FORM 25 (12) PATENT granted by (19) AP

AFRICAN REGIONAL INDUSTRIAL PROPERTY ORGANIZATION (ARIPO)

479

(11) A

(21) Application Number: AP/P/94/00642

(22) Filing Date: 17.05.94

(24) (45) Date of Grant & Publication: 21.03.96

(30) Priority Data:

(33) Country:

(31) Number:

(32) Date:

(84) Designated States:

BW GM GH KE LS MW

SD SZ UG ZM ZW

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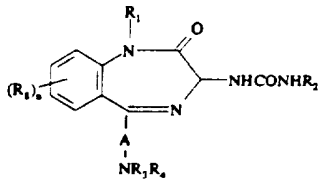
(51) International Patent Classification (Int. Cl.[6]): C07D243/14, A61K 31/55

(54) Title: AMINE DERIVATIVES

(57) Abstract: Compounds of general formula (I)



(I)

and physiologically acceptable salts thereof;
wherein R_1 represents $CH_2CONR_5R_6$ or CH_2COR_7;
R_2 represents a phenyl group optionally substituted by 1 or 2 substituents selected from halogen, alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, alkylthio, alkylsulphinyl, alkylsulphonyl, amino, substituted amino, hydroxy, alkoxy, methylenedioxy, alkoxycarbonyl, oxazolyl or oxadiazolyl;
A represents a C_{1-4} straight or branched alkylene chain;
R_3 and R_4 independently represent hydrogen or C_{1-4}alkyl or R_3 and R_4 together with the nitrogen atom to which they are attached form a saturated 5-7 membered heterocyclic ring, which ring may contain an additional heteroatom selected from oxygen, sulphur or nitrogen;
R_5 represents hydrogen or C_{1-4}alkyl;
R_6 represents C_{1-4}alkyl or phenyl, optionally substituted by halogen, or R_5 and R_6 together with the nitrogen atom to which they are attached represent a saturated 5 to 7 membered heterocyclic ring which may be optionally substituted by 1 or 2 methyl groups or fused to a benzene ring;
R_7 represents a group selected from C_{1-4}alkyl, or optionally substituted phenyl;
R_8 represents hydrogen or a halogen atom;
n is zero, 1 or 2, are antagonists of gastrin and CCK.

(56) Documents cited: EP 0514133 (MERCK SHARP & DOHME LTD.)

AP 479

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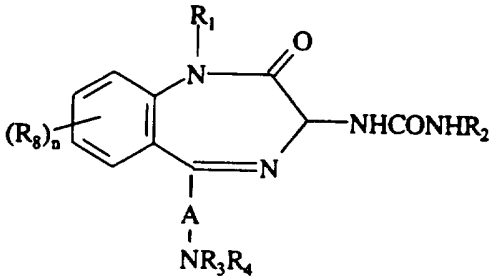
Amine Derivatives

This invention relates to novel amine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

In particular the invention relates to 5-aminoalkyl-1,4-benzodiazepine derivatives which modulate the effects of gastrin and/or cholecystokinin (CCK) in mammals.

Thus the invention provides compounds of general formula (I)



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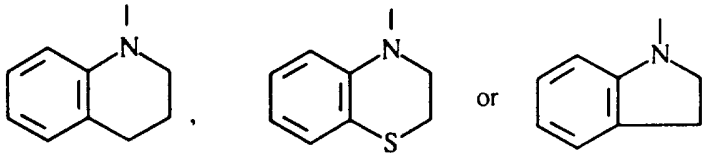
R_3 and R_4 independently represent hydrogen or C_{1-4}alkyl or R_3 and R_4 together with the nitrogen atom to which they are attached form a saturated 5-7 membered heterocyclic ring, which ring may contain an additional heteroatom selected from oxygen, sulphur or nitrogen;
R_5 represents hydrogen or C_{1-4}alkyl;
R_6 represents C_{1-4}alkyl or phenyl, optionally substituted by halogen,



When NR_3R_4 represents a 5-7 membered saturated heterocyclic ring this may be for example pyrrolidino, piperidino, hexamethylenimino, morpholino, thiomorpholino and oxides thereof, piperazino or an N-substitued derivative thereof e.g. N-methyl piperazino or N-alkoxycarbonyl piperazino.

When R_3 and R_4 represent C_{1-4}alkyl examples of suitable groups include methyl, ethyl, ispropyl, propyl or n-butyl.

The alkylene chain A in the compounds of formula (I) is preferably a straight chain alkylene such as methylene, ethylene, propylene or butylene.

When R_8 represents halogen examples of suitable groups include chlorine or fluorine.

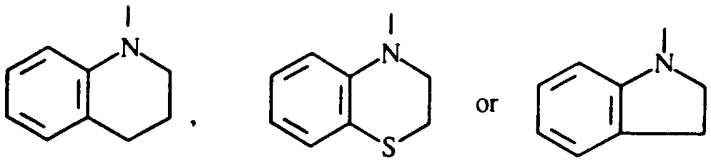
The term oxazolyl refers to a 1,3 oxazolyl group which is linked to the rest of the molecule via the carbon atom in the 2 or 5 position.

The term oxadiazolyl refers to a 1, 2, 4 oxadiazolyl group which is linked to the rest of the molecule via the carbon atom in the 3 or 5 position.

In compounds of formula (I) the term substituted amino means C_{1-4}alkylamino, e.g. isopropylamino, diC_{1-4}alkylamino e.g. dimethylamino, C_{1-4}alkanoylamino or C_{1-4}alkoxycarbonylamino e.g. t-butoxycarbonylamino .

When R_2 is phenyl containing a single substituent this is preferably in the meta or para position.

A preferred class of compounds of formula (I) include those wherein R_1 represents the group $CH_2CONR_5R_6$. Within this class particularly preferred compounds are those wherein R_5 represents methyl or ethyl and R_6 represents



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A further preferred group of compounds of formula (I) are those wherein R_1 represents the group $CH_2CONR_5R_6$, A represents a methylene chain, NR_3R_4 represents a saturated 5-7 membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, sulphur or nitrogen. From within this group particularly preferred compounds include those wherein R_5 is methyl or ethyl and R_6 is phenyl optionally substituted by fluorine or chlorine or NR_5R_6 represents a pyrrolidino, 2,5-dimethylpyrrolidino, 3,3-dimethylpyrrolidino, piperidino, 3,3-dimethylpiperidino, or 1-tetrahydroquinolino, R_2 represents phenyl optionally substituted by one or 2 groups selected from fluorine, methyl, methoxy, trifluoromethyl amino, cyano, hydroxy, oxazol-5-yl or 1,2,4-oxadiazol-3-yl and R_8 represents hydrogen or R_8 represents fluorine or chlorine and n is 1.

Particularly preferred compounds of the invention include
2-{3-[3-(3-Methoxy-phenyl)-ureido]-5-morpholin-4-ylmethyl-2-oxo-2,3-dihydro-benzo [e] [1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide;
N-Methyl-2-[5-morpholin-4-ylmethyl-2-oxo-3-(3-phenyl-ureido)-2,3 -dihydro-benzo[e] [1,4]diazepin-1-yl]-N-phenyl-acetamide;
N-Methyl-2-{5-morpholin-4-ylmethyl-2-oxo-3-[3-(3-trifluoromethyl -phenyl)-ureido]-2,3- dihydro-benzo[e][i ,4]diazepin-1-yl}-N-phenyl-acetamide;
2-{3-[3-(3-Cyano-phenyl)-ureido]-5-morpholin-4-ylmethyl-2-oxo-2, 3-dihydro-benzo[e] [1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide;
1-[5-(Morpholin-4-yl-methyl)-2-oxo-1-(2-oxo-2-pyrrolidin-1-yl-ethyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-oxazol-5-yl-phenyl)-urea;
N-Ethyl-N-(4-fluoro-phenyl)-2-{3-[3-(4-fluoro-phenyl)-ureido]-5-(morpholin-4-yl-methyl)-2-oxo-2,3-dihydro-benzo[e][1,4]diazepin-1-yl}-acetamide;
and the enantiomers thereof; and physiologically acceptable salts thereof.

The physiologically acceptable salts of the compounds of formula (I) include conventional salts formed for example from pharmaceutically acceptable inorganic or organic acids as well as quaternary ammonium acid addition salts. Examples of suitable salts include hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, perchloric, fumaric, acetic, propionic, succinic, glycolic, formic, lactic, maleic, tartaric, citric, pamoic, malonic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, fumaric, toluenesulphonic, methanesulphonic, naphthalene-2-sulphonic, benzenesulphonic and the like. Other acids such as

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N-Methyl-2-[5-morpholin-4-ylmethyl-2-oxo-3-(3-phenyl-ureido)-2,3 -dihydro-benzo[e] [1,4]diazepin-1-yl]-N-phenyl-acetamide;
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2-{3-[3-(3-Cyano-phenyl)-ureido]-5-morpholin-4-ylmethyl-2-oxo-2, 3-dihydro-benzo[e] [1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide;
1-[5-(Morpholin-4-yl-methyl)-2-oxo-1-(2-oxo-2-pyrrolidin-1-yl-ethyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-oxazol-5-yl-phenyl)-urea;
N-Ethyl-N-(4-fluoro-phenyl)-2-{3-[3-(4-fluoro-phenyl)-ureido]-5-(morpholin-4-yl-methyl)-2-oxo-2,3-dihydro-benzo[e][1,4]diazepin-1-yl}-acetamide;
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the invention are useful for the treatment of gastrointestinal disorders especially those where there is an advantage in lowering gastric acidity. Such disorders include peptic ulceration, reflux oesophagitis and Zollinger Ellison syndrome. They may also be useful for the treatment of gastrointestinal disorders such as irritable bowel syndrome, excess pancreatic secretion, acute pancreatitis, motility disorders, antral G cell hyperplasia, fundic mucosal hyperplasia or gastrointestinal neoplasms. The compounds of the invention are also useful for the treatment of central nervous system disorders where CCK and/or gastrin are involved. For example anxiety disorders (including panic disorder, agoraphobia, social phobia, simple phobia, obsessive compulsive disorders, post traumatic stress disorder, and general anxiety disorder), depression, tardive dyskinesia, Parkinson's disease or psychosis. They may also be useful for the treatment of dependency on drugs or substances of abuse and withdrawal, Gilles de la Tourette syndrome, or dysfunction of appetite regulatory systems; as well as the treatment of certain tumours of the lower oesophagus, stomach, intestines and colon. Compounds of the invention are also useful for directly inducing analgesia, or enhancing opiate or non-opiate mediated analgesia, as well as anaesthesia or loss of the sensation of pain.

The invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy, in particular in human medicine.

According to another aspect the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of conditions where modification of the effects of gastrin and/or CCK is of therapeutic benefit.

According to a further aspect of the invention we provide a method for the treatment of a mammal, including man, in particular in the treatment of conditions where modification of the effects of gastrin and/or CCK is of therapeutic benefit which method comprises administering an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof to the patient.

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According to another aspect the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of conditions where modification of the effects of gastrin and/or CCK is of therapeutic benefit.

According to a further aspect of the invention we provide a method for the treatment of a mammal, including man, in particular in the treatment of conditions where modification of the effects of gastrin and/or CCK is of therapeutic benefit which method comprises administering an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof to the patient.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycollate, or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; and preservatives, for example, methyl or propyl p-hydroxybenzoates or ascorbic acid. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition according to the invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycollate, or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; and preservatives, for example, methyl or propyl p-hydroxybenzoates or ascorbic acid. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

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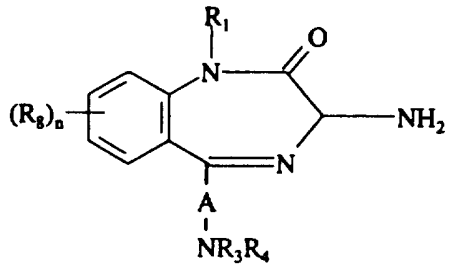
In a particular aspect of the process with a compound of formula (II) wherein R_9 is a 1-imidazole group, this compound may be formed in situ, in which case the amine R_2NH_2 will be reacted with the compound of formula (III)



(III)

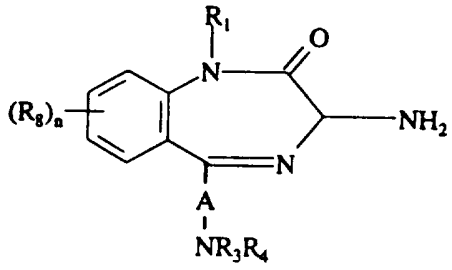
in the presence of carbonyl diimidazole under the aforementioned conditions.

Compounds of formula (II) may be prepared from compounds of formula (III). Thus a compound of formula (II) wherein R_9 is 1- imidazole may be prepared by reacting a compound of formula (III) with carbonyldiimidazole in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane) or an ether (e.g. tetrahydrofuran) at a temperature ranging from 0^0 to 80^0C, conveniently at room temperature.

Compounds of formula (II) wherein R_1, R_3, R_4 and A have the meanings defined in formula (I) and R_9 is an optionally substituted phenoxy group may be prepared by reaction of a compound of formula (III) with the appropriate haloformate R_9COHal wherein Hal is chlorine or bromine. The reaction is preferably carried out in the presence of a base such as a tertiary amine e.g. triethylamine or pyridine, and in a solvent such as a halohydrocarbon e.g. dichloromethane.

Compounds of formula (I) may also be prepared by reacting a compound of formula (III) wherein R_1, R_3, R_4 and A have the meanings defined above for formula (I) with the isocyanate R_2NCO or carbamoyl chloride $R_2NHCOCl$ (wherein R_2 has the meaning defined in formula (I)). The reaction conveniently takes place in the presence of a suitable solvent such as a halohydrocarbon (e.g. dichloromethane), an ether (e.g. tetrahydrofuran) or a nitrile (e.g. acetonitrile) or a mixture thereof at a temperature in the range of O^o to 80^o C.

In a particular aspect of the process with a compound of formula (II) wherein R_9 is a 1-imidazole group, this compound may be formed in situ, in which case the amine R_2NH_2 will be reacted with the compound of formula (III)



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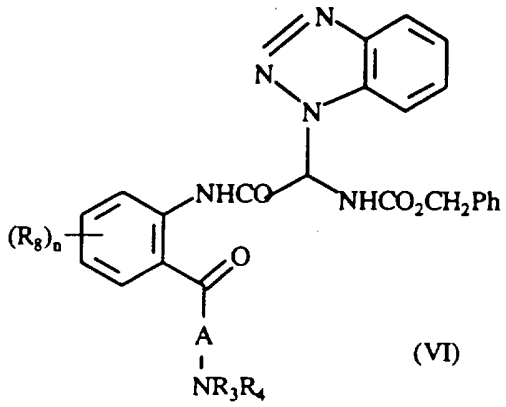
The reaction is preferably carried out at a temperature within the range -30^0 to 40^{0}C.

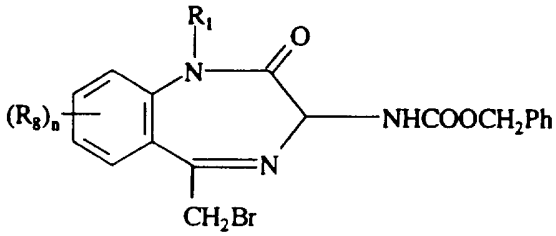
The compound of formula (V) may be prepared by cyclisation of the ketone derivative (VI)



(VI)

The cyclisation may be carried out by treating the compound (VI) with ammonia in a suitable solvent such as an ether e.g. tetrahydrofuran followed by reaction with sodium acetate in glacial acetic acid.

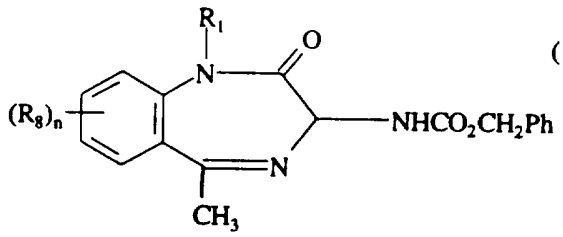
Compounds of formula (IV) wherein A is a methylene group may also be prepared by reaction of the compound of formula (VII) wherein R_1 is as defined in formula (I)



(VII)

with an amine R_3R_4NH, preferably in a solvent such as halohydrocarbon e.g. dichloromethane.

Compounds of formula (VII) may be prepared by bromination of the compound of formula (VIII)

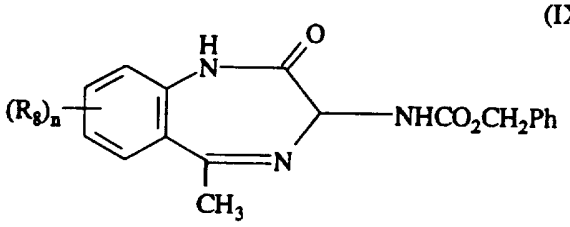


(VIII)

The bromination reaction may be carried out using a reagent such as N-bromosuccinimide or 5,5-dibromobarbituric acid.

Compounds of formula (IV) wherein A is an ethylene group may be prepared from a compound of formula of (VIII) with the amine HNR_3R_4 and formaldehyde under conventional Mannich reaction conditions.

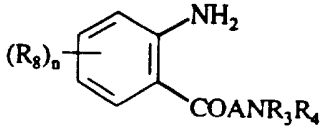
The compounds of formula (VIII) may be prepared by alkylation of the compound of formula (IX)



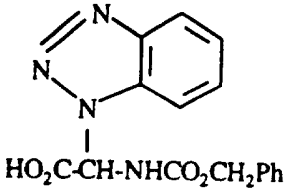
(IX)

using the same conditions as that described above for preparing the corresponding compound of formula (IV) from compound (V).

The compounds of formula (VI) may be prepared by condensation of the amino ketone (X) with the benzotriazole derivative (XI)



(X)

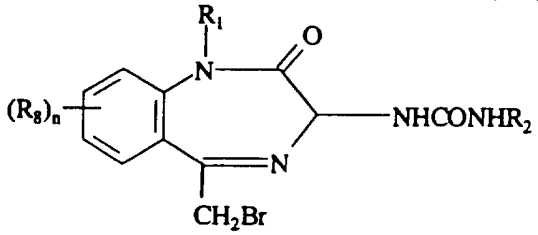


(XI)

The condensation reaction may be carried out using conventional procedures, for example by the reaction of (X) with (XI) in the presence of dicyclohexylcarbodiimide in a solvent such as tetrahydrofuran.

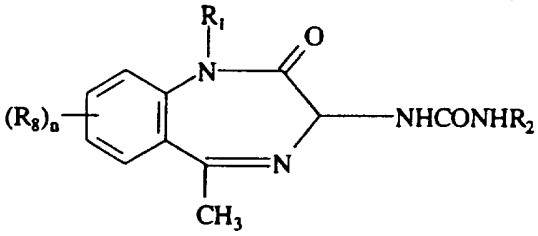
The compounds of formula (X) are either known compounds or may be prepared by analogous methods described for preparing known compounds.

Compounds of formula (I) wherein A represents a methylene group may also be prepared by reaction of the bromomethyl derivative (XII)



(XII)

wherein R_1 and R_2 are as defined in formula (I) with the amine R_3R_4NH, wherein R_3 and R_4 are as defined in formula (I). The reaction is preferably carried out in an aprotic solvent such as a halohydrocarbon e.g. dichloromethane. The bromomethyl derivatives (XII) may be prepared by bromination of the corresponding methyl compound (XIII)



(XIII)

The bromination reaction may be carried out using a reagent such as 5,5-dibromobarbituric acid in a solvent such as a halohydrocarbon e.g. dichloromethane, or chloroform or mixtures thereof.

The methyl derivative (XIII) may be prepared from the corresponding intermediate (VIII) using the general procedures described above for converting the compound of formula (IV) into a compound of formula (I).

