US005811429A

# United States Patent [19]

Connell et al.

[11] Patent Number: 5,811,429

[45] Date of Patent: Sep. 22, 1998

[54] **BICYCLIC HETEROCYCLIC COMPOUNDS**

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[73] Assignee: **Bayer Aktiengesellschaft**, Leverkusen, Germany

[21] Appl. No.: **761,921**

[22] Filed: **Dec. 9, 1996**

[30] **Foreign Application Priority Data**

Dec. 15, 1995 [DE] Germany ..... 195 46 918.6

[51] **Int. Cl.**[6] ..... **C07D 239/72**; C07D 413/00; A61K 31/505; A61K 31/535

[52] **U.S. Cl.** ..... **514/259**; 514/234.5; 544/116; 544/284; 544/287; 544/289

[58] **Field of Search** ..... 544/116, 284, 544/287, 289; 514/234.5, 259

[56] **References Cited**

U.S. PATENT DOCUMENTS

| | | | |
|---|---|---|---|
| 5,314,880 | 5/1994 | Whittaker et al. | 514/80 |
| 5,409,926 | 4/1995 | Reilly et al. | 514/234.8 |

FOREIGN PATENT DOCUMENTS

| | | |
|---|---|---|
| 0 513 533 A2 | 11/1992 | European Pat. Off. . |
| 0 560 162 A1 | 9/1993 | European Pat. Off. . |
| 0 560 163 A1 | 9/1993 | European Pat. Off. . |
| 0 565 986 A2 | 10/1993 | European Pat. Off. . |
| 0 610 698 A2 | 8/1994 | European Pat. Off. . |

*Primary Examiner*—Mukund J. Shah
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*Attorney, Agent, or Firm*—Sprung Kramer Schaefer & Briscoe

[57] **ABSTRACT**

The bicyclic heterocyclic compounds are prepared by reaction of correspondingly substituted carboxylic acids with amines, in particular with phenylglycinolamine. The bicyclic heterocyclic compounds according to the invention are suitable as active compounds in medicaments, in particular in medicaments having an antiatherosclerotic action.

**6 Claims, No Drawings**

# BICYCLIC HETEROCYCLIC COMPOUNDS

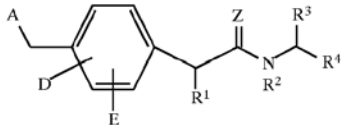
The present invention relates to bicyclic heterocyclic compounds, processes for their preparation and their use in medicaments, in particular as antiatherosclerotic medicaments.

It is known that increased blood levels of triglycerides (hypertriglyceridaemia) and cholesterol (hypercholesterolaemia) are associated with the origin of atherosclerotic changes to the vascular wall and coronary heart disease.

Moreover, a significantly increased risk of developing coronary heart disease exists if these two risk factors occur in combination, which in turn is accompanied by excessive production of apolipoprotein B-100. There is therefore still a great need to provide active medicaments for combating atherosclerosis and coronary heart disease.

Benzimidazole derivatives having a PAF-antagonistic action furthermore are described in U.S. Pat. No. 5,314,880.

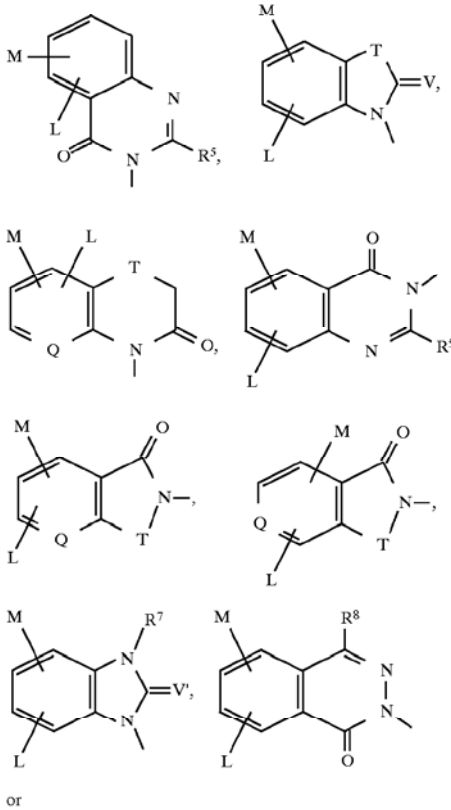
The present invention relates to bicyclic heterocyclic compounds of the general formula (I)



