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 1A) and 1-(3-iodo-2,2-dimethyl-propyl)-piperidine stirred 2 h at RT, gave the title compound as white solid. MS: 466.3 (MH^+ , 2Cl).

Example 175

1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-((S)-2-hydroxy-3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

A) 1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-(R)-1-oxiranylmethyl-

5 [1,4]diazepan-5-one

In analogy to the procedure described for example 167A to 167C, 1-[(E)-3-(3-chloro-4-fluoro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 54) and toluene-4-sulfonic acid (S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester gave the title compound as light yellow viscous oil. MS: 353.1 (MH⁺, 1Cl).

10 B) 1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-((S)-2-hydroxy-3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

In analogy to the procedure described for example 167D, 1-[(E)-3-(3-chloro-4-fluorophenyl)-acryloyl]-4-(R)-1-oxiranylmethyl-[1,4]diazepan-5-one and piperidine gave the title compound as off-white foam. MS: 438.3 (MH⁺, 1Cl).

15

Example 176

(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(2-hydroxy-2-methyl-3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

A) (rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(2-hydroxy-2-methyl-3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

20 In analogy to the procedure described for example 166, 1-[(E)-3-(3,4-dichloro-phenyl)-
acryloyl]-[1,4]diazepan-5-one (intermediate 1A) and 2-chloromethyl-2-methyloxirane
with 0.3 equivalent of potassium iodide gave the intermediate 1-[(E)-3-(3,4-dichloro-
phenyl)-acryloyl]-4-(2-methyl-oxiranylmethyl)-[1,4]diazepan-5-one which was reacted
with no work up with piperidine in ethanol to give the title compound as light yellow
25 waxy solid. MS: 468.2 (MH⁺, 2Cl).

Example 177

(rac)-1-[(E)-3-(3,4-Difluoro-phenyl)-acryloyl]-4-(2-hydroxy-3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

A) (rac)-1-[(E)-3-(3,4-Difluoro-phenyl)-acryloyl]-4-oxiranylmethyl-[1,4]diazepan-5-one

- 5 In analogy to the procedure described for example 166A, 1-[(E)-3-(3,4-difluoro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 55) and 2-bromomethyl-oxirane gave the title compound as yellow oil. MS: 337.2 (MH⁺).

B) (rac)-1-[(E)-3-(3,4-Difluoro-phenyl)-acryloyl]-4-(2-hydroxy-3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

- 10 In analogy to the procedure described for example 166B, (rac)-1-[(E)-3-(3,4-difluoro-phenyl)-acryloyl]-4-oxiranylmethyl-[1,4]diazepan-5-one and piperidine gave the title compound as light yellow viscous oil. MS: 422.2 (MH⁺).

Example 178

- 15 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-((S)-3-hydroxy-4-piperidin-1-yl-butyl)-[1,4]diazepan-5-one

A) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-((S)-3,4-dihydroxy-butyl)-[1,4]diazepan-5-one

- 20 In analogy to the procedure described for example 167A and 167B, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 1A)) and methanesulfonic acid 2-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester (prepared from 2-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl)-ethanol and methanesulfonyl chloride) gave the title compound as a white foam. MS: 401.3 (MH⁺, 2Cl).

B) Methanesulfonic acid (S)-4-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-2-hydroxy-butyl ester

- 25 In analogy to the procedure described for example 167C, 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-((S)-3,4-dihydroxy-butyl)-[1,4]diazepan-5-one with 2,4,6-trimethyl-pyridine and methanesulfonyl chloride in CH₂Cl₂ gave the intermediate mesylate as a white foam. MS: 479.0 (MH⁺, 2Cl).

C) 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-((S)-3-hydroxy-4-piperidin-1-yl-butyl)-[1,4]diazepan-5-one

In analogy to the procedure described for example 166B, Methanesulfonic acid (S)-4-[4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl]-2-hydroxy-butyl ester with catalytic amount of sodium iodide, 1.2 equivalent of cesium carbonate and 5 equivalent of piperidine gave after 2 h at 60 °C the epoxide as intermediate. A further equivalent of cesium carbonate was added and the reaction heated at 80 °C over night to give the title compound as a colorless gum with 99% ee. MS: 368.1 (MH⁺, 2Cl). (The enantiomeric purity was determined with a chiralpak-ADH column, 25cm*4.6mm, No.DL182 and 50% n-heptane + 50% (EtOH+0.01M NH₄AcOH) as eluent. The purity corresponds to the purity of 2-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl)-ethanol).

Example 179

(rac)-2-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-5-piperidin-1-yl-pentanoic acid methyl ester

A) (rac)-5-Bromo-2-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-pentanoic acid methyl ester

A solution of 0.501 g (1.60 mmol) of 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 1A) and 0.447 g (1.60 mmol) of methyl 2,5-dibromopentane in 7 ml of DMF was treated at 0 °C with 0.077 g (1.76 mmol) of NaH (55 % in oil). The reaction was stirred for 20 h at RT, cooled (0 °C) and treated again with 0.224 g (0.80 mmol) of methyl 2,5-dibromopentane and 0.038 g (0.88 mmol) of NaH (55 % in oil). After 1 h at 0 °C and 3 h at RT, the reaction was neutralized with cold aqueous 10 % KHSO₄ and extracted with Et₂O (3x). The organic phases were washed with aqueous 10 % KHSO₄, aqueous 10 % NaCl, dried over Na₂SO₄ evaporated and purified by flash silica gel column (CH₂Cl₂/Et₂O 95:5 to 70:30) to yield 0.39 g (48%) of the title compound as white foam. MS: 505.1 (MH⁺, 1Br).

B) (rac)-2-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-5-iodo-pentanoic acid methyl ester

In analogy to the procedure described in example 6D, 4-(5-chloro-pentyl)-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one and sodium iodide were stirred at RT for 4 h to give the title compound as yellow foam. MS: 552.2 (MH⁺, 2Cl).

C) (rac)-2-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-5-piperidin-1-yl-pentanoic acid methyl ester

A solution of 0.111 g (0.20 mmol) of 2-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-5-iodo-pentanoic acid methyl ester in 1 ml of DMA was treated at 0 °C with 0.021 ml (0.21 mmol) of piperidine and stirred 30 min at 0 °C and 1h at RT. 0.065 g (0.20 mmol) of cesium carbonate was added at 0 °C and stirring was continued for 2h. After additional 3 h at RT, the reaction was extracted with aqueous saturated NaHCO₃/Et₂O (3x). The organic phases were washed with aqueous saturated NaHCO₃, aqueous 10 % NaCl, dried over Na₂SO₄ evaporated and precipitated with CH₂Cl₂/n-pentane to yield 0.86 g (84%) of the title compound as a white foam. MS: 510.3 (MH⁺, 2Cl).

Example 180

Lithium; (rac)-2-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-5-piperidin-1-yl-pentanoate

A) Lithium; (rac)-2-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-5-piperidin-1-yl-pentanoate

A solution of 0.041 g (0.08 mmol) of the above prepared (rac)-2-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-5-piperidin-1-yl-pentanoic acid methyl ester in 4 ml of THF/MeOH (1:1), treated at 0 °C with 0.084 mL (0.08 mmol) of 1N LiOH, and kept at ambient temperature for 20 h. Water (0.32 ml) was added and heated for 1h at 40 °C. The reaction was evaporated and precipitated with CH₂Cl₂/Et₂O to give 0.028 g (70%) of the title compound as white powder. MS: 494.2 (M-H⁻, 2Cl).

Example 181

(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(1-hydroxymethyl-4-piperidin-1-yl-butyl)-[1,4]diazepan-5-one

A) (rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(1-hydroxymethyl-4-piperidin-1-yl-butyl)-[1,4]diazepan-5-one

A solution of 0.041 g (0.08 mmol) of (rac)-2-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-5-piperidin-1-yl-pentanoic acid methyl ester in 0.5 ml of ethanol was treated at 0 °C with 0.006 g (0.16 mmol) of sodium borohydride in 0.5 ml of ethanol during 5 min. The reaction was stirred for 21 h at RT, cooled (0 °C) and treated

- again with 0.006 g (0.16 mmol) of sodium borohydride in 0.5 ml ethanol. After 5 h at RT the reaction was neutralized with cold aqueous 10 % KHSO_4 and extracted with cold saturated $\text{NaHCO}_3/\text{EtOAc}$ (3x). The organic phases were washed with aqueous 10 % NaCl , dried over Na_2SO_4 , evaporated and purified by flash silica gel column
- 5 (CH₂Cl₂/MeOH 9:1 to 4:1 and then, to elute the product, with CH₂Cl₂/MeOH/25% NH_4OH 9:1:0.1) to yield after precipitation with CH₂Cl₂/n-pentane 0.022 g (57%) of the title compound as white foam. MS: 482.3 (MH^+ , 2Cl).

Example 182

- (rac)-3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-2-piperidin-1-ylmethyl-propionic acid ethyl ester
- 10

A) 2-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-ylmethyl}-acrylic acid ethyl ester

- A suspension of 2.50 g (7.98 mmol) of 1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one (intermediate 1A) and 1.15 ml (7.98 mmol) of ethyl 2-(bromomethylacrylate) in 80 ml of DMF was treated at -20 °C with 0.38 g (8.78 mmol) of NaH (55 % in oil) and warmed up naturally to 18 °C (2.5 h). After cooling (0 °C)
- 15 additionally 0.12 ml (0.80 mmol) of ethyl 2-(bromomethylacrylate) was added and after 30 min no starting material was left, based on TLC. The reaction was extracted with aqueous 10% KHSO_4 /ether (3x), the organic phases were washed with a aqueous 10%
- 20 NaCl solution, dried (Na_2SO_4) and evaporated to give 3.51 g (quantitative, 90% purity) of the crude title compound as light yellow viscous oil, which was used directly in the next step. MS: 425.1 (MH^+ , 2Cl).

B) (rac)-3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-2-piperidin-1-ylmethyl-propionic acid ethyl ester

- A suspension of 0.80 g (1.88 mmol) of 2-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-ylmethyl}-acrylic acid ethyl ester, 0.56 ml (5.64 mmol) of piperidine and 1.83 g (5.61 mmol) of cesium carbonate in 32 ml of acetonitrile was stirred over night at RT. Additional 0.37 ml (3.76 mmol) of piperidine were added and after 1 h, cesium carbonate was filtrated and the solvent evaporated. Purification by flash silica gel column
- 25 (CH₂Cl₂/MeOH 98:2 to 96:4) gave 0.43 g (44%) of the title compound as colorless foam. MS: 510.4 (MH^+ , 2Cl).
- 30

Example 183

Lithium; (rac)-3-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-2-piperidin-1-ylmethyl-propionate

- 5 A) Lithium; (rac)-3-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-2-piperidin-1-ylmethyl-propionate

In analogy to the procedure described in example 180, (rac)-3-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-2-piperidin-1-ylmethyl-propionic acid ethyl ester gave the title as colorless solid. MS: 480.1 (M-H⁺, 2Cl).