Compounds of the invention may be converted into other componds of the invention. Thus compounds of formula (I) wherein R_2 is a phenyl group substituted by amino may be prepared from the corresponding compound wherein R_2 is a phenyl group substituted by an alkoxycarbonylamino group by conventional means such as acid hydrolysis. For example compounds wherein R_2 is phenyl substituted by amino may be prepared by reaction of the corresponding t-butylcarbonylamino compound with trifluroacetic in a suitable solvent such as dichloromethane.

Acid addition salts of compounds of formula (I) may be prepared by reaction with the appropriate physiologically acceptable acid in a suitable solvent followed if necessary by addition of suitable non solvent.

The compounds of formulae (II), (III), (IV), (V), (VI) and (VII) are novel and form further aspects of the invention.

In general, the compounds R_2NH_2, R_2NCO or $R_2HNCOCl$ are either known or may be prepared according to methods used for the preparation of known compounds. For example the amines R_2NH_2 may be prepared by reduction of the corresponding nitro compounds R_2NO_2. The reduction may be effected for example by catalytic hydrogenation using a suitable metal catalyst such as palladium on carbon in a suitable solvent such as an alcohol (e.g. ethanol) at room temperature.

Compounds of formula (I) contain at least one asymmetric carbon atom, namely the carbon atom of the diazepine ring to which the substituted urea grouping is attached. Specific enantiomers of the compounds of formula (I) may be obtained by resolution of the racemic compound using conventional procedures such as salt formation with a suitable optically active acid or by the use of chiral H.P.L.C. Alternatively the required enantiomer may be prepared from the corresponding enantiomeric amine of formula (III) using any of the processes described above for preparing compounds of formula (I) from the amine (III). The enantiomers of the amine (III) may be prepared from the racemic amine (III) using conventional procedures such as salt formation with a suitably optically active acid. Alternatively the racemic amine (III) may be reacted with an optically active

carbonate ester to yield an optically active carbamate thereof. The resultant diastereoisomers may then be separated by conventional means. Each separate diastereosiomeric carbamate may then be converted into the corresponding enantiomeric amine (III) by conventional processes.

The following examples, which are non-limiting, illustrate the invention. Temperatures are in °C. "Dried" refers to drying with anhydrous Mg_2SO_4. All chromatography was carried out on silica gel. The following abbreviations are used. T.l.c. - thin layer chromatography; CDI-carbonyldiimidazole; DCM - dichloromethane; DE - Diethyl ether; THF - tetrahydrofuran; DMF - N,N-dimethylformamide; EA - ethyl acetate; MeOH - methanol; $CHCl_3$ - chloroform; NaH - sodium hydride; ir - infra red spectra determined as a mull in mineral oil unless otherwise stated.

Intermediate 1

Phenylmethyl [2[(2-acetylphenyl)amino]-1-[(1-methylethyl)thio]-2-oxoethyl] carbamate

A suspension of [(1-methylethyl)thio]- [(phenylmethoxy)carbonyl]amino]acetic acid (10.49g) in dry DCM (175ml) at 0° under nitrogen was treated with 4-methylmorpholine (3.93g) followed by the dropwise addition of isobutyl chloroformate (5.31g). The mixture was stirred at 0° for 40min and a solution of 2-aminoacetophenone (5.00g) in dry DCM (60ml) was added dropwise. The mixture was stirred at 0° for 1h then at 23° for 18h. The mixture was washed with 2N hydrochloric acid, 2N sodium carbonate solution, saturated brine and dried. Solvent evaporation in vacuo gave the title compound (14.82g) which was used without further purification.

T.l.c. (1:1 DE-hexane) Rf 0.3

Intermediate 2

Phenylmethyl [2,3-dihydro-5-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]carbamate

Ammonia gas was passed through a solution of phenylmethyl[2-[(2-acetylphenyl)amino]-1-[(1-methylethyl)thio]-2-oxoethyl]carbamate (14.74g) in dry THF (250ml) at 0° for 0.5h. Mercury (II) chloride (10.00g) was added and

the mixture was rapidly stirred for 6h whilst continuing to pass ammonia gas through the mixture. The mixture was filtered through hyflo and the solvent removed from the filtrate by evaporation in vacuo. The residue was treated with acetic acid (290ml) and sodium acetate (13.35g) and the resulting mixture stirred at 23° for 18h. The solvent was evaporated in vacuo and the residue was purified by chromatography. Elution with EA gave the title compound (5.70g).
T.l.c. (3:2 EA-hexane) Rf 0.4

Intermediate 3
Phenylmethyl [2,3-dihydro-5-methyl-1-[2-(methylphenylamino)-2-oxoethyl]-2-oxo- 1H-1,4-benzodiazepin-3-yl]carbamate.
80% Sodium hydride in oil (102mg) was added to a solution of phenylmethyl [2,3-dihydro-5-methyl-2-oxo-1H-1,4-benzodiazepin-3- yl]carbamate (1.00g) in dry DMF (10ml) under nitrogen. The mixture was stirred for 0.5h at 23° and was treated with a solution of 2- bromo-N-methyl-N-phenylacetamide (707mg) in dry DMF (1ml). The mixture was stirred at 23° for 1h, partitioned between phosphate buffer solution (pH6.5) and EA, the organic phase was washed with water and dried. The solvent was evaporated in vacuo and the residue was purified by chromatography on alumina. Elution with MeOH-DCM (1:50) gave the title compound (568mg).
T.l.c. (1:50 MeOH-DCM) Rf 0.2

Intermediate 4
3-Amino-2,3-dihydro-N,5-dimethyl-2-oxo-N-phenyl-1H-1,4-benzodia zepine-1-acetamide
A mixture of 5% palladium on carbon (300mg) and phenylmethyl [2,3- dihydro-5-methyl-1-[2-(methylphenylamino)-2-oxoethyl]-2-oxo-1H-1,4- benzodiazepin-3-yl]carbamate (500mg) in MeOH-water 4:1 (40ml) at 40° under nitrogen was treated with ammonium formate (201mg) and the mixture stirred at 40° for 1h. The mixture was cooled to 23° and was filtered through hyflo. The filtrate was evaporated in vacuo and the residue partitioned between 2N sodium carbonate solution and chloroform. The organic phase was dried and the solvent evaporated in vacuo. The residue was purified by chromatography, elution with MeOH-DCM (1:9) gave the title compound (302mg).

T.l.c. (1:9 MeOH-DCM) Rf 0.3

Intermediate 5

2,3-Dihydro-N,5-dimethyl-2-oxo-N-phenyl-[3[[(3-cyanophenyl)amino]carbonyl]amino]- 1H-1,4-benzodiazepine-1-acetamide

3-Cyanophenyl isocyanate (144mg) was added to a solution of intermediate 4 (336mg) in dichloromethane (10ml) under nitrogen and the mixture stirred for 4h. The reaction mixture was filtered to give the title compound (305mg) as a white solid, m.p. 210-211^0.

Intermediate 6

2-{5-Bromomethyl-3-[3-(3-cyano-phenyl)-ureido]-2-oxo-2,3-dihydro - benzo[e][1,4] diazepin- 1-yl}-N-methyl-N-phenyl-acetamide.

A solution of intermediate 5 (2.99g) in dry DCM (300ml) and $CHCl_3$ (100ml) at 23° under nitrogen was treated with 5,5-dibromobarbituric acid (0.93g). After 18 hours silica (Merck 9385; 20g) was added and the mixture evaporated in vacuo. The mixture was purified by flash chromatography eluting with (1 to 2 to 5%) MeOH in DCM to give the title compound as a white foam (1.89g), m.p. 100° dec.

T.l.c. (5%MeOH-DCM) Rf 0.29

Intermediate 7

5-Bromomethyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepine-3-carba mic acid benzyl ester.

5,5-Dibromobarbituric acid (5.1g) was added to a solution of 2,3-dihydro-5-methyl- 2-oxo-1H-benzo[e][1,4]-diazepine-3-carbamic acid benzyl ester (11g) in dry DCM (750ml) at 23° under nitrogen. The solution grew progressively cloudier and deeper orange over 20h whereupon silica (50g) was added and the mixture evaporated to dryness. The residue was chromatographed on silica (Et_3N-deactivated, Merck 9385) with 1% MeOH in DCM as eluent to give the title compound (7.1g) as a pale yellow solid, m.p. 154°dec.

T.l.c. Et_3N-deactivated SiO_2 (100:1 DCM-MeOH) Rf 0.55

Intermediate 8

5-Morpholin-4-ylmethyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin e-3-carbamic acid benzyl ester.

Morpholine (7.5ml) was added to a solution of intermediate 7 (6.9g) in dry DCM (190ml) at 23° under nitrogen. After 3h the cloudy orange mixture was poured into water (200ml) and the layers separated. The aqueous phase was re-extracted with DCM (150ml) and the combined, dried organic extracts evaporated. The residue was chromatographed with 2 to 3% MeOH in DCM as eluent to give the title compound (3.38g) as a beige foam, m.p. 91° dec.

T.l.c. (95:5 DCM-MeOH) Rf 0.28

I.r. 3235; 1698; 1500; 1456; 1241; 1116cm^{-1}

Intermediate 9

1-(3-Cyano-phenyl)-3-(5-morpholin-4-ylmethyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-urea.

A solution of intermediate 8 (3.38g) in absolute EtOH (160ml) was hydrogenated at 23° and 1 atmosphere pressure in the presence of 10% palladium on charcoal as catalyst (1g). After 3h the mixture was filtered through hyflo and the filtrate evaporated to give a purple foam. A solution of the foam in MeCN (54ml) was treated with 3- cyanophenyl isocyanate (1.21g) and after 1h DE was added to the resulting suspension. The solid was filtered off and dried at 50° in vacuo to give the title compound (1.44g) as an off-white solid, m.p. 249-50°.

T.l.c. (9:1 DCM-MeOH) Rf 0.46

Intermediate 10

1-(3-Cyano-phenyl)-3-[1-(3,3-dimethyl-2-oxo-butyl)-5-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-urea.