(I)

in which

A represents a radical of the formula



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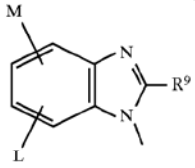


wherein

L and M are identical or different and denote hydrogen, halogen, trifluoromethyl, carboxyl, cycloalkyl having 3 to 6 carbon atoms, hydroxyl, phenyl or straight-chain or branched alkyl, alkoxycarbonyl or alkoxy having in each case up to 6 carbon atoms,

Q denotes a nitrogen atom or the —CH group,

T denotes a group of the formula $—SO_2$ or —CO or an oxygen or sulphur atom,

V denotes an oxygen or sulphur atom,

$R^5$, $R^6$, $R^7$ and $R^8$ are identical or different and denote hydrogen, straight-chain or branched alkyl having up to 6 carbon atoms, benzyl or phenyl, which are optionally substituted by halogen or by straight-chain or branched alkyl having up to 6 carbon atoms,

$R^9$ denotes trifluoromethyl, benzyl or a 5- to 7-membered, optionally benzo-fused heterocyclic radical having up to 3 heteroatoms from the series consisting of S, N and/or O, which is optionally substituted up to 3 times in an identical or different manner by halogen, phenyl, hydroxyl or by straight-chain or branched alkyl or alkoxy having in each case up to 4 carbon atoms, or denotes

a group of the formula $—S(O)_a—R^{10}$,

wherein

a denotes the number 0, 1 or 2,

$R^{10}$ denotes straight-chain or branched alkyl or alkenyl having in each case up to 8 carbon atoms, which are optionally substituted by straight-chain or branched acyl having up to 6 carbon atoms or by aryl or aroyl having in each case up to 10 carbon atoms, which in turn can be substituted up to twice in an identical or different manner by halogen, trifluoromethyl or by straight-chain or branched acyl having up to 5 carbon atoms, or denotes

aryl having 6 to 10 carbon atoms, which is optionally substituted by halogen, hydroxyl, trifluoromethyl or straight-chain or branched alkyl or alkoxy having in each case up to 5 carbon atoms,

D and E are identical or different and represent hydrogen, halogen, trifluoromethyl, hydroxyl or carboxyl, or represent straight-chain or branched alkyl, alkoxy or alkoxycarbonyl having in each case up to 6 carbon atoms,

Z represents an oxygen or sulphur atom,

$R^1$ represents cycloalkyl having 3 to 10 carbon atoms, or represents straight-chain or branched alkyl having 1 to 10 carbon atoms, or represents

phenyl, which is optionally substituted up to twice in an identical or different manner by halogen, nitro, cyano, hydroxyl or straight-chain or branched alkyl or alkoxy having in each case up to 4 carbon atoms,

$R^2$ represents hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

$R^3$ represents hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, or represents

cycloalkyl having 3 to 7 carbon atoms, or represents phenyl, or represents a 5- to 7-membered aromatic heterocyclic radical having up to 3 heteroatoms from the series consisting of S, N and/or O, which are optionally substituted up to 3 times in an identical or different manner by halogen, nitro, phenyl, hydroxyl or by straight-chain or branched alkyl or alkoxy having up to 6 carbon atoms,

$R^4$ represents hydrogen, or represents a group of the formula $—CH_2—OH$ or $CH_2O—CO—R^{11}$,

wherein

$R^{11}$ denotes hydrogen, straight-chain or branched alkyl having up to 8 carbon atoms or phenyl, which is optionally substituted up to 3 times in an identical or different manner by halogen, hydroxyl, cyano or straight-chain or branched alkyl or alkoxy having in each case up to 4 carbon atoms,

and salts thereof.