Examples 184-187

- 10 The following examples were produced from the appropriate [1,4]-diazepan-5-one derivative and 1-(3-chloropropyl)piperidine in analogy to the procedure described in intermediate 4A:

Example No.	Compound Name	[1,4]-diazepan-5-one derivative	MS: (MH ⁺)
184	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-3-methyl-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-3-methyl-[1,4]diazepan-5-one (Intermediate 77)	452.2
185	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-methyl-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-methyl-[1,4]diazepan-5-one (Intermediate 78)	452.1
186	(R)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-2-methyl-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one	(R)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-2-methyl-[1,4]diazepan-5-one (Intermediate 79)	452.1
187	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-6-methyl-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-6-methyl-[1,4]diazepan-5-one (Intermediate 80)	452.2

Example 188

1-[(E)-3-(3-Chloro-phenyl)-acryloyl]-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one

To a suspension of (E)-3-(3-Chloro-phenyl)-acrylic acid (26 mg, 0.12 mmol), 4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one-dihydrochloride (intermediate 4) (24 mg, 0.1 mmol), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (46 mg, 0.12 mmol) in DMF (1 ml) was added Et₃N (21 ul, 0.15 mmol) and the mixture shaken for 1h. The reaction was then directly purified by preparative HPLC affording the title product (28 mg, 69%) as a white powder. MS: 404.2 (MH⁺).

Examples 189-22410 General Procedure for Examples 189-224

A solution of 3-{4-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propionaldehyde (intermediate 59) (0.1 mmol) in DCE (0.5 ml) was added to the appropriate amine (0.1 mmol), which are either commercially available or are described in the intermediate section, followed by a freshly prepared solution of pyridine-borane complex (25 ul, 8M in pyridine, 0.2 mmol) and acetic acid (25 ul) in EtOH (0.5 ml). The reaction was then shaken overnight, concentrated and the residue purified by preparative HPLC.

Example No.	Compound Name	Amine	MS: (MH ⁺)
189	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one	(-)-6-Aza-spiro[2.5]octan-4-ol (intermediate 83)	464.4
190	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(+, cis)-3-hydroxy-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(3S, 4S)-4-Methyl-piperidin-3-ol (intermediate 85)	452.4
	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-((-, cis)-3-hydroxy-4-	(-, cis)-4-Methyl-piperidin-3-ol	452.4

191	methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(intermediate 86)	
192	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-((+)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one	(+)-6-Aza-spiro[2.5]octan-4-ol (intermediate 82)	464.4
193	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-((R)-3-hydroxy-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(R)-piperidin-3-ol	438.2
194	8-(3-{4-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-1,3,8-triazaspiro[4.5]decan-2,4-dione	1,3,8-Triaza-spiro[4.5]decan-2,4-dione (intermediate 11)	506.2
195	8-(3-{4-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one	2,8-Diaza-spiro[4.5]decan-1-one (intermediate 14)	493.2
196	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(4-hydroxy-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	piperidin-4-ol	438.2
197	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(tetrahydro-pyran-4-ylamino)-propyl]-[1,4]diazepan-5-one	Tetrahydro-pyran-4-ylamine	438.2
198	8-(3-{4-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-2,8-diaza-spiro[4.5]decan-3-one	2,8-Diaza-spiro[4.5]decan-3-one (intermediate 18)	491.2
199	1-(3-{4-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-piperidine-4-carbonitrile	Piperidine-4-carbonitrile	447.2

200	N-[1-(3-{4-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-piperidin-4-yl]-methanesulfonamide	N-Piperidin-4-yl-methanesulfonamide (intermediate 29)	515.2
201	[1-(3-{4-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-piperidin-4-yl]-carbamic acid methyl ester	Piperidin-4-yl-carbamic acid methyl ester (intermediate 38)	495.2
202	Ethyl-carbamic acid 1-(3-{4-[(E)-3-(3-chloro-4-fluoro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-piperidin-4-yl ester	Ethyl-carbamic acid piperidin-4-yl ester (intermediate 41)	509.2
203	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-{3-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-propyl}-[1,4]diazepan-5-one	4-(5-Methyl-[1,3,4]oxadiazol-2-yl)-piperidine (intermediate 42)	504.2
204	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-{3-[4-(5-methyl-[1,3,4]oxadiazol-2-yl)-piperidin-1-yl]-propyl}-[1,4]diazepan-5-one	4-(5-Methyl-[1,3,4]oxadiazol-2-yl)-piperidine (intermediate 43)	504.2
205	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(3-hydroxy-3-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-methyl-piperidin-3-ol (intermediate 101)	452.2
206	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(4-dimethylamino-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	4-dimethylamino-piperidine	465.2
207	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(4-[1,2,4]triazol-1-yl)-piperidin-1-yl]-propyl]-[1,4]diazepan-5-	4-(2H-[1,2,4]Triazol-1-yl)-piperidine (intermediate 28)	489.2

	one		
208	(rac, trans)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(3-hydroxy-2-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac, trans)-2-Methyl-piperidin-3-ol (intermediate 87)	452.2
209	(rac, cis)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(3-hydroxy-2-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac, cis)-2-Methyl-piperidin-3-ol (intermediate 88)	452.2
210	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(2-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-2-hydroxymethyl-piperidine	452.2
211	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(3-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-hydroxymethyl-piperidine	452.2
212	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(4-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	4-hydroxymethyl-piperidine	452.2
213	(rac, trans)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(4-fluoro-3-hydroxy-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac, trans)-4-Fluoro-piperidin-3-ol (intermediate 89)	456.2
214	(rac, trans)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(3-fluoro-4-hydroxy-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac, trans)-3-Fluoro-piperidin-4-ol (intermediate 90)	456.2
215	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(cis-3-hydroxy-4-	(rac,cis)-4-hydroxymethyl-	468.3

	hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	piperidin-3-ol (intermediate 47)	
216	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(cis-3-hydroxy-4-methoxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,cis)-4-methoxymethyl piperidin-3-ol (intermediate 49)	482.3
217	(rac)-1-[(E)-3-(3-Chloro-fluoro-phenyl)-acryloyl]-4-[3-(trans-3-hydroxy-4-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,trans)-4-hydroxymethyl piperidin-3-ol (intermediate 48)	468.3
218	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(cis-3-methoxy-4-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,cis)-3-methoxy-piperidin-4-yl-methanol (intermediate 50)	482.3
219	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(cis-3-hydroxy-4-hydroxymethyl-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,cis)-4-hydroxymethyl-4-methyl-piperidin-3-ol (intermediate 52)	482.4
220	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(trans-3-hydroxy-4-hydroxymethyl-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,trans)-4-hydroxymethyl-4-methyl-piperidin-3-ol (intermediate 53)	482.3
221	(rac)-1-[(E)-3-(3-Chloro-fluoro-phenyl)-acryloyl]-4-[3-(5-hydroxy-2-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-6-methyl-piperidin-3-ol (intermediate 66)	452.3
222	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(5-hydroxy-2-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-6-hydroxymethyl-piperidin-2-ol (intermediate 65)	468.3

223	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(3-hydroxy-4,4-dimethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-4,4-dimethyl-piperidin-3-ol (intermediate 84)	466.3
224	(rac,cis)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(3-hydroxy-5-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac, cis)-5-methyl-piperidin-3-ol (intermediate 75)	452.3

Examples 225-279General Procedure for Examples 225-279

- 5 A solution of 3-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propionaldehyde (intermediate 2) (0.1 mmol) in DCE (0.5 ml) was added to the appropriate amine (0.1 mmol) which are either commercially available or are described in the intermediate section, followed by a freshly prepared solution of pyridine-borane complex (25 ul, 8M in pyridine, 0.2 mmol) and acetic acid (25 ul) in EtOH (0.5 ml). The reaction was then shaken overnight, concentrated and the residue purified by preparative HPLC.

10

Example No.	Compound Name	Amine	MS: (MH ⁺)
225	(rac,trans)-1-[(E)-3-(3,4-Dichlorophenyl)-acryloyl]-4-[3-(3-hydroxy-2-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac, trans)-2-methyl-piperidin-3-ol (intermediate 87)	468.2
226	(rac,cis)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-hydroxy-2-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac, cis)-2-methyl-piperidin-3-ol (intermediate 88)	468.2
227	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(2-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-2-hydroxymethyl-piperidine	468.2
228	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-hydroxymethyl-piperidine	468.2
229	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-	4-hydroxymethyl-piperidine	468.2

	one		
230	(rac, trans)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-fluoro-3-hydroxy-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac, trans)-4-Fluoro-piperidin-3-ol (intermediate 89)	472.2
231	(rac, trans)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-fluoro-4-hydroxy-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac, trans)-3-Fluoro-piperidin-4-ol (intermediate 90)	472.2
232	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-hydroxy-3-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-methyl-piperidin-3-ol (intermediate 101)	468.2
233	(rac, cis)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-fluoro-4-hydroxy-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac, cis)-3-Fluoro-piperidin-4-ol (intermediate 93)	472.3
234	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{3-[4-(2-methoxy-ethyl)-piperazin-1-yl]-propyl}-[1,4]diazepan-5-one	1-(2-Methoxy-ethyl)-piperazine	497.3
235	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-methyl-piperidine	452.3
236	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-methoxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-methoxymethyl-piperidine	482.3
237	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-oxo-piperazin-1-yl)-	Piperazin-2-one	453.3

	propyl]-[1,4]diazepan-5-one		
238	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-hydroxy-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-4-methyl-piperidin-3-ol (intermediate 91)	468.3
239	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(5-oxo-[1,4]diazepan-1-yl)-propyl]-[1,4]diazepan-5-one	[1,4]Diazepan-5-one	467.2
240	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-isopropyl-piperazin-1-yl)-propyl]-[1,4]diazepan-5-one	1-Isopropyl-piperazine	481.3
241	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-cyclopropyl-piperazin-1-yl)-propyl]-[1,4]diazepan-5-one	1-Cyclopropyl-piperazine	479.3
242	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-cyclopentyl-piperazin-1-yl)-propyl]-[1,4]diazepan-5-one	1-Cyclopentyl-piperazine	507.3
243	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-methyl-piperidin-4-ol (intermediate 94)	468.3
244	[1-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-piperidin-4-yl]-carbamic acid methyl ester	Piperidin-4-yl-carbamic acid methyl ester (intermediate 38)	511.3
245	[1-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-piperidin-4-yl]-methyl-carbamic acid methyl ester	Methyl-piperidin-4-yl-carbamic acid methyl ester (intermediate 39)	525.3