3-Cyanophenyl isocyanate (278mg) was added to a solution of 3-amino-2,3-dihydro- 1-(3,3,-dimethyl-2-oxo-butyl)-5-methyl-2-oxo-1H-1,4-benzodiazep ine (500mg) in dry MeCN (13ml) at 23° under nitrogen. After 30 min the resulting thick slurry was stirred with DE (5ml) filtered and the filtercake washed with EA and DE then dried in vacuo at 50° to give the title compound (571mg) as a white solid, m.p. 246-7°

T.l.c. (9:1 DCM-MeOH) Rf 0.51

I.r. 3340; 2229; 1719; 1678; 1646; 1557; 1517cm^{-1}

Intermediate 11

1-[5-Bromomethyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-2,3-dihydro-1H-benzo[e] [1,4]diazepin-3-yl]-3-(3-cyano-phenyl)-urea.

5,5-Dibromobarbituric acid (38mg) was added to a suspension of intermediate 10 (100mg) in dry DCM (10ml) at 23° under nitrogen. After 6.5h, dry THF (4ml) was added to induce solubility and stirring was continued for 17h. Silica (2g) was added to the pale orange solution and the mixture evaporated to dryness. The residue was chromatographed with 0 to 0.25 to 0.5 to 1 to 2% MeOH in DCM as eluent to give the title compound (80mg) as a white solid, m.p. 135°dec.

T.l.c. (2% MeOH-DCM) Rf 0.23

Intermediate 12

5-Bromomethyl-1-(methyl-phenyl-carbamoylmethyl)-2-oxo-2,3-dihydro-1H-benzo[e] [1,4]diazepine-3-carbamic acid, benzyl ester

A solution of intermediate 3 (200mg) in DE (5ml) and chloroform (5ml) under nitrogen, was trated with 5,5-dibromobarbituric acid (61mg) and the mixture stirred at 23^0 for 18h. MeOH (5ml) and silica (1g) were added and the solvent was evaporated in vacuo. The residue was chromatographed with MeOH-DCM (0.2:10) as eluent to give the title compound (175mg) as a white foam.

T.l.c. (10:0.5 DCM-MeOH) Rf 0.69

I.r. 3418; 3325; 1727; 1670; 1496; 1453cm^{-1}.

Intermediate 13

1-(Methyl-phenyl-carbamoylmethyl)-5-morpholin-4-ylmethyl-2-oxo-2,3-dihydro-1H-benzo[e] [1,4]diazepine-3-carbamic acid, benzyl ester

A solution of intermediate 12 (2.75g) in DCM (50ml) was treated with morpholine (2.18g) and the mixture was stirred at 23^0 under nitrogen for 1h. The mixture was washed with water (2x40ml), brine (40ml) and dried then evaporated in vacuo. The residue was chromatographed with DCM-MeOH (10:0.3) as eluent to give the title compound (2.38g) as an orange foam.

I.r. (Solution in $CHCl_3$) 3425; 1723; 1670; 1497; 1452; 1394cm^{-1}.

Intermediate 14

2-(3-Amino-5-morpholin-4-ylmethyl-2-oxo-2,3-dihydro-benzo[e] [1,4]diazepin-1-yl)-N- methyl-N-phenyl-acetamide

A solution of intermediate 13 (1.82g) in EtOH (50ml) was hydrogenated over 10% palladium on carbon (250mg) at 23^0 and 1 atmosphere pressure. After 4h the mixture was filtered through hyflo and the filtrate evaporated to give the title compound (1.35g) as a pale yellow foam.

T.l.c. (9:1 DCM-MeOH) Rf 0.25

I.r. (Solution in $CHCl_3$) 3395; 1669; 1598; 1497; 1451; 1116cm^{-1}.

Intermediate 15

R-Carbonic acid (4-nitro-phenyl) ester (1-phenyl-ethyl) ester.

A solution of (R)-sec-phenethyl alcohol (500mg) and pyridine (324mg) in DCM (15ml) at 0-5^0 under nitrogen was treated dropwise with a solution of 4-nitrophenyl chloroformate (825mg) in DCM (10ml). The mixture was allowed to warm to 23^0 and was stirred for 18h. The mixture was partitioned between phosphate buffer (pH 6.5) and DCM. The organic phase was washed with 8% sodium bicarbonate solution and was dried (Na_2SO_4). Solvent evaporation in vacuo gave a residue which was azeotroped with toluene and then purified by chromatography. Elution with EA-hexane (1:9) gave the title compound as a colourless oil (290mg).

T.l.c. (1:4 EA-hexane) Rf 0.45

I.r. (film) 3086; 2986; 1765; 1526; 1349; 1258; 1220; 1064; 861; 700cm^{-1}.

Intermediate 16

R-5-Methyl-1-(methyl-phenyl-carbamoylmethyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepine-3-carbamic acid 1-phenyl-ethyl ester.

A solution of intermediate 4 (200mg) and intermediate 15 (256mg) in MeCN (14ml) under nitrogen was treated with Et_3N (60mg) and the mixture was heated under reflux for 18h. The mixture was cooled to 23^0 and was partitioned between phosphate buffer (pH 6.5) and EA. The organic phase was dried (Na_2SO_4) and the solvent evaporated in vacuo. The residue was purified by chromatography. Elution with EA-hexane (7:3) gave the title compound as a white foam (79mg).

T.l.c. (7:3 EA-Hexane) Rf 0.26

I.r. 3425; 3318; 1724; 1669; 1632; 1596; 1270; 1244; 1206; 1071; 766; 701cm^{-1}.

Intermediate 17

2-(3-Amino-5-methyl-2-oxo-2,3-dihydro-benzo[e][1,4]diazepin-1-yl) -N-methyl-N-phenyl- acetamide. (Isomer 2)

A solution of intermediate 16 (442mg) in EtOH (14ml) was hydrogenated over 10% palladium on carbon (90mg). After 7h the mixture was filtered through hyflo and the solvent evaporated in vacuo to give the title compound as a white foam (311mg).

T.l.c. (1:20 MeOH-DCM) Rf 0.24

I.r. 1660; 1595; 1317; 1275; 1251; 1200; 1122; 964; 770; 724; 702; 558cm^{-1}.

Intermediate 18

2-{3-[3-(3-Methoxy-phenyl)-ureido]-5-methyl-2-oxo-2,3-dihydro-benzo[e] [1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide. (Isomer 1)

A solution of intermediate 17 (208mg) in DCM (5ml) under nitrogen was treated with 3-methoxyphenyl isocyanate (92mg) and the mixture was stirred for 4h at 23^0. The solvent was evaporated in vacuo and the residue was purified by chromatography. Elution with MeOH-DCM (1:20) gave the title compound as a white solid (221mg), m.p. 238-9^0.

T.l.c. (1:20 MeOH-DCM) Rf 0.30

I.r. 3311; 1666; 1637; 1612; 1558; 1523; 1496; 1158; 1036; 766; 701; 557cm^{-1}.

Intermediate 19

1-(Methyl-phenyl-carbamoylmethyl)-5-(4-methyl-piperazin-1-ylmethyl)-2-oxo-2,3- dihydro- 1H-benzo[e][1,4]diazepine-3-carbamic acid benzyl ester.

N-Methyl piperazine (0.51ml) was added to a stirred solution of intermediate 12 (0.5g) in dry DCM (10ml) at 23° under nitrogen. After 3 hours the mixture was poured into water (75ml) and extracted with EA (50ml x 3). The combined organic extracts were washed with saturated brine, dried and evaporated in vacuo. The crude product was purified by flash chromatography on silica (Merck 9385 - Et_3N deactivated) eluting with 2 to 4% MeOH in DCM to give the title compound as an orange foam (385mg), m.p. 65-70°.

T.l.c. SiO_2-Et_3N deactivated (2% MeOH-DCM) Rf 0.39.

Intermediate 20

2-{3-[3-(3-Methoxy-phenyl)-ureido]-5-methyl-2-oxo-2,3-dihydro-benzo[e][1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide.

A solution of intermediate 4 (500mg) in dry MeCN (10ml) was treated with 3-methoxyphenylisocyanate (195µl) and the mixture was stirred at 23^0 under nitrogen for 5 hours. DE (10ml) was added and the resultant mixture was filtered, washing the filter-cake with hexane to give the title compound as a cream solid (599mg), m.p. 215.

T.l.c. (EA) Rf 0.38

Intermediate 21

3-Amino-2,3-dihydro-1-(3,3-dimethyl-2-oxo-butyl)-5-methyl-2-oxo -1H-1,4-benzodiazpine

(a) N-[5-Methyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,3-dihydro-benzo[e][1,4]diazepin-3-yl]-carbamic acid benzyl ester

Sodium hydride (80% in oil, 235mg) was added to a solution of Intermediate 2, (2g) in dry DMF (20ml) under nitrogen and cooled in an ice-bath. After 45min, a solution of 1-bromopinacolone (1.23g) in dry DMF (5ml) was added and stirred for 2h 20min as the ice-bath was allowed to melt. The reaction mixture was partioned between water (150ml) and EA (2x150ml) and the combined EA extracts were washed with water (100ml), saturated brine (100ml) and dried. The solution was evaporated and the residue chromatographed with hexane-EA (1:2) as eluent to give the title compound (2.47g) as a white foam, m.p. 68^0.

b. 3-Amino-2,3-dihydro-1-(3,3-dimethyl-2-oxo-butyl)-5-methyl-2-oxo -1H-1,4-benzodiazpine

A 3-necked flask was flushed thoroughly with nitrogen and charged successively with 5% palladium on carbon (50%) wet paste; 1.66g) water (45ml), a solution of Intermermediate 21a (2.42g) in methanol (180ml) and ammonium formate (1.09g). The mixture was stirred at 40^0 under nitrogen for 1.5h then cooled and filtered through hyflo. The filtrate was evaporated and the residue partioned between 2N sodium carbonate solution (100ml) and EA (2 x 150ml). The combined organic extracts were washed with saturated brine

(100ml), dried and evaporated to give the title compound (1.63g) as a fawn solid, m.p. 96-8°.