The bicyclic heterocyclic compounds according to the invention can also be in the form of their salts. Salts with organic or inorganic bases or acids may be mentioned in general here.

Physiologically acceptable salts are preferred in the context of the present invention. Physiologically acceptable salts of the compounds according to the invention can be salts of the substances according to the invention with mineral acids, carboxylic acids or sulphonic acids. Particularly preferred salts are, for example, those with hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid or benzoic acid.

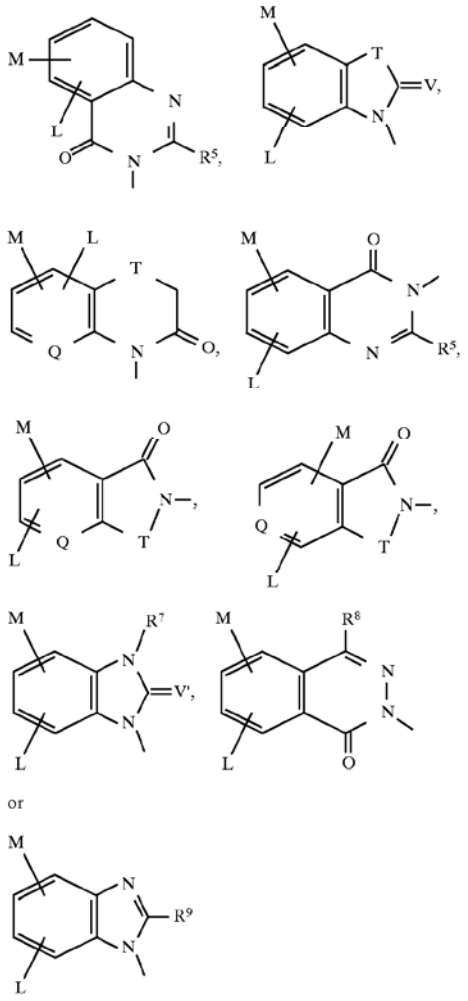
Physiologically acceptable salts can likewise be metal or ammonium salts of the compounds according to the invention which have a free carboxyl group. Particularly preferred salts are, for example, sodium, potassium, magnesium or calcium salts, as well as ammonium salts which are derived from ammonia or organic amines, such as, for example, ethylamine, di- or triethylamine, di- or triethanolamine, dicyclohexylamine, dimethylaminoethanol, arginine, lysine, ethylenediamine or 2-phenylethylamine.

The compounds according to the invention can exist in stereoisomeric forms which either behave as mirror images (enantiomers) or do not behave as mirror images (diastereomers). The invention relates both to the enantiomers or diastereomers and to the particular mixtures thereof These mixtures of the enantiomers and diastereomers can be separated into the stereoisomerically uniform constituents in a known manner.

In the context of the invention, a heterocyclic radical, which is optionally benzo-fused, in general represents a saturated or unsaturated 5- to 7-membered, preferably 5- or 6-membered, heterocyclic radical which can contain up to 3 heteroatoms from the series consisting of S, N and/or O and, in the case of a nitrogen atom, can also be bonded via this. Examples which may be mentioned are: indolyl, quinolyl, benzo[b]thienyl, benzo[b]furyl, pyridyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, morpholinyl or piperidyl. Quinolyl, furyl, pyridyl and thienyl are preferred.