246	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-isopropyl-3-methyl-piperazin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-1-Isopropyl-2-methyl-piperazine	495.7
247	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-methoxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	4-methoxymethyl-piperidine	482.3
248	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-hydroxymethyl-3-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-(3-methyl-piperidin-3-yl) methanol (intermediate 30)	482.3
249	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-methoxymethyl-3-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-methoxymethyl-3-methyl-piperidine (intermediate 31)	496.3
250	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(2-hydroxymethyl-2-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-(2-methyl-piperidin-2-yl) methanol (intermediate 34)	482.3
251	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one	(rac)-6-Aza-spiro[2.5]octan-4-ol (intermediate 81)	480.3
252	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(8-hydroxy-5-aza-spiro[2.5]oct-5-yl)-propyl]-[1,4]diazepan-5-one	(rac)-5-Aza-spiro[2.5]octan-8-ol (intermediate 98)	480.3
253	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(cis-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-	(rac, cis)-3-methyl-piperidin-4-ol (intermediate 96)	468.3

	one		
254	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-hydroxymethyl-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(4-methyl-piperidin-4-yl) methanol (intermediate 32)	482.3
255	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(2-hydroxymethyl-2-methyl-pyrrolidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-2-hydroxymethyl-2-methyl-pyrrolidine	468.3
256	(rac)-[1-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-piperidin-3-yl]-carbamic acid methyl ester	(rac)-Piperidin-3-yl-carbamic acid methyl ester (intermediate 40)	511.3
257	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-hydroxy-3,3-dimethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3,3-dimethyl-piperidin-4-ol (intermediate 97)	482.4
258	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-isobutyl-piperazin-1-yl)-propyl]-[1,4]diazepan-5-one	1-Isobutyl-piperazine	495.4
259	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-((+, cis)-3-hydroxy-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(+, cis)-4-Methyl-piperidin-3-ol (intermediate 85)	468.3
260	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-((- , cis)-3-hydroxy-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(-, cis)-4-Methyl-piperidin-3-ol (intermediate 86)	468.3
261	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-((+)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-	(+)-6-Aza-spiro[2.5]octan-4-ol	480.3

	[1,4]diazepan-5-one	(intermediate 82)	
262	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one	(-)-6-Aza-spiro[2.5]octan-4-ol (intermediate 83)	480.3
263	(rac)-4-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-piperazine-2-carboxylic acid methyl ester	(rac)-Piperazine-2-carboxylic acid methyl ester	497.3
264	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-methyl-3-oxo-piperazin-1-yl)-propyl]-[1,4]diazepan-5-one	1-Methyl-piperazin-2-one	467.3
265	(rac)-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-1-oxa-4,9-diaza-spiro[5.5]undecan-3-one	(rac)-1-Oxa-4,9-diaza-spiro[5.5]undecan-3-one (intermediate 102)	523.4
266	(rac,cis)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-hydroxy-4-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,cis)-4-hydroxymethyl-piperidin-3-ol (intermediate 47)	484.3
267	(rac,cis)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-hydroxy-4-methoxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,cis)-4-methoxymethyl-piperidin-3-ol (intermediate 49)	498.3
268	(rac,trans)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-hydroxy-4-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,trans)-4-hydroxymethyl-piperidin-3-ol (intermediate 48)	484.3
269	(rac,cis)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-methoxy-4-	(rac,cis)-3-methoxymethyl-	498.3

	hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	piperidin-4-ol (intermediate 50)	
270	(rac,cis)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-hydroxy-4-hydroxymethyl-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,cis)-4-hydroxymethyl-4-methyl-piperidin-3-ol (intermediate 52)	498.3
271	(rac,trans)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-hydroxy-4-hydroxymethyl-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,trans)-4-hydroxymethyl-4-methyl-piperidin-3-ol (intermediate 53)	498.3
272	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(5-hydroxy-2-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-6-methyl-piperidin-3-ol (intermediate 66)	468.3
273	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(5-hydroxy-2-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-6-hydroxymethyl-piperidin-3-ol (intermediate 65)	484.3
274	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-hydroxy-4,4-dimethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-4,4-dimethyl-piperidin-3-ol (intermediate 97)	482.3
275	(rac,cis)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-methoxy-tetrahydro-pyran-4-ylamino)-propyl]-[1,4]diazepan-5-one	(rac,cis)-3-Methoxy-tetrahydro-pyran-4-ylamine (intermediate 20)	484.2
276	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-dimethylamino-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-dimethylamino-piperidine	481.2

277	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-dimethylamino-pyrrolidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-dimethylamino-pyrrolidine	467.2
278	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-diethylamino-pyrrolidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-diethylamino-pyrrolidine	495.2
279	(rac,cis)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-hydroxy-5-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,cis)-5-methyl-piperidin-3-ol (intermediate 75)	468.3

Examples 280-326

General Procedure for Examples 280-326

- A solution of (rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-oxiranylmethyl-
 5 [1,4]diazepan-5-one (example 166A) (0.1 mmol) in DMA (0.5 ml) was added to the appropriate amine (0.15 mmol), which are either commercially available or are described in the intermediate section, and a generous spatula of cesium carbonate added. The reaction was then shaken overnight at 80 °C, filtered, and directly purified by preparative HPLC.

10

Example No.	Compound Name	Amine	MS: (MH ⁺)
280	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(3-hydroxy-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-4-methyl-piperidin-3-ol (intermediate 91)	484.3

281	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(3-hydroxy-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-hydroxypiperidine	470.2
282	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-((trans)-3-hydroxy-2-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac, trans)-2-methyl-piperidin-3-ol (intermediate 87)	484.3
283	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(3-methoxy-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-methoxypiperidine	484.3
284	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(trans-4-fluoro-3-hydroxy-piperidin-1-yl)-2-hydroxy-propyl]-[1,4]diazepan-5-one	(rac, trans)-4-Fluoro-piperidin-3-ol (intermediate 89)	488.2
285	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(4-hydroxy-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	Piperidin-4-ol	470.2
286	(rac)1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(trans-3-fluoro-4-hydroxy-piperidin-1-yl)-2-hydroxy-propyl]-[1,4]diazepan-5-one	(rac, trans)-3-fluoro-piperidin-4-ol (intermediate 90)	488.3
287	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(cis-4-fluoro-3-hydroxy-piperidin-1-yl)-2-hydroxy-propyl]-[1,4]diazepan-5-one	(rac, cis)-3-fluoro-piperidin-4-ol (intermediate 93)	488.2
288	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(3-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-	(rac)-3-methylpiperidine	468.3

	one		
289	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(3-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-hydroxymethyl-piperidine	484.3
290	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(2-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-2-hydroxymethyl-piperidine	484.3
291	(rac)-(1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(4-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	Piperidin-4-ol	484.3
292	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(3-hydroxy-pyrrolidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-hydroxy-pyrrolidine	456.2
293	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(3-methoxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-methoxymethyl-piperidine	498.3
294	(rac)-[1-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-2-hydroxy-propyl)-piperidin-4-yl]-carbamic acid methyl ester	Piperidin-4-yl-carbamic acid methylester (intermediate 38)	527.3
295	(rac)-[1-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-2-hydroxy-propyl)-piperidin-4-yl]-methyl-carbamic acid methyl ester	Methyl-piperidin-4-yl-carbamic acid methyl ester (intermediate 39)	541.3
296	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(4-isopropyl-	1-Isopropyl-piperazine	497.4

	piperazin-1-yl)-propyl]-[1,4]diazepan-5-one		
297	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-cyclopropyl-piperazin-1-yl)-2-hydroxy-propyl]-[1,4]diazepan-5-one	1-Cyclopropyl-piperazine	495.3
298	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-cyclopentyl-piperazin-1-yl)-2-hydroxy-propyl]-[1,4]diazepan-5-one	1-Cyclopentyl-piperazine	523.4
299	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{2-hydroxy-3-[4-(2-methoxy-ethyl)-piperazin-1-yl]-propyl]-[1,4]diazepan-5-one	1-(2-Methoxy-ethyl)-piperazine	513.4
300	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-methyl-piperidin-4-ol (intermediate 94)	484.3
301	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(4-isopropyl-3-methyl-piperazin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-1-Isopropyl-2-methyl-piperazine	511.3
302	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(4-methyl-piperazin-1-yl)-propyl]-[1,4]diazepan-5-one	1-Methyl-piperazine	469.3
303	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(3-hydroxy-3-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-methyl-piperidin-3-ol (intermediate 101)	484.3

304	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(4-methoxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	4-methoxymethyl-piperidine	498.3
305	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(3-hydroxymethyl-3-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-(3-methyl-piperidin-3-yl) methanol (intermediate 30)	498.3
306	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(3-methoxymethyl-3-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-methoxymethyl-3-methyl-piperidine (intermediate 31)	512.3
307	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(2-hydroxy-2-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-(2-methyl-piperidin-2-yl) methanol (intermediate 34)	498.3
308	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(cis-4-hydroxy-2-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,cis)-2-hydroxymethyl-piperidin-4-ol (intermediate 45)	500.3
309	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one	(rac)-6-Aza-spiro[2.5]octan-4-ol (intermediate 81)	496.5
310	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(4-hydroxy-3-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3-hydroxymethyl-piperidin-4-ol (intermediate 35)	500.5
311	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(4-hydroxy-3-methoxymethyl-piperidin-1-yl)-propyl]-	(rac)-3-methoxymethyl-piperidin-4-ol (intermediate 35)	514.5

	[1,4]diazepan-5-one		
312	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(4-methoxy-3-methoxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-4-methoxy-3-methoxymethyl-piperidine (intermediate 37)	528.5
313	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(trans-4-hydroxy-2-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,trans)-2-hydroxymethyl-piperidin-4-ol (intermediate 46)	500.5
314	(rac)-N-[1-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-2-hydroxy-propyl)-piperidin-4-yl]-acetamide	N-Piperidin-4-yl-acetamide	511.5
315	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(trans-3-hydroxy-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,trans)-4-methyl-piperidin-3-ol (intermediate 100)	484.5
316	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(trans-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,trans)-3-methyl-piperidin-4-ol (intermediate 95)	484.5
317	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(8-hydroxy-5-aza-spiro[2.5]oct-5-yl)-propyl]-[1,4]diazepan-5-one	(rac)-5-Aza-spiro[2.5]octan-8-ol (intermediate 81)	496.3
318	(rac)-1-[3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(cis-4-hydroxy-3-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,cis)-3-methyl-piperidin-4-ol (intermediate 96)	484.3
319	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(4-	(4-methyl-piperidin-4-yl) methanol	498.3

	hydroxymethyl-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(intermediate 32)	
320	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{2-hydroxy-3-[(2-hydroxy-ethyl)-methyl-amino]-propyl]-[1,4]diazepan-5-one	2-Methylamino-ethanol	444.3
321	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{3-[ethyl-(2-hydroxy-ethyl)-amino]-2-hydroxy-propyl]-[1,4]diazepan-5-one	2-Ethylamino-ethanol	458.3
322	(rac)-1-[3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(2-hydroxymethyl-2-methyl-pyrrolidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-2-hydroxymethyl-2-methyl-pyrrolidine	484.3
323	(rac)-[1-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-2-hydroxy-propyl)-piperidin-3-yl]-carbamic acid methyl ester	(rac)-Piperidin-3-yl-carbamic acid methyl ester (intermediate 40)	527.3
324	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(4-hydroxy-3,3-dimethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-3,3-dimethyl-piperidin-4-ol (intermediate 97)	498.3
325	(rac)-1-[3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(4-isobutyl-piperazin-1-yl)-propyl]-[1,4]diazepan-5-one	1-Isobutyl-piperazine	511.4
326	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(1-oxa-8-aza-spiro[4.5]dec-8-yl)-propyl]-[1,4]diazepan-5-one	1-Oxa-8-aza-spiro[4.5]decane (intermediate 27)	510.3

Examples 327-335General Procedure for Examples 327-335

- 5 A solution of 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(R)-1-oxiranylmethyl-[1,4]diazepan-5-one (example 167C) (0.1 mmol) in DMA (0.5 ml) was added to the appropriate amine (0.15 mmol), which are either commercially available or are described in the intermediate section, and a generous spatula of cesium carbonate added. The reaction was then shaken overnight at 80 °C, filtered, and directly purified by preparative HPLC.