T.l.c. (9:1 DCM-MeOH) Rf 0.33.

Intermediate 22

N-[5-Methyl-1-(2-oxo-2-pyrrolidin-1-yl-ethyl)-2-oxo-1,3-dihydro-benzo[e][1,4] diazepin-3-yl]-carbamic acid benzyl ester

NaH (80% in oil; 102mg) was added to a solution of intermediate 2(1.00g) in dry DMF (10ml) at 0°. The mixture was stirred at 0° for 0.5h and a solution of 2-N-pyrrolidinyl-2-oxo-ethylbromide (596mg) in DMF (1ml) was added. The mixture was stirred at 23° for 4h. Phosphate buffer (pH 6.5;50ml) was added and the mixture extracted with ethyl acetate (50ml). The organic phase was washed with water (2x50ml) and dried (Na_2SO_4). Solvent evaporation in vacuo gave a residue which was chromatographed with EA then MeOH-EA (1:9) as eluent to give the title compound (959mg) as a white solid, m.p. 165-6°.

T.l.c. (EA) Rf 0.16

I.r. (Solution in $CHBr_3$) 3147; 2974; 2874; 1719; 1683; 1654; 1057; 1449; 1079; 765cm^{-1}

Intermediate 23

N-[5-(Bromo-methyl)-1-(2-oxo-2-pyrrolidin-1-yl-ethyl)-2-oxo-1,3-dihydro-benzo[e][1,4]diazepin-3-yl]-carbamic acid benzyl ester.

A solution of intermediate 22(4.00g) in DE (50ml) and $CHCl_3$ (50ml) under nitrogen at 23° was treated with 5,5-dibromobarbituric acid (1.32g) and the mixture stirred at 23° for 18h. MeOH (20ml) and silica (Merck 9385;15g) were added and the solvent evaporated in vacuo. The residue was chromatographed with MeOH-DCM (0.2:10) as eluent to give the title compound as a white solid (3.88g).

T.l.c. (10:0.2 DCM-MeOH) Rf 0.36

I.r. 3389; 1733; 1686; 1662; 1650; 1596; 1330; 1217; 1200; 1084; 777cm^{-1}

Intermediate 24

N-[5-(Morpholin-4-yl-methyl)-1-(2-oxo-2-pyrrolidin-1-yl-ethyl)-2-oxo-1,3-dihydro-benzo[e][1,4]diazepin-3-yl]-carbamic acid benzyl ester.

A solution of intermediate 23 (3.78g) in DMF (20ml) under nitrogen at 23° was treated with morpholine (3.21g) and the mixture was stirred for 1h. Water was added and the mixture extracted with EA. The extract was washed with water and saturated brine then was dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue purified by chromatography. Elution with DCM-MeOH (100:3) gave the title compound as a pale orange foam (1.095g).
T.l.c. (100:3 DCM - MeOH) Rf 0.27
I.r. (KBr disc) 3426; 2979; 1723; 1688; 1661; 1510; 1453; 1394; 1323; 1116; 1090; 929cm^{-1}

Intermediate 25
3-Amino-5-(morpholin-4-yl-methyl)-1-(2-oxo-2-pyrrolidin-1-yl-ethyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one.
A solution of intermediate 24 (3.584g) in EtOH (100ml) was hydrogenated over 10% palladium on carbon (500mg) at 23°. After 3.5h the mixture was filtered through hyflo and the filtrate evaporated in vacuo to give the title compound as a beige foam (2.536g).
T.l.c. (9:1 DCM-MeOH) Rf 0.22
I.r (KBr disc) 3396; 2981; 1657; 1448; 1322; 1256; 1116; 865cm^{-1}

Intermediate 26
Ethyl-(4-fluoro-phenyl)-amine.
Iodoethane (3.6ml) was added to a mixture of 4-fluoroaniline (4.26ml) and potassium carbonate (6.9g) in dry DMF (100ml). After 18.5h at 23°, the resulting suspension was poured into water (400ml) and extracted with EA (400ml). The organic extract was washed with water (200ml) then saturated brine (200ml), dried and evaporated. The residual oil was chromatographed with 2 to 3 to 4% EA in hexane as eluent to give the title compound (3.667g) as a yellow oil.
T.l.c. (4:1 Hexane-EA) Rf 0.62

Intermediate 27
2-Bromo-N-ethyl-N-(4-fluoro-phenyl)-acetamide.
A solution of bromoacetyl bromide (2.24ml) in dry DCM (15ml) was added dropwise over 20 min to a solution of intermediate 26 (3.58g) and Et_3N (3.59ml)

in dry DCM (30ml) at 0° under nitrogen. After 2.5h at 0° the solution was partitioned between water (200ml) and DCM (200 + 100ml). The combined organic extracts were dried and evaporated and the residue chromatographed with 10 to 15 to 20% EA in hexane as eluent to give the title compound (2.641g) as a pale orange oil.
T.l.c. (9:1 hexane-EA) Rf 0.15

Intermediate 28
N-(1-{[Ethyl-(4-fluoro-phenyl)-carbamoyl]-methyl}-5-methyl-2-oxo-1,3-dihydro-benzo[e][1,4]diazepin-3-yl)-carbamic acid, benzyl ester.
NaH (80% in oil; 348mg) was added to a solution of intermediate 2 (2.92g) in dry DMF (30ml) at 0° under nitrogen. After 1h, the orange solution was treated with a solution of intermediate 27 (2.608g) in dry DMF (10ml). Stirring was continued at 0° for 2h whereupon the solution was poured into water (200ml) and extracted with EA (200 + 100ml). The combined extracts were washed with saturated brine (200ml), dried and evaporated. The residue was chromatographed with EA-DCM (4:1) as eluent to give the title compound (3.75g) as a pale yellow foam.
T.l.c. (4:1 EA-DCM) Rf 0.26
I.r. (Solution in $CHCl_3$) 3425; 1724; 1671; 1515; 1510; 1248; 1094; 845cm^{-1}

Intermediate 29
N-{1-[Ethyl-(4-fluoro-phenyl)-carbamoyl-methyl]-5-(morpholin-4-yl-methyl)-2-oxo-1,3-dihydro-benzo[e][1,4]diazepin-3-yl}-carbamic acid benzyl ester.
5,5-Dibromobarbituric acid (765mg) was added to a solution of intermedaite 28 (2.69g) in $CHCl_3$ (30ml) and DE (30ml) at 23° under nitrogen. After 30h morpholine (2.3ml) was added and stirring continued for a further 16h whereupon the cloudy orange solution was poured into water (100ml). The layers were separated and the aqueous phase extracted with $CHCl_3$ (100ml). The combined, dried organic extracts were evaporated and the residue chromatographed with EA-DCM (3:1) as eluent to give the title compound (2.22g) as a crunchy orange foam.
T.l.c. (4:1 EA-DCM) Rf 0.17
I.r. (Solution in $CHCl_3$) 3621; 3425; 1726; 1672; 1510; 1233; 1202; 1116; 845cm^{-1}

Intermediate 30

2-[3-Amino-5-(morpholin-4-yl-methyl)-2-oxo-2,3-dihydro-benzo[e][1,4]diazepin-1-yl]-N-ethyl-N-(4-fluoro-phenyl)-acetamide.

A solution of intermediate 29(1.144g) in absolute EtOH (25ml) was hydrogenated at 23° and 1 atmosphere pressure in the presence of 10% palladium on charcoal as catalyst (160mg). After stirring for 6h and allowing to stand under hydrogen overnight the mixture was filtered through hyflo and the filtrate evaporated to give the title compound (879mg) as a crunchy green-brown foam, m.p. 95-9° dec.

T.l.c. (9:1 DCM-MeOH) Rf 0.18

Intermediate 31

3-(1,2,4-Oxadiazol-3-yl)-phenylamine.

A solution of 3-(1,2,4-oxidazol-3-yl)nitrobenzene (3.0g) in EA (50ml) was hydrogenated at 1atm. and 23° over Raney nickel (1 pipette-full). After 4.5h the catalyst was removed by filtration through hyflo. The filtrate was evaporated to give a pale cream solid (2.57g) identified as the hydroxylamine.

T.l.c. (1:1 EA - Hexane) Rf 0.27

A solution of the hydroxylamine (2.54g) in EA (40ml) was further hydrogenated at room temperature and pressure over Raney nickel (1 pipette-full). After 4.5h the catalyst was removed by filtration through hyflo and the filtrate evaporated to give a yellow solid.Crystallization from EA gave pure product.The mother liquors were chromatographed with hexane - DE (3:1) as eluent to give more product which was combined with the crystallized material to give the title compound (548mg) as a cream solid.

T.l.c. (2:1 DE-Hexane) Rf 0.35

Example 1

2-{3-[3-(3-Cyano-phenyl)-ureido]-2-oxo-5-piperidin-1-ylmethyl-2, 3-dihydro-benzo[e] [1,4] diazepin-1-yl}-N-methyl-N-phenyl-acetamide.