Preferred compounds of the general formula (I) are those in which

A represents a radical of the formula



or



wherein

L and M are identical or different and denote hydrogen, fluorine, chlorine, bromine, trifluoromethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, hydroxyl, phenyl or straight-chain or branched alkyl, alkoxycarbonyl or alkoxy having in each case up to 5 carbon atoms,

Q denotes a nitrogen atom or the —CH group,

T denotes a group of the formula $—SO_2$ or —CO or an oxygen or sulphur atom,

V denotes an oxygen or sulphur atom,

$R^5$, $R^6$, $R^7$ and $R^8$ are identical or different and denote hydrogen, straight-chain or branched alkyl having up to 5 carbon atoms, benzyl or phenyl, which are optionally substituted by fluorine, chlorine, bromine or by straight-chain or branched alkyl having up to 5 carbon atoms,

$R^9$ denotes trifluoromethyl, benzyl, benzothienyl, thienyl, pyridyl, quinolyl, imidazolyl, furyl, pyrryl, oxazolyl or thiazolyl, which are optionally substituted up to 3 times in an identical or different manner by fluorine, chlorine, bromine, phenyl, hydroxyl or by straight-chain or branched alkyl or alkoxy having in each case up to 3 carbon atoms, or denotes

a group of the formula —$S(O)_a$—$R^{10}$,

wherein

a denotes the number 0 or 1,

$R^{10}$ denotes straight-chain or branched alkyl or alkenyl having in each case up to 6 carbon atoms, which are optionally substituted by straight chain or branched acyl having up to 5 carbon atoms or by phenyl, benzoyl or naphthyl, which in turn can be substituted up to twice in an identical or different manner by fluorine, chlorine, bromine, trifluoromethyl or by straight-chain or branched acyl having up to 4 carbon atoms, or denotes naphthyl or phenyl, which are optionally substituted by fluorine, chlorine, bromine, hydroxyl, trifluoromethyl or straight-chain or branched alkyl or alkoxy having in each case up to 4 carbon atoms,

D and E are identical or different and represent hydrogen, fluorine, chlorine, bromine, trifluoromethyl, hydroxyl or straight-chain or branched alkyl or alkoxy having in each case up to 4 carbon atoms,

Z represents an oxygen or sulphur atom,

$R^1$ represents cyclobutyl, cyclopentyl, cyclohexl, cycloheptyl or cyclooctyl, or represents straight-chain or branched alkyl having up to 7 carbon atoms, or represents

phenyl, which is optionally substituted by fluorine, chlorine, bromine, nitro, cyano, hydroxyl or straight-chain or branched alkyl or alkoxy having in each case up to 3 carbon atoms,

$R^2$ denotes hydrogen or methyl,

$R^3$ represents hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, benzyl, cyclopropyl, cyclopentyl or cyclohexyl, or represents phenyl, pyridyl, thienyl or furyl, which are optionally substituted up to twice in an identical or different manner by fluorine, chlorine, bromine, phenyl, nitro, hydroxyl or by straight-chain or branched alkyl or alkoxy having up to 4 carbon atoms,

$R^4$ represents hydrogen, or represents a group of the formula —$CH_2$—OH or —$CH_2O$—CO—$R^{11}$,

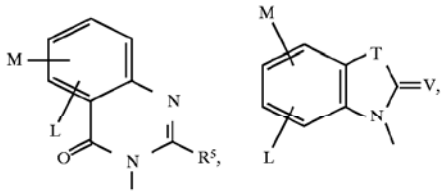
wherein

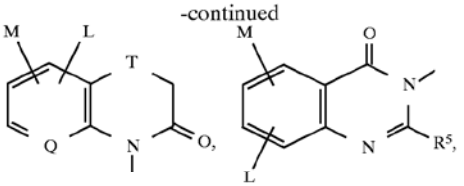
$R^{11}$ denotes hydrogen, straight-chain or branched alkyl having up to 6 carbon atoms or phenyl, which is optionally substituted up to twice in an identical or different manner by fluorine, chlorine, bromine, cyano, hydroxyl or straight-chain or branched alkyl or alkoxy having in each case up to 3 carbon atoms,

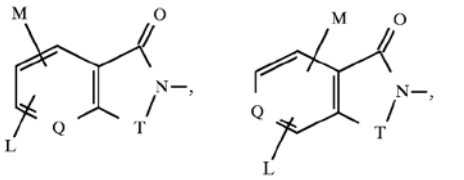
and salts thereof.