10

Example No.	Compound Name	Amine	MS: (MH ⁺)
327	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one	(-)-6-Aza-spiro[2.5]octan-4-ol (intermediate 83)	496.3
328	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-(cis-3-hydroxy-4-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,cis)-4-hydroxymethyl-piperidin-3-ol (intermediate 47)	500.3
329	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-(cis-3-hydroxy-4-methoxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,cis)-4-methoxymethyl-piperidin-3-ol (intermediate 49)	514.3
330	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-((cis)-3-hydroxy-4-hydroxymethyl-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,cis)-4-hydroxymethyl-4-methyl-piperidin-3-ol (intermediate 52)	514.3

331	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-((trans)-3-hydroxy-4-hydroxymethyl-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,trans)-4-hydroxymethyl-4-methyl-piperidin-3-ol (intermediate 53)	514.3
332	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-(+)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one	(+)-6-Aza-spiro[2.5]octan-4-ol (intermediate 82)	496.3
333	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-(trans-3-hydroxy-4-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,trans)-4-hydroxymethyl-piperidin-3-ol (intermediate 48)	500.3
334	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-(3-hydroxy-4,4-dimethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-4,4-dimethyl-piperidin-3-ol (intermediate 84)	498.3
335	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-(cis-3-hydroxy-5-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac, cis)-5-methyl-piperidin-3-ol (intermediate 75)	484.3

Examples 336-344

General Procedure for Examples 336-344

- 5 A solution of 1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-((R)-2-oxiranyl-ethyl)-[1,4]diazepan-5-one (intermediate 56) (0.1 mmol) in DMA (0.5 ml) was added to the appropriate amine (0.15 mmol), which are either commercially available or are described in the intermediate section, and a generous spatula of cesium carbonate added. The

reaction was then shaken overnight at 80 °C, filtered, and directly purified by preparative HPLC.

Example No.	Compound Name	Amine	MS: (MH ⁺)
336	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one	(-)-6-Aza-spiro[2.5]octan-4-ol (intermediate 83)	480.3
337	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-(cis-3-hydroxy-4-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,cis)-4-hydroxymethyl-piperidin-3-ol (intermediate 47)	484.3
338	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-(cis-3-hydroxy-4-methoxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,cis)-4-methoxymethyl-piperidin-3-ol (intermediate 49)	498.3
339	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-(trans-3-hydroxy-4-hydroxymethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,trans)-4-hydroxymethyl-piperidin-3-ol (intermediate 48)	484.3
340	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-((cis)-3-hydroxy-4-hydroxymethyl-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,cis)-4-hydroxymethyl-4-methyl-piperidin-3-ol (intermediate 52)	498.3
341	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-((trans)-3-hydroxy-4-hydroxymethyl-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,trans)-4-hydroxymethyl-4-methyl-piperidine-3-ol (intermediate 53)	498.3

342	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-(+)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one	(+)-6-Aza-spiro[2.5]octan-4-ol (intermediate 82)	480.3
343	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-(3-hydroxy-4,4-dimethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-4,4-dimethyl-piperidin-3-ol (intermediate 84)	482.3
344	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-(cis-3-hydroxy-5-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac,cis)-5-methyl-piperidin-3-ol (intermediate 75)	468.3

Examples 345-357

General Procedure for Examples 345-357

A solution of 3-{4-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-acetaldehyde (intermediate 3) (0.1 mmol) in DCE (0.5 ml) was added to the appropriate amine (0.1 mmol), which are either commercially available or are described in the intermediate section, followed by a freshly prepared solution of pyridine-borane complex (25 ul, 8M in pyridine, 0.2 mmol) and acetic acid (25 ul) in EtOH (0.5 ml). The reaction was then shaken overnight, concentrated and the residue purified by preparative HPLC.

Example No.	Compound Name	Amine	MS: (MH ⁺)
345	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-(3-dimethylamino-piperidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(rac)-3-dimethylamino-piperidine	469.2

346	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-(3-dimethylamino-pyrrolidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(rac)-3-dimethylamino-pyrrolidine	453.2
347	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-(3-diethylamino-pyrrolidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(rac)-3-diethylamino-pyrrolidine	481.2
348	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(rac)-2-methyl-pyrrolidine	424.3
349	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-(trans-2,5-dimethyl-pyrrolidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(rac,trans)-2,5-dimethyl-pyrrolidine	438.3
350	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-(2-hydroxymethyl-2-methyl-pyrrolidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(rac)-2-hydroxymethyl-2-methyl-pyrrolidine	454.3
351	(rac)-[1-(2-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-ethyl)-piperidin-3-yl]-carbamic acid methyl ester	(rac)-Piperidin-3-yl-carbamic acid methyl ester (intermediate 40)	497.3
352	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-(4-hydroxy-3,3-dimethyl-piperidin-1-yl)-ethyl]-[1,4]diazepan-5-one	(rac)-3,3-dimethyl-piperidin-4-ol (intermediate 97)	468.3
353	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-(4-isobutyl-piperazin-1-yl)-ethyl]-[1,4]diazepan-5-one	1-Isobutyl-piperazine	481.3

354	(rac)-N-[1-(2-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-ethyl)-piperidin-3-yl]-acetamide	(rac)-N-Piperidin-3-yl-acetamide	481.3
355	(rac,trans)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-(2-hydroxy-cyclohexylamino)-ethyl]-[1,4]diazepan-5-one	(rac,trans)-2-hydroxy-cyclohexylamine	454.2
356	4-(2-Cyclohexylamino-ethyl)-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-[1,4]diazepan-5-one	cyclohexylamine	454.2
357	(rac,cis)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-(2-hydroxy-cyclohexylamino)-ethyl]-[1,4]diazepan-5-one	(rac,cis)-2-hydroxy-cyclohexylamine	454.2

Examples 358-381

General Procedure for Examples 358-381

A solution of (rac)-1-[(E)-3-(3,4-dichloro-phenyl)-acryloyl]-4-oxiranylmethyl-
 5 [1,4]diazepan-5-one (example 166A) (0.1 mmol) in DMA (0.5 ml) was added to the appropriate amine (0.15 mmol), which are either commercially available or are described in the intermediate section, and a generous spatula of cesium carbonate added. The reaction was then shaken overnight at 80 °C, filtered, and directly purified by preparative HPLC.

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Example No.	Compound Name	Amine	MS: (MH ⁺)
358	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(4-hydroxy-3-methyl-piperidin-1-yl)-butyl]-	(rac)-3-methyl-piperidin-4-ol (intermediate 94)	498.3

	[1,4]diazepan-5-one		
359	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(3-hydroxy-4-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-4-methyl-piperidin-3-ol (intermediate 91)	498.3
360	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(4-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	4-methoxymethyl-piperidine	512.3
361	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(3-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-methoxymethyl-piperidine	512.3
362	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(trans-3-hydroxy-2-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac, trans)-2-methyl-piperidin-3-ol (intermediate 87)	498.3
363	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(2-hydroxymethyl-2-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-(2-methyl-piperidin-2-yl)-methanol (intermediate 34)	512.3
364	(rac)-[1-(4-[4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl]-2-hydroxy-butyl)-piperidin-4-yl]-carbamic acid methyl ester	Piperidin-4-yl-carbamic acid methylester (intermediate 38)	541.3
365	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(trans-4-fluoro-3-hydroxy-piperidin-1-yl)-3-hydroxy-butyl]-[1,4]diazepan-5-one	(rac, trans)-4-Fluoro-piperidin-3-ol (intermediate 89)	502.3
366	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(4-hydroxy-3-	(rac)-3-hydroxymethyl-piperidin-4-ol	514.5

	hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(intermediate 35)	
367	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(4-hydroxy-3-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-methoxymethyl-piperidin-4-ol (intermediate 36)	528.5
368	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(4-methoxy-3-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-4-methoxy-3-methoxymethyl-piperidine (intermediate 37)	542.5
369	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(trans-4-hydroxy-2-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,trans)-2-hydroxymethyl-piperidin-4-ol (intermediate 46)	514.5
370	(rac)-N-[1-(4-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-2-hydroxy-butyl)-piperidin-4-yl]-acetamide	N-Piperidin-4-yl-acetamide	525.5
371	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(trans-3-hydroxy-4-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,trans)-4-methyl-piperidin-3-ol (intermediate 100)	498.5
372	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(trans-4-hydroxy-3-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,trans)-3-methyl-piperidin-4-ol (intermediate 95)	498.5
373	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(2-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-2-methoxymethyl-piperidine	512.3

374	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(2-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-2-hydroxymethyl-piperidine	498.3
375	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(2-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-2-methylpiperidine	482.3
376	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(3-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-methylpiperidine	482.3
377	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(4-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	4-methylpiperidine	482.3
378	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(3-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-hydroxymethyl-piperidine	498.3
379	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(4-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	4-hydroxymethyl-piperidine	498.3
380	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(3-methoxymethyl-3-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-methoxymethyl-3-methyl-piperidine (intermediate 31)	526.4
381	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-hydroxy-4-(2-hydroxymethyl-2-methyl-pyrrolidin-1-	(rac)-2-hydroxymethyl-2-methyl-pyrrolidine	498.3

	yl)-butyl]-[1,4]diazepan-5-one		
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Examples 382-409General Procedure for Examples 382-409

A solution of 1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-(4-iodo-butyl)-[1,4]diazepan-5-one (intermediate 99) (0.1 mmol) in DMA (0.5 ml) was added to the
 5 appropriate amine (0.15 mmol), which are either commercially available or are described in the intermediate section, and a generous spatula of cesium carbonate and sodium iodide added. The reaction was then shaken at room temperature for 1h, then raised to 80 °C for a further 1h, filtered, and directly purified by preparative HPLC.