A solution of intermediate 6 (300mg) in DCM (5ml) at 23° under nitrogen was treated with piperidine (0.27ml). After 2 hours the mixture was poured into

water (75ml) and extracted with EA (100mlx2). The combined organic extracts were washed with saturated brine, dried and evaporated in vacuo. The crude product was partially purified by flash chromatography on silica (Merck 9385-Et_3N deactivated) eluting with 2% MeOH in DCM. Complete purification was obtained by flash chromatography on silica (Merck 9385 - Et_3N deactivated) eluting with 1 to 2% MeOH in DCM to give the title compound as a cream solid (135mg), m.p. 145-150°
I.r. 3260; 2222; 1704; 1686; 1591; 1383; 1223; 1125cm^{-1}

Example 2
2-{3-[3-(3-Cyano-phenyl)-ureido]-2-oxo-5-pyrrolidin-1-ylmethyl-2 ,3-dihydro-benzo[e] [1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide.
A solution of intermediate 6 (300mg) in DCM (5ml) at 23° under nitrogen was treated with pyrrolidine (0.22ml). After 2 hours the mixture was evaporated in vacuo to give a brown oil which was purified by flash chromatography on silica (Merck 9385 - Et_3N deactivated) eluting with 2% MeOH in DCM. Product fractions, after evaporation in vacuo, were triturated with EA - hexane. The solid was dissolved in EA-THF (4:1; 100ml) and the solution was washed with water and saturated brine then was dried and evaporated in vacuo to give the title compound as a pale peach solid (154mg), m.p. 140 - 145° dec.
T.l.c. Et_3N deactivated SiO_2 (2%MeOH-DCM) Rf 0.22
I.r. 3342; 2226; 1685; 1593; 1559; 1496; 1381cm^{-1}

Example 3
2-{3-[3-(3-Cyano-phenyl)-ureido]-5-(isopropylamino-methyl)-2-oxo -2,3-dihydro-benzo[e] [1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide.
A solution of intermediate 6 (300mg) in DCM (5ml) at 23° under nitrogen was treated with isopropylamine (0.23ml). After 2 hours the mixture was evaporated in vacuo to give an oil which was purified by flash chromatography on silica (Merck 9385 - Et_3N deactivated) eluting with 2% MeOH - DCM. Trituration with EA - hexane gave a cream solid which was dissolved in EA - THF (4:1; 100ml) and washed with water (100ml) and saturated brine, dried and evaporated in vacuo to give the title compound as a cream solid (132mg), m.p. 160° dec.
T.l.c. Et_3N deactivated SiO_2(2% MeOH-DCM) Rf 0.16
I.r. 3316; 2231; 1674; 1591; 1561; 1455; 1432; 1384; 1240; 1198cm^{-1}

Example 4

2-{3-[3-(3-Cyano-phenyl)-ureido]-2-oxo-5-[1,4]thiazinan-4-ylmethy l-2,3-dihydro-benzo[e][1,4] diazepin-1-yl}-N-methyl-N-phenyl-acetamide.

A solution of intermediate 6 (1g) in dry DCM (20ml) was treated with thiomorpholine (0.90ml) at 23° under nitrogen. After 2 hours the mixture was poured into water (75ml) and extracted with EA (3x75ml). The combined organic extracts were washed with saturated brine, dried and evaporated in vacuo. The crude product was purified by flash chromatography eluting with EA to give, after trituration with EA-hexane, the title compound as a white solid (458mg), m.p. 165°.

T.l.c. Et_3N deactivated SiO_2 (EA) Rf 0.52

I.r. 3267; 2229; 1687; 1557; 1450; 1382; 1221cm^{-1}

Example 5

1-(3-Cyano-phenyl)-3-{1-[2-(cis-2,5-dimethyl-pyrrolidin-1-yl)-2-oxo-ethyl]-5-morpholin- 4-ylmethyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl}urea.

NaH (80% in oil; 23mg) was added to a suspension of intermediate 9 (253mg) in dry DMF (3ml) at 0° under nitrogen. After 30min the resulting solution was treated with a solution of 2-(cis-2,5-dimethylpyrrolidin-1-yl)-2-oxo-ethyl bromide (145mg) in dry DMF (0.5ml) and stirring was continued at 0° for 2.25h and at 23° for 20h. The dark solution was poured into water (20ml) and extracted with EA (2x30ml) then the combined extracts were washed with water (20ml) then saturated brine (40ml), dried and evaporated. Trituration of the residue with EA-DE gave the title compound (196mg) as a white solid, m.p. 234-5° dec.

T.l.c. (95:5 DCM-MeOH) Rf 0.26

I.r. 3263; 2224; 1685; 1650; 1590; 1557; 1449; 1378; 1115; 1001cm^{-1}

Example 6

2-{3-[3-(3-Cyano-phenyl)-ureido]-5-morpholin-4-ylmethyl-2-oxo-2, 3-dihydro-benzo[e] [1,4]diazepin-1-yl)-N-(4-fluoro-phenyl)-N-methyl-acetamide.

NaH (80% in oil; 23mg) was added to a suspension of intermediate 9 (250mg) in dry DMF (3ml) at 0°under nitrogen. After 40 min a solution of 2-bromo-N-(4-fluorophenyl)-N-methyl-acetamide (162mg) in dry DMF (0.5ml) was added to the

resulting solution and stirring was continued at 23° for 22h. The yellow solution was then poured into water (20ml) and extracted with EA (2x30ml) and the combined extracts were washed with water (20ml) then saturated brine (40ml) dried and evaporated. A solution of the residue in MeOH was preadsorbed onto silica and chromatographed with 0 to 1 to 2 to 3 to 4% MeOH in DCM as eluent to give the title compound (260mg) as an orange solid, m.p. 182-4° dec.
T.l.c. (95:5 DCM-MeOH) Rf 0.19
I.r. 3341; 2229; 1674; 1510; 1223; 1116cm^{-1}

Example 7
2-{3-[3-(3-Cyano-phenyl)-ureido]-5-morpholin-4-ylmethyl-2-oxo-2, 3-dihydro-benzo[e] [1,4]diazepin-1-yl}-N-ethyl-N-phenyl-acetamide.
NaH (80% in oil; 23mg) was added to a suspension of intermediate 9 (250mg) in dry DMF (3ml) at 0° under nitrogen. After 40 min a solution of 2-bromo-N-ethyl-N-phenyl acetamide (160mg) in dry DMF (0.5ml) was added to the resulting solution and stirring was continued at 23° for 22h. The orange solution was then poured into water (20ml) and extracted with EA (2x30ml) and the combined extracts were washed with water (20ml) then saturated brine (30ml) dried and evaporated. Trituration of the residue with EA-DE gave the title compound (239mg) as a white solid, m.p. 211 - 2° dec.
T.l.c. (95:5 DCM-MeOH) Rf 0.26
I.r. 3294; 2225; 1684; 1666; 1456; 1203; 777cm^{-1}

Example 8
1-(3-Cyano-phenyl)-3-[1-(3,3-dimethyl-2-oxo-butyl)-5-morpholin-4 -ylmethyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-urea.
Morpholine (62µl) was added to a suspension of intermediate 11 (72mg) in dry DCM (2ml) at 23° under nitrogen. After 1h the mixture was poured into water (20ml) and extracted with EA (20+15ml). The combined extracts were washed with saturated brine (20ml) dried and evaporated. The residue was triturated with EA-DE, filtered off and dried in vacuo to give the title compound (53mg) as a white solid, m.p. 168-9°dec.
T.l.c. (95:5 DCM-MeOH) Rf 0.26
I.r. 3279; 2229; 1688; 1455 cm^{-1}

Example 9

2-{3-[3-(3-Methoxy-phenyl)-ureido]-5-morpholin-4-ylmethyl-2-oxo-2,3-dihydro-benzo [e] [1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide.

3-Methoxyphenyl isocyanate (53mg) was added to a solution of intermediate 14 (150mg) in DCM (5ml) under nitrogen. The solution was stirred at 23^0 for 3h. The solvent was evaporated in vacuo and the residue purified by chromatography. Elution with MeOH-DCM (1:20) gave the title compound as a pale straw coloured solid (176mg), m.p. 164-6^0 dec.

T.l.c. (1:20 MeOH-DCM) Rf 0.25

I.r. (Solution in CHCl3) 3431; 1670; 1599; 1495; 1454; 1425; 1392; 1289; 1158; 1116cm-^{1}.

Example 10

N-Methyl-2-[5-morpholin-4-ylmethyl-2-oxo-3-(3-phenyl-ureido)-2,3 -dihydro-benzo[e] [1,4]diazepin-1-yl]-N-phenyl-acetamide.

Phenyl isocyanate (42mg) was added to a solution of intermediate 14 (150mg) in MeCN (5ml) under nitrogen and the mixture was stirred at 23 for 2h. DE was added and the mixture was filtered to give the title compound as a white solid (160mg), m.p. 157-8^0 dec.

T.l.c. (1:20 MeOH-DCM) Rf 0.33

I.r. (Solution in $CHCl_3$) 3430; 1670; 1599; 1498; 1452; 1392; 1311; 1292; 1116; 1002cm^{-1}.

Example 11

N-Methyl-2-{5-morpholin-4-ylmethyl-2-oxo-3-[3-(3-trifluoromethyl -phenyl)-ureido]-2,3- dihydro-benzo[e][1,4]diazepin-1-yl}-N-phenyl-acetamide.

3-Trifluoromethylphenyl isocyanate (103µl) was added dropwise to a stirred solution of intermediate 14 (300mg) in dry DCM (3ml). The mixture was stirred at room temperature under nitrogen for 18 hrs. Purification by column chromatography eluting with DCM-MeOH-. 880 ammonia (94.5:5:0.5), gave the title compound (87mg) as a white solid, m.p. 190^0 dec.

T.l.c. (94.5:5:0.5 DCM-MeOH-880 ammonia) Rf 0.22

I.r. 2924; 2854; 1688; 1671; 1450; 1339;1116 cm^{-1}

Example 12

(3-{3-[1-(Methyl-phenyl-carbamoylmethyl)-5-morpholin-4-ylmethyl-2-oxo-2,3-dihydro- 1H-benzo[e][1,4]diazepin-3-yl]-ureido}-phenyl)-carbamic acid tert-butyl ester.

Carbonyl diimidazole (97mg) was added to a solution of intermediate 14 (230mg) in THF (10ml) under nitrogen and the mixture was stirred at 23 for 1h. (3-Amino-phenyl)-carbamic acid t-butyl ester (114mg) was added and the mixture was heated under reflux for 18h. The mixture was cooled to 23 and was partitioned between water and EA. The organic phase was dried (Na_2SO_4) and the solvent evaporated in vacuo to give a residue which was purified by chromatography. Elution with MeOH-DCM (1:20) gave the title compound as a straw coloured solid (78mg).