Example No.	Compound Name	Amine	MS: (MH ⁺)
382	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-(4-piperidin-1-yl-butyl)-[1,4]diazepan-5-one	Piperidine	436.3
383	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(3-hydroxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-piperidin-3-ol	452.3
384	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(4-hydroxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	Piperidin-4-ol	452.3
385	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(3-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-hydroxymethyl-piperidine	466.3
386	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(4-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	4-hydroxymethyl-piperidine	466.3

387	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(2-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-2-hydroxymethyl-piperidine	466.3
388	(rac, trans)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(3-hydroxy-2-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac, trans)-2-methyl-piperidin-3-ol (intermediate 87)	466.3
389	(rac, trans)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(4-fluoro-3-hydroxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac, trans)-4-Fluoro-piperidin-3-ol (intermediate 89)	470.3
390	(rac, cis)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(3-fluoro-4-hydroxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac, cis)-3-fluoro-piperidin-4-ol (intermediate 93)	470.3
391	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(3-hydroxy-3-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-methyl-piperidin-3-ol (intermediate 101)	466.3
392	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(3-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-methoxymethyl-piperidine	480.3
393	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(3-hydroxy-pyrrolidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-hydroxy-pyrrolidine	438.3
394	(rac, trans)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(3-fluoro-4-hydroxy-piperidin-1-yl)-butyl]-	(rac, trans)-3-fluoro-piperidin-4-ol (intermediate 90)	470.3

	[1,4]diazepan-5-one		
395	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(3-methoxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-methoxypiperidine	466.3
396	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(4-isopropyl-piperazin-1-yl)-butyl]-[1,4]diazepan-5-one	1-Isopropyl-piperazine	479.4
397	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(4-cyclopropyl-piperazin-1-yl)-butyl]-[1,4]diazepan-5-one	1-Cyclopropyl-piperazine	477.3
398	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(4-cyclopentyl-piperazin-1-yl)-butyl]-[1,4]diazepan-5-one	1-Cyclopentyl-piperazine	505.4
399	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(4-(2-methoxy-ethyl)-piperazin-1-yl)-butyl]-[1,4]diazepan-5-one	1-(2-Methoxy-ethyl)-piperazine	495.4
400	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(4-hydroxy-3-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-methyl-piperidin-4-ol (intermediate 94)	466.3
401	[1-(4-{4-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-butyl)-piperidin-4-yl]-carbamic acid methyl ester	Piperidin-4-yl-carbamic acid methylester (intermediate 38)	509.3
402	[1-(4-{4-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-butyl)-piperidin-4-yl]-methyl carbamic acid methyl ester	Methyl-piperidin-4-yl-carbamic acid methyl ester (intermediate 39)	523.3

403	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(4-isopropyl-3-methyl-piperazin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-1-Isopropyl-2-methyl-piperazine	493.4
404	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(4-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	4-methoxymethyl-piperidine	480.4
405	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(3-hydroxy-3-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-(3-methyl-piperidin-3-yl)-methanol (intermediate 30)	480.4
406	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(3-methoxymethyl-3-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-methoxymethyl-3-methyl-piperidine (intermediate 31)	494.4
407	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(2-hydroxymethyl-2-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-(2-methyl-piperidin-2-yl)-methanol (intermediate 34)	480.4
408	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(cis-4-hydroxy-2-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,cis)-2-hydroxymethyl-piperidin-4-ol (intermediate 45)	482.3
409	(rac)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(4-hydroxy-3-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-4-methyl-piperidin-3-ol (intermediate 91)	466.3

Examples 410-421General Procedure for Examples 410-421

A solution of 1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-(4-iodo-butyl)-[1,4]diazepan-5-one (intermediate 57) (0.1 mmol) in DMA (0.5 ml) was added to the
 5 appropriate amine (0.15 mmol), which are either commercially available or are described in the intermediate section, and a generous spatula of cesium carbonate and sodium iodide added. The reaction was then shaken at room temperature for 1h, then raised to 80 °C for a further 1h, filtered, and directly purified by preparative HPLC.

Example No.	Compound Name	Amine	MS: (MH ⁺)
410	(rac)-1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-[4-(cis-3-methoxy-4-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,cis)-(3-methoxy-piperidin-4-yl)-methanol (intermediate 50)	496.4
411	(rac)-1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-[4-(cis-3-hydroxy-4-hydroxymethyl-4-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,cis)-4-hydroxymethyl-4-methyl-piperidin-3-ol (intermediate 52)	496.4
412	(rac)-1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-[4-(trans-3-hydroxy-4-hydroxymethyl-4-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,trans)-4-hydroxymethyl-4-methyl-piperidin-3-ol (intermediate 53)	496.4
413	(rac)-1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-[4-(5-hydroxy-2-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-6methyl-piperidin-3-ol (intermediate 66)	466.4
414	(rac)-1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-[4-(5-hydroxy-2-hydroxymethyl-piperidin-1-yl)-butyl]-	(rac)-6-ydroxymethyl-piperidin-3-ol	482.4

	[1,4]diazepan-5-one	(intermediate 65)	
415	1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-[4-((+)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-butyl]-[1,4]diazepan-5-one	(+)-6-Aza-spiro[2.5]octan-4-ol (intermediate 82)	478.4
416	1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-[4-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-butyl]-[1,4]diazepan-5-one	(-)-6-Aza-spiro[2.5]octan-4-ol (intermediate 83)	478.4
417	(rac)-1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-[4-(2-hydroxymethyl-5-methoxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-(5-methoxy-piperidin-2-yl)-methanol (intermediate 67)	496.3
418	(rac)-1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-[4-(5-hydroxy-2-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-6-methoxymethyl-piperidin-3-ol (intermediate 74)	496.4
419	(rac)-1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-[4-(cis-3-hydroxy-2-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,cis)-2-hydroxymethyl-piperidin-3-ol (intermediate 62)	482.3
420	(rac)-1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-[4-(3-hydroxy-4,4-dimethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-4,4-dimethyl-piperidin-3-ol (intermediate 84)	480.3
421	(rac,cis)-1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-[4-(3-hydroxy-5-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,cis)-5-methyl-piperidin-3-ol (intermediate 75)	466.3

Examples 422-490General Procedure for Examples 422-490

A solution of 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(4-iodo-butyl)-[1,4]diazepan-5-one (Example 9B) (0.1 mmol) in DMA (0.5 ml) was added to the appropriate amine
 5 (0.15 mmol), which are either commercially available or are described in the intermediate section, and a generous spatula of cesium carbonate and sodium iodide added. The reaction was then shaken at room temperature for 1h, then raised to 80 °C for a further 1h, filtered, and directly purified by preparative HPLC.

Example No.	Compound Name	Amine	MS: (MH ⁺)
422	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(4-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	4-hydroxymethyl-piperidine	482.3
423	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-methoxymethyl-piperidine	496.3
424	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(4-hydroxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	piperidin-4-ol	468.3
425	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-hydroxymethyl-piperidine	482.3
426	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(4-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	4-hydroxymethyl-piperidine	482.3

427	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(2-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-2-hydroxymethyl-piperidine	482.3
428	(rac, trans)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-hydroxy-2-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac, trans)-2-methyl-piperidin-3-ol (intermediate 87)	482.3
429	(rac, trans)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(4-fluoro-3-hydroxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac, trans)-4-Fluoro-piperidin-3-ol (intermediate 89)	486.2
430	(rac, cis)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-fluoro-4-hydroxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac, cis)-3-fluoro-piperidin-4-ol (intermediate 93)	486.2
431	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-hydroxy-3-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-methyl-piperidin-3-ol (intermediate 101)	482.3
432	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-Methoxymethyl-piperidine	496.3
433	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-hydroxy-pyrrolidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-Pyrrolidin-3-ol	454.2
434	(rac, trans)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-fluoro-4-hydroxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac, trans)-3-fluoro-piperidin-4-ol (intermediate 90)	486.2

435	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-methoxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-methoxypiperidine	482.3
436	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(4-isopropyl-piperazin-1-yl)-butyl]-[1,4]diazepan-5-one	1-Isopropyl-piperazine	495.3
437	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(4-cyclopropyl-piperazin-1-yl)-butyl]-[1,4]diazepan-5-one	1-Cyclopropyl-piperazine	493.3
438	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(4-cyclopentyl-piperazin-1-yl)-butyl]-[1,4]diazepan-5-one	1-Cyclopentyl-piperazine	521.3
439	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{4-[4-(2-methoxy-ethyl)-piperazin-1-yl]-butyl}-[1,4]diazepan-5-one	1-(2-Methoxy-ethyl)-piperazine	511.3
440	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(4-hydroxy-3-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-methyl-piperidin-4-ol (intermediate 94)	482.3
441	[1-(4-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-butyl)-piperidin-4-yl]-carbamic acid methyl ester	Piperidin-4-yl-carbamic acid methylester (intermediate 38)	525.3
442	[1-(4-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-butyl)-piperidin-4-yl]-methyl-carbamic acid methyl ester	Methyl-piperidin-4-yl-carbamic acid methyl ester (intermediate 39)	539.3
443	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(4-isopropyl-3-methyl-piperazin-1-yl)-butyl]-[1,4]diazepan-5-	(rac)-1-Isopropyl-2-methyl-piperazine	509.3

	one		
444	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(4-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	4-methoxymethyl-piperidine	496.3
445	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-hydroxymethyl-3-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-(3-methyl-piperidin-3-yl)-methanol (intermediate 30)	496.4
446	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-methoxymethyl-3-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-methoxymethyl-3-methyl-piperidine (intermediate 31)	510.4
447	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(2-hydroxymethyl-2-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-(2-methyl-piperidin-2-yl)-methanol (intermediate 34)	496.3
448	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-hydroxy-4-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-4-methyl-piperidin-3-ol (intermediate 91)	482.3
449	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(2-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-2-methoxymethyl-piperidine	496.4
450	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(4-hydroxy-3-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3-hydroxymethyl-piperidin-4-ol (intermediate 35)	498.5
451	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(4-hydroxy-3-	(rac)-3-methoxymethyl-piperidin-4-ol	512.5

	methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(intermediate 36)	
452	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(4-methoxy-3-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-4-methoxy-3-methoxymethyl-piperidine (intermediate 37)	526.6
453	N-[1-(4-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-butyl)-piperidin-4-yl]-acetamide	N-Piperidin-4-yl-acetamide	509.5
454	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(trans-3-hydroxy-4-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,trans)-4-methyl-piperidin-3-ol (intermediate 100)	482.5
455	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(trans-4-hydroxy-3-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,trans)-3-methyl-piperidin-4-ol (intermediate 95)	482.5
456	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-butyl]-[1,4]diazepan-5-one	(rac)-6-Aza-spiro[2.5]octan-4-ol (intermediate 81)	494.3
457	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(8-hydroxy-5-aza-spiro[2.5]oct-5-yl)-butyl]-[1,4]diazepan-5-one	(rac)-5-Aza-spiro[2.5]octan-8-ol (intermediate 98)	494.3
458	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(cis-4-hydroxy-3-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,cis)-3-methyl-piperidin-4-ol (intermediate 96)	482.3
459	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(4-hydroxymethyl-4-	(4-methyl-piperidin-4-yl)-methanol	496.3

	methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(intermediate 32)	
460	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{4-[(2-hydroxy-ethyl)-methyl-amino]-butyl}-[1,4]diazepan-5-one	2-Methylamino-ethanol	442.3
461	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-{4-[(2-hydroxy-ethyl)-ethyl-amino]-butyl}-[1,4]diazepan-5-one	2-Ethylamino-ethanol	456.3
462	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(2-hydroxymethyl-2-methyl-pyrrolidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-(2-methyl-pyrrolidin-2-yl)-methanol (intermediate 34)	482.3
463	(rac)-N-[1-(4-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-butyl)-piperidin-3-yl]-acetamide	(rac)-Piperidin-3-yl-carbamic acid methyl ester (intermediate 40)	525.4
464	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(4-hydroxy-3,3-dimethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-3,3-dimethyl-piperidin-4-ol (intermediate 97)	496.4
465	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(4-isobutyl-piperazin-1-yl)-butyl]-[1,4]diazepan-5-one	1-Isobutyl-piperazine	509.4
466	(rac)-N-[1-(4-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-butyl)-piperidin-3-yl]-acetamide	(rac)-N-Piperidin-3-yl-acetamide	509.4
467	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(1-oxa-8-aza-spiro[4.5]dec-8-yl)-butyl]-[1,4]diazepan-5-one	1-Oxa-8-aza-spiro[4.5]decane (intermediate 27)	508.4

468	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(cis-3-hydroxy-4-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,cis)-4-hydroxymethyl-piperidin-3-ol (intermediate 47)	498.4
469	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(cis-3-hydroxy-4-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,cis)-4-methoxymethyl-piperidin-3-ol (intermediate 49)	512.4
470	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(cis-3-methoxy-4-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,cis)-3-methoxy-4-methoxymethyl-piperidine (intermediate 51)	526.4
471	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(trans-3-hydroxy-4-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,trans)-4-hydroxymethyl-piperidin-3-ol (intermediate 48)	498.4
472	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(cis-3-methoxy-4-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,cis)-(3-methoxy-piperidin-4-yl)-methanol (intermediate 50)	512.4
473	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(cis-3-hydroxy-4-hydroxymethyl-4-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,cis)-4-hydroxymethyl-4-methyl-piperidin-3-ol (intermediate 52)	512.4
474	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(trans-3-hydroxy-4-hydroxymethyl-4-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,trans)-4-hydroxymethyl-4-methyl-piperidin-3-ol (intermediate 53)	512.4
475	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(5-hydroxy-2-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-	(rac)-6-methyl-piperidin-3-ol (intermediate 66)	482.4

	one		
476	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(5-hydroxy-2-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-6-hydroxymethyl-piperidin-3-ol (intermediate 65)	498.4
477	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(2-hydroxymethyl-5-methoxy-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-(5-methoxy-piperidin-2-yl)-methanol (intermediate 67)	512.3
478	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(5-hydroxy-4-methoxy-2-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-4-methoxy-6-methoxymethyl-piperidin-3-ol (intermediate 68)	542.3
479	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(5-hydroxy-2-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-6-methoxymethyl-piperidin-3-ol (intermediate 63)	512.3
480	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(cis-3-hydroxy-2-hydroxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,cis)-2-hydroxymethyl-piperidin-3-ol (intermediate 62)	498.3
481	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(4-hydroxy-4,4-dimethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-4,4-dimethyl-piperidin-3-ol (intermediate 84)	496.3
482	(rac,cis)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-hydroxy-5-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,cis)-5-methyl-piperidin-3-ol (intermediate 75)	482.3

483	(rac)-N-[(2RS,4SR,5RS)-1-(4-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-butyl)-5-methoxy-2-methoxymethyl-piperidin-4-yl]-acetamide	N-((2RS,4SR,5RS)-5-Methoxy-2-methoxymethyl-piperidin-4-yl)-acetamide (intermediate 69)	583.3
484	(rac, trans)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(5-hydroxy-2-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac,trans)-6-methoxymethyl-piperidin-3-ol (intermediate 74)	512.3
485	(rac)-2-[1-(4-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-butyl)-6-hydroxymethyl-piperidin-3-yloxy]-acetamide	(rac)-2-(6-Hydroxymethyl-piperidin-3-yloxy)-acetamide (intermediate 72)	555.3
486	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-hydroxy-2-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-2-Methoxymethyl-piperidin-3-ol (intermediate 73)	512.3
487	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(5-hydroxy-2-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac, trans)-6-Methyl-piperidin-3-ol (intermediate 70)	482.3
488	(rac, cis)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-hydroxy-2-methoxymethyl-6-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac, cis)-2-Methoxymethyl-6-methyl-piperidin-3-ol (intermediate 64)	526.3
489	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-hydroxy-2,6-bis-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-2,6-Bis-methoxymethyl-piperidin-3-ol (intermediate 71)	556.3

490	(rac)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[4-(3-hydroxy-5-methoxymethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	(rac)-5-Methoxymethyl-piperidin-3-ol (intermediate 76)	498.3
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Examples 491-494

General Procedure for Examples 491-494

A solution of 3-{4-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propionaldehyde (intermediate 60) (0.1 mmol) in DCE (0.5 ml) was added to the appropriate amine (0.1 mmol), which are either commercially available or are described in the intermediate section, followed by a freshly prepared solution of pyridine-borane complex (25 ul, 8M in pyridine, 0.2 mmol) and acetic acid (25 ul) in EtOH (0.5 ml). The reaction was then shaken overnight, concentrated and the residue purified by preparative HPLC.

Example No.	Compound Name	Amine	MS: (MH ⁺)
491	1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-[3-((+, cis)-3-hydroxy-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(+, cis)-4-Methyl-piperidin-3-ol (intermediate 85)	452.3
492	1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-[3-((- , cis)-3-hydroxy-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(-, cis)-4-Methyl-piperidin-3-ol (intermediate 86)	452.3
493	1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-[3-((+)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one	(+)-6-Aza-spiro[2.5]octan-4-ol (intermediate 82)	464.3

494	1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-[3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one	(-)-6-Aza-spiro[2.5]octan-4-ol (intermediate 83)	464.3
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Examples 495-498

General Procedure for Examples 495-498

- 5 To a suspension of 4-[3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one dihydrochloride (intermediate 92, 0.1 mmol), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (46 mg, 0.12 mmol), the appropriate carboxylic acid in DMF (1 ml) was added Et₃N (21 μ l, 0.15 mmol) and the mixture shaken for 1h. The reaction was then directly purified by preparative HPLC.

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Example No.	Compound Name	Acid	MS: (MH ⁺)
495	1-[(E)-3-(3,4-Difluoro-phenyl)-acryloyl]-4-[3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one	(E)-3-(3,4-Difluoro-phenyl)-acrylic acid	448.4
496	1-[(E)-3-(3-Chloro-phenyl)-acryloyl]-4-[3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one	(E)-3-(3-Chloro-phenyl)-acrylic acid	446.4
497	1-[(E)-3-(5,6-Dichloro-pyridin-3-yl)-acryloyl]-4-[3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one	(E)-3-(5,6-Dichloro-pyridin-3-yl)-acrylic acid (Example 12B)	481.3
498	1-[(E)-3-(4-Chloro-phenyl)-acryloyl]-4-[3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-	(E)-3-(4-Chloro-phenyl)-acrylic acid	446.4

	yl)-propyl]-[1,4]diazepan-5-one		
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Examples 499-501General Procedure for Examples 499-501

- A solution of (rac)-4,4-dimethyl-piperidin-3-ol hydrochloride (intermediate 84) (0.15 mmol) in DMA (0.5 ml) was added to the appropriate epoxide (0.10 mmol) and a generous spatula of cesium carbonate added. The reaction was then shaken overnight at 80 °C, filtered, and directly purified by preparative HPLC.

Example No.	Compound Name	Epoxide	MS: (MH ⁺)
499	(rac)-1-[(E)-3-(3,4-Difluoro-phenyl)-acryloyl]-4-[2-hydroxy-3-(3-hydroxy-4,4-dimethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-1-[(E)-3-(3,4-Difluoro-phenyl)-acryloyl]-4-oxiranylmethyl-[1,4]diazepan-5-one (Example 177A)	466.3
500	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[(R)-3-hydroxy-4-(3-hydroxy-4,4-dimethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-((R)-2-oxiranyl-ethyl)-[1,4]diazepan-5-one (intermediate 56)	496.3
501	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[(R)-3-hydroxy-4-(3-hydroxy-4,4-dimethyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-((R)-2-oxiranyl-ethyl)-[1,4]diazepan-5-one (Example 172C)	512.3

Examples 502-505General Procedure for Examples 502-505

A solution of (rac, cis)-5-methyl-piperidine-3-ol hydrochloride (intermediate 75) (0.15 mmol) in DMA (0.5 ml) was added to the appropriate epoxide (0.10 mmol) and a generous spatula of cesium carbonate added. The reaction was then shaken overnight at 80 °C, filtered, and directly purified by preparative HPLC.