T.l.c. (1:20 MeOH-DCM) Rf 0.32

Mass spectrum MH^+ (observed) 656

Example 13

2-{3-[3-(3-Amino-phenyl)-ureido]-5-morpholin-4-ylmethyl-2-oxo-2, 3-dihydro-benzo[e] [1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide.

A solution of Example 12 (70mg) in DCM (5ml) was treated with trifluoroacetic acid (0.3ml) and stirred for 1h. EA was added, the mixture washed with 2N sodium carbonate solution, dried (Na_2SO_4) and evaporated in vacuo. The residue was triturated with DE to give the title compound as a beige solid (31mg), m.p. 158-60^0.

T.l.c. (1:20 MeOH-DCM) Rf 0.22

I.r. 3353; 1667; 1613; 1596; 1556; 1496; 1321; 1204; 1115; 773cm^{-1}.

Example 14

(+)-2-{3-[3-(3-Methoxy-phenyl)-ureido]-5-morpholin-4-ylmethyl-2-oxo-2,3-dihydro-benzo [e][1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide.

3-Methoxyphenyl isocyanate (106mg) was added to a stirred solution of intermediate 14 (300mg) in DCM (10ml) under nitrogen and the mixture was stirred at 23^0 for 2h. The solvent was evaporated in vacuo and the residue purified by chromatography. Elution with MeOH-DCM (1:20) gave a straw coloured solid (205mg) a portion (75mg) of which was further purified by chiral h.p.l.c. to give the title compound as a white solid (26mg), m.p. 169-70 dec.

T.l.c. (1:20 MeOH-DCM) Rf 0.25

I.r. (Solution in $CHCl_3$) 3431; 1670; 1600; 1496; 1454; 1427; 1289; 1158; 1116; 1002cm^{-1}.

H.p.l.c. Column: CHIRALCEL-OD 25cm x 4.6mmid
Eluent: EtOH-Hexane (1:1)
Flow: 1ml/min.
Wavelength: 230nm
Temperature: 23^0
R_t: 4.96 min

Example 15

(+)2-{3-[3-(3-Methoxy-phenyl)-ureido]-5-morpholin-4-ylmethyl-2-oxo-2,3-dihydro- benzo [e][1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide.

A solution of intermediate 18 (189mg) in chloroform (8ml) and DE (3ml) under nitrogen was treated with 5,5-dibromobarbituric acid (56mg) and the mixture stirred at 23^0 in the dark for 18h. Morpholine (68mg) was added and the mixture was stirred for 2h at 23^0. The mixture was partitioned between EA and phosphate buffer (pH6.5). The organic phase was dried (Na_2SO_4) and the solvent evaporated in vacuo to give a residue which was purified by chromatography. Elution with EA then MeOH-DCM (1:20) gave the title compound as a white solid (147mg), m.p. 164-6^0 dec.
T.l.c. (1:20 MeOH-DCM) Rf 0.35
I.r. 3339; 1668; 1598; 1549; 1290; 1203; 1156;1115;771;703cm^{-1}

Example 16

2-{3-[3-(3-Cyano-phenyl)-ureido]-5-(4-methyl-piperazin-1-ylmethyl)-2-oxo-2,3-dihydro- benzo[e][1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide.

A solution of intermediate 19 (352mg) in EtOH (20ml) was hydrogenated at 23°and 1 atm pressure using 10% palladium on carbon (80mg) as a catalyst. After 7 hours the mixture was filtered through hyflo and evaporated to give crude amine (319mg) as an orange-red oil. This was redissolved in dry MeCN (3ml) and treated with 3-cyanophenyl isocyanate (85mg) at 23° under nitrogen. After 2 hours the mixture was evaporated in vacuo to give a red oil which was purified by flash chromatography on silica (Merck 9385-Et_3N deactivated) eluting with 2 to 5 to 10% MeOH in DCM. Trituration with DE-hexane gave the title compound as a cream solid (171mg), m.p. 152-155^0.

T.l.c. SiO_2-Et_3N deactivated (5% MeOH-DCM) Rf 0.20.
I.r. 3338; 2228; 1671; 1594; 1557; 1496; 1455cm^{-1}.

Example 17

2-{3-[3-(3-Methoxy-phenyl)-ureido]-5-(2-dimethylamino-ethyl)-2-oxo-2,3-dihydro- benzo[e] [1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide.

A mixture of intermediate 20 (100mg) and Eschenmoser's salt (46mg) in dimethoxyethane (5ml) was heated to reflux for 4 hours then was poured into EA (50ml) and extracted with 2N HCl (25ml x 2). The combined aqueous extracts were basified to pH8 with 2N Na_2CO_3 solution then extracted with EA (30ml x 2). The combined organic extracts were dried and evaporated in vacuo. The crude product was purified by flash chromatography on silica (Merck 9385 - Et_3N deactivated) eluting with 2 to 3 to 4 to 5% MeOH in DCM to give the title compound as a cream solid (31mg), m.p. 134^0.
T.l.c. SiO_2-Et_3N deactivated (5% MeOH-DCM) Rf 0.13.
I.r. (Solution in $CHCl_3$) 2954; 1670; 1600; 1495; 1455; 1158; cm^{-1}.

Example 18

2-{3-[3-(3-Cyano-phenyl)-ureido]-5-morpholin-4-ylmethyl-2-oxo-2, 3-dihydro-benzo[e] [1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide

A solution of intermediate 14 (113mg) in DCM (5ml) was treated with 3-cyanophenyl isocyanate (39mg) and the mxiture stirred at 23^0 under nitrogen for 18h. The solvent was removed in vacuo and the residue chromatographed with EA-EtOH (10:0.5) s eluent to give the title compound (64mg) as a white solid, m.p. 165-7^0.
T.l.c. (10:0.5 EA-EtOH) Rf 0.24
I.r. 3264; 2225; 1677; 1460; 1378cm^{-1}.

Example 19

1-[5-(Morpholin-4-yl-methyl)-2-oxo-1-(2-oxo-2-pyrrolidin-1-yl-ethyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-oxazol-5-yl-phenyl)-urea.

A solution of 3-(oxazol-5-yl)phenylamine (250mg) in THF (6ml) under nitrogen at 0° was treated with Et_3N (79mg) followed by triphosgene (77mg). More Et_3N (79mg) was added and the mixture was stirrred at 0° for 0.5h. A solution of intermediate 25 (125mg)in THF (5ml), was added and the mixture was stirred at

23° for 2h. Phosphate buffer (pH6.5;30ml) was added and the mixture extracted with EA (30ml). The organic phase was dried (Na_2SO_4) and the solvent evaporated in vacuo. The residue was chromatographed. Elution with MeOH-EA (0.5:10) then MeOH-DCM (0.5:10) gave the title compound as a pale straw solid (199mg), m.p. 208-9°.
T.l.c. (9:1 DCM-MeOH) Rf 0.42
I.r. 3284; 1683; 1663; 1551; 1499; 1324; 1205; 1116; 1003; 774cm^{-1}

Example 20

1-[5-(Morpholin-4-yl-methyl)-2-oxo-1-(2-oxo-2-pyrrolidin-1-yl-ethyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-[3-(1,2,4-oxadiazol-3-yl)-phenyl)]-urea.
A solution of intermediate 31 (100mg) in THF (6ml) at 0° under nitrogen was treated with Et_3N (63mg). Triphosgene (62mg) was then added followed by more Et_3N (62mg). The mixture was stirred at 0° for 0.5h. A solution of Intermediate 25 (200mg) in THF (5ml) was added and the mixture stirred at 23° for 2h. Phosphate buffer (pH 6.5;30ml) was added and the mixture extracted with DCM (30ml). The organic phase was dried (Na_2SO_4) and the solvent evaporated in vacuo to give a residue which was chromatographed with MeOH-DCM (0.5:10 to 1:10) as eluent to give the title compound (97mg) as a pale straw coloured solid, m.p.197-9^{o}dec.
T.l.c. (10:0.5 DCM-MeOH) Rf 0.27
I.r. (Solution in DMSO) 1684; 1656; 1615; 1599; 1568; 1540; 1510; 1347; 1204cm^{-1}

Example 21

N-Ethyl-N-(4-fluoro-phenyl)-2-{3-[3-(4-fluoro-phenyl)-ureido]-5-(morpholin-4-yl-methyl)-2-oxo-2,3-dihydro-benzo[e][1,4]diazepin-1-yl}-acetamide.
4-Fluorophenyl isocyanate (49mg) in dry MeCN (0.5ml) was added to a solution of intermediate 30(150mg) in dry MeCN (1ml) at 23° under nitrogen. After 1h DE (3ml) was added and the solid filtered off and dried in vacuo to give the title compound (100mg) as a white solid, m.p. 197° dec.
T.l.c. (9:1 DCM-MeOH) Rf 0.51
I.r. 3340; 2926; 1672; 1509; 1461; 1378cm^{-1}

Example 22

(+)-2-{3-[3-(3-Methoxy-phenyl)-ureido]-5-morpholin-4-ylmethyl-2-oxo-2,3-dihydro-benzo [e][1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide hydrochloride salt

A solution of the (+)-2-{3-[3-(3-Methoxy-phenyl)-ureido]-5-morpholin-4-ylmethyl-2-oxo-2,3-dihydro-benzo [e][1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide (200mg) in dry DCM (20ml) under nitrogen was treated with 1M hydrogen chloride in diethyl ether (0.77ml) and the solution was stirred for 5 min. The solvent was removed in vacuo and the residue azeotroped with toluene (2 x 10ml) to give the title compound (215mg) as a pale straw coloured solid, m.p. 160-170^0 dec.