Example No.	Compound Name	Epoxide	MS: (MH ⁺)
502	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[(R)-3-hydroxy-4-(cis-3-hydroxy-5-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[(R)-2-oxiranyl-ethyl]-[1,4]diazepan-5-one (intermediate 56)	482.3
503	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[(R)-3-hydroxy-4-(cis-3-hydroxy-5-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one	1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[(R)-2-oxiranyl-ethyl]-[1,4]diazepan-5-one (Example 172C)	498.3
504	(rac)-1-[(E)-3-(3,4-Difluoro-phenyl)-acryloyl]-4-[2-hydroxy-3-(cis-3-hydroxy-5-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one	(rac)-1-[(E)-3-(3,4-Difluoro-phenyl)-acryloyl]-4-oxiranylmethyl-[1,4]diazepan-5-one (Example 177A)	452.3
505	(rac)-1-[(E)-3-(3,4-Difluoro-phenyl)-acryloyl]-4-[3-hydroxy-4-(cis-3-	(rac)-1-[(E)-3-(3,4-Difluoro-phenyl)-	466.3

	hydroxy-5-methyl-piperidin-1-yl)- butyl]-[1,4]diazepan-5-one	acryloyl]-4-(2-oxiranyl- ethyl)-[1,4]diazepan-5- one (intermediate 58)	
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5 Example A

Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet	
Kernel:		
Compound of formula (I)	10.0 mg	200.0 mg
Microcrystalline cellulose	23.5 mg	43.5 mg
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg
Sodium starch glycolate	12.5 mg	17.0 mg
Magnesium stearate	1.5 mg	4.5 mg
(Kernel Weight)	120.0 mg	350.0 mg
Film Coat:		
Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg
Polyethylene glycol 6000	0.8 mg	1.6 mg
Talc	1.3 mg	2.6 mg
Iron oxyde (yellow)	0.8 mg	1.6 mg
Titan dioxide	0.8 mg	1.6 mg

- 10 The active ingredient is sieved and mixed with microcrystalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidone in water. The granulate is mixed with sodium starch glycolate and magnesium stearate and compressed to yield kernels of 120 or 350 mg respectively. The kernels are lacquered with an aqueous solution / suspension of the above mentioned film coat.

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

<u>Ingredients</u>	<u>Per capsule</u>
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

- 5 The components are sieved and mixed and filled into capsules of size 2.

Example C

Injection solutions can have the following composition:

Compound of formula (I)	3.0 mg
Polyethylene Glycol 400	150.0 mg
Acetic Acid	q.s. ad pH 5.0
Water for injection solutions	Ad 1.0 ml

- 10 The active ingredient is dissolved in a mixture of Polyethylene Glycol 400 and water for injection (part). The pH is adjusted to 5.0 by Acetic Acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

Example D

- 15 Soft gelatin capsules containing the following ingredients can be manufactured in a conventional manner:

Capsule contents	
Compound of formula (I)	5.0 mg
Yellow wax	8.0 mg
Hydrogenated Soya bean oil	8.0 mg
Partially hydrogenated plant oils	34.0 mg
Soya bean oil	110.0 mg
Weight of capsule contents	165.0 mg
Gelatin capsule	
Gelatin	75.0 mg
Glycerol 85 %	32.0 mg
Karion 83	8.0 mg (dry matter)
Titan dioxide	0.4 mg
Iron oxide yellow	1.1 mg

The active ingredient is dissolved in a warm melting of the other ingredients and the mixture is filled into soft gelatin capsules of appropriate size. The filled soft gelatin capsules are treated according to the usual procedures.

5 Example E

Sachets containing the following ingredients can be manufactured in a conventional manner:

Compound of formula (I)	50.0 mg
Lactose, fine powder	1015.0 mg

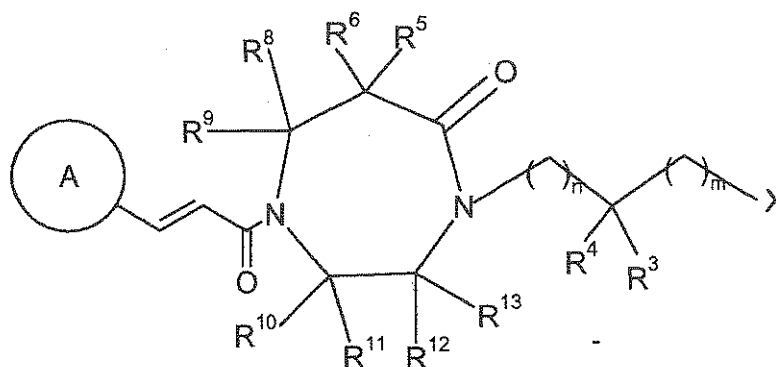
Microcrystalline cellulose (AVICEL PH 102)	1400.0 mg
Sodium carboxymethyl cellulose	14.0 mg
Polyvinylpyrrolidon K 30	10.0 mg
Magnesiumstearate	10.0 mg
Flavoring additives	1.0 mg

The active ingredient is mixed with lactose, microcrystalline cellulose and sodium carboxymethyl cellulose and granulated with a mixture of polyvinylpyrrolidon in water. The granulate is mixed with magnesiumstearate and the flavouring additives and filled

5 into sachets.

Claims

1. Compounds of formula (I)



(I)

5 wherein

A is aryl or heteroaryl, said aryl and said heteroaryl being optionally substituted by one to three substituents independently selected from the group consisting of halogen, benzyloxy, heteroaryl- C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy and halo C_{1-6} alkoxy, or said aryl and said heteroaryl being optionally substituted by C_{1-6} alkylenedioxy;

10 X is $-N(R^1)(R^2)$ or $-N^+(R^1)(R^2)(R^7)$;

i) R^1 and R^2 are, independently to each other, hydrogen, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, hydroxy C_{2-6} alkyl, C_{1-6} alkoxy C_{2-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-6} alkyl, C_{7-10} bicycloalkyl, phenyl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl, heterocyclyl or heterocyclyl C_{1-6} alkyl, in which the cycloalkyl of said C_{3-7} cycloalkyl and said C_{3-7} cycloalkyl C_{1-6} alkyl, the phenyl of said phenyl C_{1-3} alkyl, the heteroaryl of said heteroaryl C_{1-3} alkyl and the heterocyclyl of said heterocyclyl and said heterocyclyl C_{1-6} alkyl are optionally substituted by one to three substituents independently selected from the group consisting of R^d ;

15 or

20 R^1 and R^2 , together with the nitrogen atom to which they are attached, form heterocyclyl optionally substituted by one to three substituents independently selected from the group consisting of R^d , and one of the ring carbon atoms of

said heterocyclyl formed by R^1 and R^2 being optionally replaced with a carbonyl group; and/or

5 one of the ring carbon atoms of the heterocyclyl formed by R^1 and R^2 may be a ring carbon atom of another ring which is C_{3-7} cycloalkyl or heterocyclyl, one or two ring carbon atoms of said another ring being optionally replaced by a carbonyl group, and said another ring being optionally substituted by C_{1-6} alkyl;

10 R^3 and R^4 are, independently to each other, hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-6} alkyl, C_{1-6} alkoxy-carbonyl, carboxyl, hydroxy- C_{1-6} alkyl, C_{1-6} alkoxy- C_{1-6} alkyl, halogen or halo C_{1-6} alkyl; or

15 R^3 and R^4 , together with the carbon atom to which they are attached, form C_{3-7} cycloalkyl or heterocyclyl optionally substituted by one to three substituents independently selected from the group consisting of C_{1-4} alkyl, halo C_{1-4} alkyl and halogen; or

20 ii) R^1 is hydrogen, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, hydroxy C_{1-6} alkyl, C_{1-6} alkoxy C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-6} alkyl, C_{7-10} bicycloalkyl, phenyl C_{1-3} alkyl, heteroaryl C_{1-3} alkyl, heterocyclyl or heterocyclyl C_{1-6} alkyl, in which the cycloalkyl of said C_{3-7} cycloalkyl and said C_{3-7} cycloalkyl C_{1-6} alkyl, the phenyl of said phenyl C_{1-3} alkyl, the heteroaryl of said heteroaryl C_{1-3} alkyl and the heterocyclyl of said heterocyclyl and said heterocyclyl C_{1-6} alkyl are optionally substituted by one to three substituents independently selected from the group consisting of R^d ;

25 R^3 is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-6} alkyl, halogen or halo C_{1-6} alkyl;

30 R^2 and R^4 , together with the nitrogen atom to which R^2 is attached, the carbon atom to which R^4 is attached and the C_{1-2} alkylene between said nitrogen atom and said carbon atom, if any, form heterocyclyl optionally substituted by one to three substituents independently selected from the group consisting of C_{1-6} alkyl and fluorine;

R^7 is C_{1-6} alkyl;

R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} are, independently to each other, hydrogen, C_{1-6} alkyl or C_{3-7} cycloalkyl;

R^d is hydroxy, cyano, NR^aR^b , halogen, C_{1-6} alkyl, halo C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkoxycarbonyl, acyl, $-C(O)NR^aR^b$, $-NR^a-C(O)-R^b$, $-NR^a-C(O)-OR^b$, $-NR^a-C(O)-NR^b$, $-NR^a-SO_2-R^b$, $-NR^a-SO_2-NR^bR^c$, $-OC(O)NR^aR^b$, $-OC(O)OR^a$, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylthio, phenyl, phenyl C_{1-3} alkyl, heteroaryl, heteroaryl C_{1-3} alkyl and heterocyclyl, and the phenyl of said phenyl and said phenyl C_{1-3} alkyl, the heteroaryl of said heteroaryl and said heteroaryl C_{1-3} alkyl, and the heterocyclyl being optionally substituted by one to three substituents independently selected from the group consisting of hydroxy, cyano, NR^aR^b , halogen, C_{1-6} alkyl, halo C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkoxycarbonyl, acyl, $-C(O)NR^aR^b$, $-NR^a-C(O)-R^b$, $-NR^a-C(O)-OR^b$, $-NR^a-C(O)-NR^b$, $-NR^a-SO_2-R^b$, $-NR^a-SO_2-NR^bR^c$, $-OC(O)NR^aR^b$, $-OC(O)OR^a$, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl and C_{1-6} alkylthio, and one or two ring carbon atoms of the heterocyclyl being optionally replaced with a carbonyl group;

R^a , R^b and R^c are independently hydrogen or C_{1-6} alkyl;

n is an integer of 0 to 3;

m is an integer of 0 to 3;

$m+n$ is an integer of 1 to 5;

or pharmaceutically acceptable salts thereof;

wherein, unless otherwise indicated,

the term "aryl" means phenyl or naphthyl;

the term "heterocyclyl" means non-aromatic mono- or bi-cyclic radicals of four to nine ring atoms in which one to three ring atoms are heteroatoms independently selected from N, O and S(O)_n (where n is an integer from 0 to 2), the remaining ring atoms being C;

the term "heteroaryl" means a monocyclic or bicyclic radical of 5 to 10 ring atoms having one to three ring heteroatoms independently selected from N, O, and S, the remaining ring atoms being C;

the term "acyl" means R-C(O)-, in which R is C₁₋₆ alkyl, halo C₁₋₆ alkyl, C₃₋₇ cycloalkyl or C₃₋₇ cycloalkyl C₁₋₆ alkyl.

2. The compounds according to claim 1, wherein

10 R³ and R⁴ are, independently to each other, hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₆ alkyl, halogen or halo C₁₋₆ alkyl;

R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ are hydrogen;

R^d is hydroxy, cyano, NR^aR^b, halogen, C₁₋₆ alkyl, halo C₁₋₆ alkyl, hydroxy C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy C₁₋₆ alkyl, C₁₋₆ alkoxycarbonyl, acyl, -C(O)NR^aR^b, -NR^a-C(O)-R^b, -
 15 NR^a-C(O)-OR^b, -NR^a-C(O)-NR^b, -NR^a-SO₂-R^b, -NR^a-SO₂-NR^bR^c, -OC(O)NR^aR^b, -
 OC(O)OR^a, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylthio, phenyl, phenyl C₁₋₃ alkyl, heteroaryl, heteroaryl C₁₋₃ alkyl and heterocyclyl, and the phenyl of said phenyl and said phenyl C₁₋₃ alkyl, the heteroaryl of said heteroaryl and said heteroaryl C₁₋₃ alkyl, and the heterocyclyl being optionally substituted by one to three substituents independently
 20 selected from the group consisting of hydroxy, cyano, NR^aR^b, halogen, C₁₋₆ alkyl, halo C₁₋₆ alkyl, hydroxy C₁₋₆ alkyl, C₁₋₆ alkoxycarbonyl, acyl, -C(O)NR^aR^b, -NR^a-C(O)-R^b, -NR^a-C(O)-OR^b, -NR^a-C(O)-NR^b, -NR^a-SO₂-R^b, -NR^a-SO₂-NR^bR^c, -OC(O)NR^aR^b, -
 OC(O)OR^a, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylsulfinyl and C₁₋₆ alkylthio, and one or two ring carbon atoms of the heterocyclyl being optionally replaced with a carbonyl group.

25 3. The compounds according to any one of claims 1 and 2, wherein A is phenyl optionally substituted by one to three substituents independently selected from the group consisting of halogen, benzyloxy, heteroaryl-C₁₋₆ alkoxy, C₁₋₆ alkyl, C₁₋₆ alkoxy and halo C₁₋₆ alkoxy, or A is phenyl optionally substituted by C₁₋₆ alkylenedioxy.

4. The compounds according to any one of claims 1 to 3, wherein A is phenyl substituted by one or two halogen atoms independently selected from the group consisting of chlorine and fluorine.
5. The compounds according to any one of claims 1 to 4, wherein A is phenyl substituted by two halogen atoms independently selected from the group consisting of chlorine and fluorine at its 3,4 or 3,5 position.
6. The compounds according to any one of claims 1 to 5, wherein X is $-N(R^1)(R^2)$.
7. The compounds according to claim 6, wherein at least one of R^1 and R^2 is other than hydrogen.
- 10 8. The compounds according to any one of claims 6 and 7, wherein R^1 is hydrogen, C_{1-6} alkyl, or hydroxy C_{2-6} alkyl and R^2 is C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-6} alkyl, C_{7-10} bicycloalkyl, hydroxy C_{2-6} alkyl or C_{1-6} alkoxy C_{2-6} alkyl, in which the cycloalkyl and the heterocyclyl of said heterocyclyl and said heterocyclyl C_{1-6} alkyl are optionally substituted by one or two substituents independently selected from the group
15 consisting of C_{1-6} alkyl, hydroxy, heteroaryl and C_{1-6} alkoxy.
9. The compounds according to any one of claims 6 to 8, wherein R^1 is hydrogen and R^2 is heterocyclyl.
10. The compounds according to any one of claims 6 to 9, wherein $m+n$ is an integer of 1 or 2.
- 20 11. The compounds according to any one of claims 6 to 10, wherein R^3 , R^4 , R^5 and R^6 are hydrogen.
12. The compounds according to claim 6, wherein R^1 and R^2 , together with the nitrogen atom to which they are attached, form heterocyclyl optionally substituted by one to three substituents independently selected from the group consisting of R^d , and one of
25 the ring carbon atoms of said heterocyclyl formed by R^1 and R^2 being optionally replaced with a carbonyl group; and/or
- one of the ring carbon atoms of the heterocyclyl formed by R^1 and R^2 may be a ring carbon atom of another ring which is C_{3-7} cycloalkyl or heterocyclyl, one or two ring carbon atoms of said another ring being optionally replaced by a carbonyl group, and said
30 another ring being optionally substituted by C_{1-6} alkyl.

13. The compounds according to claim 12, wherein the heterocyclyl formed by R¹ and R², together with the nitrogen atom to which they are attached, is a mono-cyclic radical of five or six ring atoms in which one more ring atom, in addition to the nitrogen atom, may be a heteroatom independently selected from N, O and S(O)_n (where n is an integer
5 from 0 to 2).

14. The compounds according to any one of claims 12 and 13, wherein the heterocyclyl formed by R¹ and R², together with the nitrogen atom to which they are attached, is piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl or 1,1-dioxo-thiomorphlinyl.

10 15. The compounds according to any one of claims 12 to 14, wherein the heterocyclyl formed by R¹ and R², together with the nitrogen atom to which they are attached, is piperidyl or pyrrolidinyl.

16. The compounds according to any one of claims 12 to 15, wherein the heterocyclyl formed by R¹ and R², together with the nitrogen atom to which they are attached, is
15 optionally substituted by one or two substituents independently selected from the group consisting of hydroxy, phenyl and hydroxy C₁₋₆ alkyl, and/or

one of the ring carbon atoms of the heterocyclyl formed by R¹ and R² may be shared by another ring which is five or six membered mono-cyclic heterocyclyl, one or two ring carbon atoms of said another ring being optionally replaced by a carbonyl group.

20 17. The compounds according to any one of claims 12 to 16, wherein m+n is an integer of 1 to 3.

18. The compounds according to any one of claims 12 to 17, wherein R³, R⁴, R⁵ and R⁶ are hydrogen.

19. The compounds according to claim 1, which is

25 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(4-piperidin-1-yl-butyl)-[1,4]diazepan-5-one,

1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one,

1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-(3-piperidin-1-yl-propyl)-[1,4]diazepan-5-one,

8-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione,

5 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(4-hydroxy-4-phenyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one,

(+/-)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(3-hydroxy-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one,

10 8-(3-{4-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-7-oxo-[1,4]diazepan-1-yl}-propyl)-1-oxa-3,8-diaza-spiro[4.5]decan-2-one,

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(tetrahydro-pyran-4-ylamino)-ethyl]-[1,4]diazepan-5-one,

(S)-1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[3-(2-hydroxymethyl-pyrrolidin-1-yl)-ethyl]-[1,4]diazepan-5-one, or

15 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-(2-pyrrolidin-1-yl-ethyl)-[1,4]diazepan-5-one.

20. The compounds according to claim 1, which is

1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-((-, cis)-3-hydroxy-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one,

20 1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(3-hydroxy-4,4-dimethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one,

(cis)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[3-(3-hydroxy-5-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one,

25 1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[2-hydroxy-3-(3-hydroxy-4-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one,

1-[(E)-3-(3,4-Dichloro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one,

1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-(3-hydroxy-4,4-dimethyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one,

1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[(S)-2-hydroxy-3-(cis-3-hydroxy-5-methyl-piperidin-1-yl)-propyl]-[1,4]diazepan-5-one,

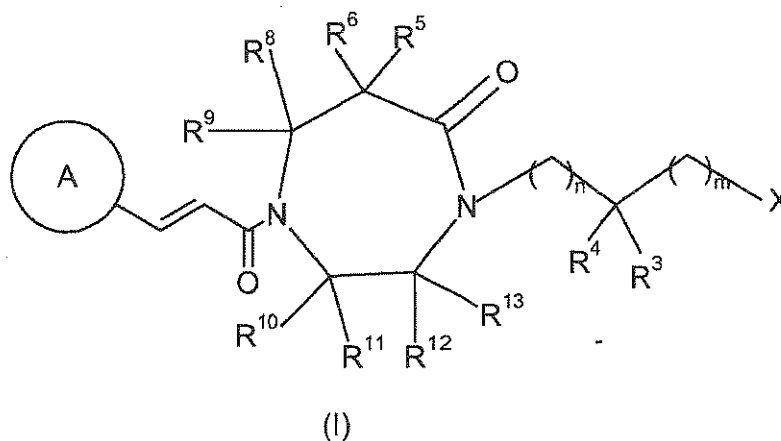
5 1-[(E)-3-(4-Chloro-3-fluoro-phenyl)-acryloyl]-4-[4-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-butyl]-[1,4]diazepan-5-one,

(cis)-1-[(E)-3-(3-Chloro-4-fluoro-phenyl)-acryloyl]-4-[4-(3-hydroxy-5-methyl-piperidin-1-yl)-butyl]-[1,4]diazepan-5-one,

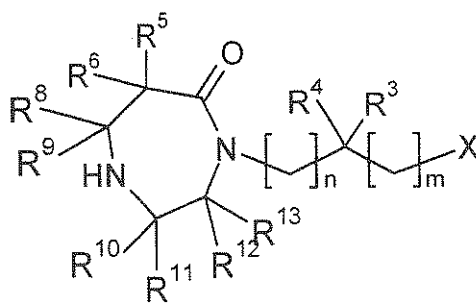
10 1-[(E)-3-(3-Chloro-phenyl)-acryloyl]-4-[3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one, or

1-[(E)-3-(5,6-Dichloro-pyridin-3-yl)-acryloyl]-4-[3-((-)-4-hydroxy-6-aza-spiro[2.5]oct-6-yl)-propyl]-[1,4]diazepan-5-one.

21. A process for manufacturing compounds of formula (I)

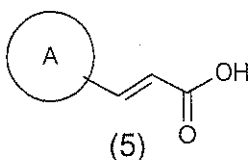


15 comprising a step of reacting compounds of formula (4)



(4)

with compounds of formula (5)



(5)

, wherein A, X, R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, m and n are as defined in claim 1.

22. Pharmaceutical compositions comprising a compound according to any of claims 1-20 and a pharmaceutically acceptable excipient.

23. The compounds according to any of claims 1-20 for use as therapeutic active substances.

24. The compounds according to any of claims 1-20 for use as therapeutic active substances for the treatment and/or prophylaxis of diseases treatable by a CCR-2 receptor antagonist, CCR-3 receptor antagonist or CCR-5 receptor antagonist.

25. Use of compounds according to any of claims 1-20 for the preparation of medicaments for the therapeutic and/or prophylactic treatment of diseases selected from the group consisting of peripheral arterial occlusive disease, critical limb ischemia, vulnerable atherosclerotic plaque patients, unstable angina, congestive heart failure, left ventricular hypertrophy, ischemia reperfusion injury, stroke, cardiomyopathy, restenosis, rheumatoid arthritis, diabetic nephropathy, irritable Bowel Disease, Crohns' disease, multiple sclerosis, neuropathic pain, atherothrombosis and/or burns/ulcers in Diabetes/CLI or asthma.