Pharmacy Examples

Tablets

a.	Active ingredient	50mg
	Lactose anhydrous USP	163mg
	Microcrystalline Cellulose NF	69mg
	Pregelatinised starch Ph.Eur.	15mg
	Magnesium stearate USP	3mg
	Compression weight	300mg

The active ingredient, microcrystalline cellulose, lactose and pregelatinised starch are sieved through a 500 micron sieve and blended in a suitable mixer. The magnesium stearate is sieved through a 250 micron sieve and blended with the active blend. The blend is compressed into tablets using suitable punches.

b.	Active ingredient	50mg
	Lactose monohydrate USP	120mg
	Pregelatinised starch Ph.Eur.	20mg
	Crospovidone NF	8mg
	Magnesium stearate USP	2mg
	Compression weight	200mg

The active ingredient, lactose and pregelatinised starch are blended together and granulated with water. The wet mass is dried and milled. The magnesium stearate and Crospovidone are screened through a 250 micron sieve and blended with the granule. The resultant blend is compressed using suitable tablet punches.

Capsules

a.

Active ingredient	50mg
Pregelatinised Starch Ph.Eur.	148mg
Magnesium stearate USP	2mg
Fill weight	200mg

The active ingredient and pregelatinised starch are screened through a 500 micron mesh sieve, blended together and lubricated with magnesium stearate (meshed through a 250 micron sieve). The blend is filled into hard gelatin capsules of a suitable size.

b.

Active ingredient	50mg
Lactose monohydrate USP	223mg
Povidone USP	12mg
Crospovidone NF	12mg
Magnesium stearate	3mg
Fill weight	300mg

The active ingredient and lactose are blended together and granulated with a solution of Povidone. The wet mass is dried and milled. The magnesium stearate and Crospovidone are screened through a 250 micron sieve and blended with the granule. The resultant blend is filled into hard gelatin capsules of a suitable size.

A preferred active ingredient for use in the pharmacy examples is the compound of Example 14.

CCK-B- Receptor Binding

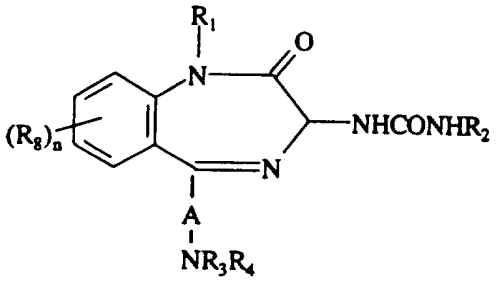
The binding affinity of the compounds of the invention for the CCK-B receptor (guinea pig cortex assay) was determined using the procedure of G Dal Forno et al J. Pharmacol. Exp & Ther. 261 - 1056-1063. The pKi values determined with respresentative compounds of invention were as follows:

Compound Ex No	pKi
1	9
2	8.4
3	8.6
4	8.8
5	8.5
6	8.7
7	8.8
8	8.8
9	8.9
10	9.1
11	9.3
13	8.2
14	9
16	8.3
17	8.6
18	8.9
19	8.5

The compounds of the invention are essentially non-toxic and therapeutically useful doses. Thus for example no untoward effects were observed when the compound of Example 14 was given to rats and dogs at doses at which the compound exhibits CCK-B antagonist activity.

CLAIMS

1. Compounds of the general formula (I)



(I)

and physiologically acceptable salts thereof;
wherein R_1 represents $CH_2CONR_5R_6$ or CH_2COR_7;
R_2 represents a phenyl group optionally substituted by 1 or 2 substituents selected from halogen, alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, alkylthio, alkylsulphinyl, alkylsulphonyl, amino, substituted amino, hydroxy, alkoxy, methylenedioxy, alkoxycarbonyl, oxazolyl or oxadiazolyl;
A represents a C_{1-4} straight or branched alkylene chain;
R_3 and R_4 independently represent hydrogen or C_{1-4}alkyl or R_3 and R_4 together with the nitrogen atom to which they are attached form a saturated 5-7 membered heterocyclic ring, which ring may contain an additional heteroatom selected from oxygen, sulphur or nitrogen;
R_5 represents hydrogen or C_{1-4}alkyl;
R_6 represents C_{1-4}alkyl or phenyl, optionally substituted by halogen, or R_5 and R_6 together with the nitrogen atom to which they are attached represent a saturated 5 to 7 membered heterocyclic ring which may be optionally substituted by 1 or 2 methyl groups or fused to a benzene ring.
R_7 represents a group selected from C_{1-4}alkyl, or optionally substituted phenyl;
R_8 represents hydrogen or a halogen atom;
n is zero, 1 or 2.

2. Compounds as claimed in Claim 1 wherein R_1 is $CH_2CONR_5R_6$ and R_5 represents methyl or ethyl and R_6 represents phenyl optionally substituted by halogen or NR_5R_6 represents a saturated heterocyclic ring selected from

pyrrolidino, 2,5-dimethylpyrrolidino, 3,3-dimethylpyrrolidino, piperidino, 3,3-dimethylpiperidino or 1-tetrahydroquinolino.

3. Compounds as claimed in Claims 1 and 2 wherein R_2 is phenyl or phenyl substituted by one or 2 groups selected from halogen, alkyl, alkoxy, amino, cyano, hydroxy, trifluoromethyl, oxazolyl or 1,2,4-oxadiazol-3-yl.

4. Compounds claimed in any of Claims 1 to 3 wherein R_2 is phenyl substituted by fluorine, oxazol-5-yl or methoxy.

5. Compounds as claimed in any of Claims 1 to 4 wherein A is a methylene chain.

6. Compounds as claimed in any of Claims 1 to 5 wherein NR_3R_4 represents a pyrrolidino, piperidino, hexamethyleneimino, morpholino, thiomorpholino or N-methylpiperazino group.

7. Compounds as claimed in any of Claims 1 to 6 wherein NR_3R_4 is morpholino.

8. Compounds as claimed in any of Claims 1 to 7 wherein R_8 is hydrogen.

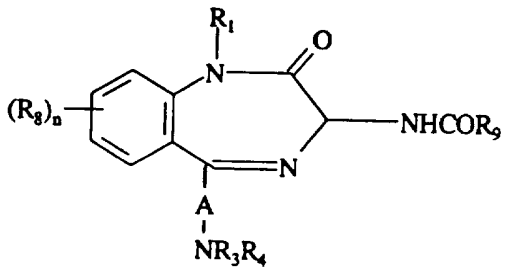
9. 2-{3-[3-(3-Methoxy-phenyl)-ureido]-5-morpholin-4-ylmethyl-2-oxo-2,3-dihydro-benzo [e] [1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide, the (+) enantiomer thereof and physiologically acceptable salts thereof.

10. A compound selected from:
N-Methyl-2-[5-morpholin-4-ylmethyl-2-oxo-3-(3-phenyl-ureido)-2,3 -dihydro-benzo[e] [1,4]diazepin-1-yl]-N-phenyl-acetamide;
N-Methyl-2-{5-morpholin-4-ylmethyl-2-oxo-3-[3-(3-trifluoromethyl -phenyl)-ureido]-2,3- dihydro-benzo[e][1,4]diazepin-1-yl}-N-phenyl-acetamide;
2-{3-[3-(3-Cyano-phenyl)-ureido]-5-morpholin-4-ylmethyl-2-oxo-2, 3-dihydro-benzo[e] [1,4]diazepin-1-yl}-N-methyl-N-phenyl-acetamide;
1-[5-(Morpholin-4-yl-methyl)-2-oxo-1-(2-oxo-2-pyrrolidin-1-yl-ethyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-3-(3-oxazol-5-yl-phenyl)-urea;

N-Ethyl-N-(4-fluoro-phenyl)-2-{3-[3-(4-fluoro-phenyl)-ureido]-5-(morpholin-4-yl-methyl)-2-oxo-2,3-dihydro-benzo[e][1,4]diazepin-1-yl}-acetamide; enantiomers thereof; and physiologically acceptable salts thereof.

11. A process for the preparation of compounds as defined in Claim 1 which comprises

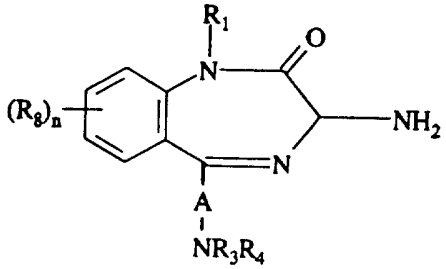
(a) reacting a compounds of formula (II) wherein R_1, A. R_3, R_4 and R_8 have the meanings defined for formula (I) and R_9 represents a leaving group.



(II)

with an amine R_2NH_2 wherein R_2 has the meanings defined in formula (I);

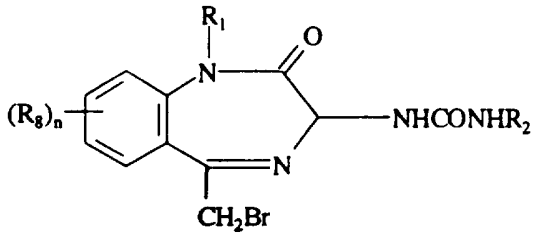
(b) reacting a compound of formula (III) wherein R_1, R_3, R_4, R_8 and A have the meanings defined in formula (I)



(III)

with the isocyanate R_2NCO or carbamoyl chloride $R_2HNCOCl$ (wherein R_2 has the meanings defined in formula (I);

(c) reacting a compound of formula (XII) wherein R_1, R_2 and R_8 have the meanings defined in formula (I).



(XII)

with the amine R_3R_4NH wherein R_3 and R_4 have the meanings defined in formula (I);

and thereafter if necessary or desired subjecting the resultant compound either before or after separation into its stereochemical isomers to one or more of the following operations.

(1) conversion of one compound of formula (I) into another compound of formula (I).

(2) conversion of a compound of formula (I) into an acid addition salt thereof.

12. Pharmaceutical compositions comprising a compound as defined in any of Claims 1 to 10 in admixture with one or more physiologically acceptable carriers or excipients.

13. Compounds as defined in any of claims 1 to 10 for use in therapy.

14. The use of a compound as defined in any one of Claims 1 to 10 in the manufacture of a medicament for the treatment of conditions where a modification of the effects of gastrin and or CCK is of therapeutic benefit.

15. A method of treatment of a mammal including man for conditions where modification of the effects of gastrin and or CCK is a therapeutic benefit comprising administration of an effective amount of a compound as defined in any of claims 1 to 10.

Dated this 17th Day of May 1994.