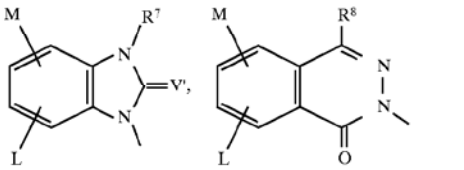
Particularly preferred compounds of the general formula (I) are those in which

A represents a radical of the formula









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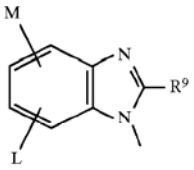


wherein

L and M are identical or different and denote hydrogen, fluorine, chlorine, bromine, hydroxyl, phenyl or straight-chain or branched alkyl or alkoxy having in each case up to 4 carbon atoms,

Q denotes a nitrogen atom or the —CH group,

T denotes a group of the formula —$SO_2$ or —CO or an oxygen or sulphur atom,

V denotes an oxygen or sulphur atom,

$R^5$, $R^6$, $R^7$ and $R^8$ are identical or different and denote hydrogen, straight-chain or branched alkyl having up to 4 carbon atoms, benzyl or phenyl, which are optionally substituted by fluorine, chlorine, bromine or by straight-chain or branched alkyl having up to 4 carbon atoms,

$R^9$ denotes trifluoromethyl, benzyl, benzothienyl, thienyl, pyridyl, imidazolyl, furyl or thiazolyl, which are optionally substituted up to 3 times in an identical or different manner by fluorine, chlorine, bromine, phenyl, hydroxyl or by straight-chain or branched alkyl or alkoxy having in each case up to 3 carbon atoms, or denotes

a group of the formula —$S(O)_a$—$R^{10}$,

wherein

a denotes the number 0 or 1,

$R^{10}$ denotes straight-chain or branched alkyl or alkenyl having in each case up to 5 carbon atoms, which are optionally substituted by straight-chain or branched acyl having up to 4 carbon atoms or by phenyl, benzoyl or naphthyl, which in turn can be substituted up to twice in an identical or different manner by fluorine, chlorine, bromine, trifluoromethyl or by straight-chain or branched acyl having up to 3 carbon atoms, or denotes

naphthyl or phenyl, which are optionally substituted by fluorine, chlorine, bromine, hydroxyl, trifluoromethyl or straight-chain or branched alkyl or alkoxy having in each case up to 3 carbon atoms,

D and E are identical or different and represent hydrogen, fluorine, chlorine, bromine or trifluoromethyl,

Z represents oxygen,

$R^1$ represents cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl, or represents straight-chain or branched alkyl having up to 6 carbon atoms,

$R^2$ represents hydrogen or methyl,

$R^3$ represents phenyl and

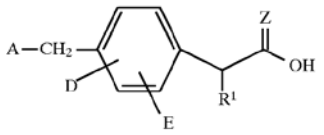
$R^4$ represents the group $—CH_2—OH$,

and salts thereof

A process has furthermore been found for the preparation of the compounds of the general formula (I) according to the invention,

characterized in that

acids of the general formula (II)

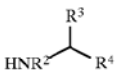



(II)

in which

A, D, E, Z and $R^1$ have the meaning given,

are reacted with compounds of the general formula (III)



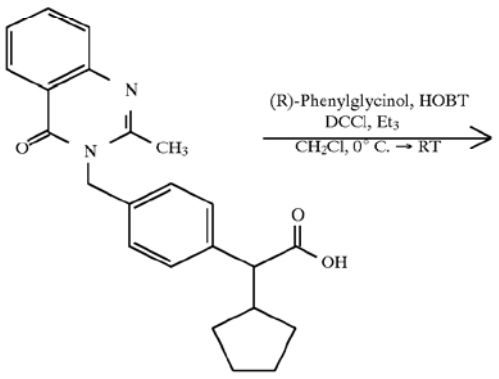

(III)

in which

$R^2$, $R^3$ and $R^4$ have the meaning given,

in inert solvents and in the presence of bases and/or auxiliaries.

The process according to the invention can be illustrated by way of example by the following equation:

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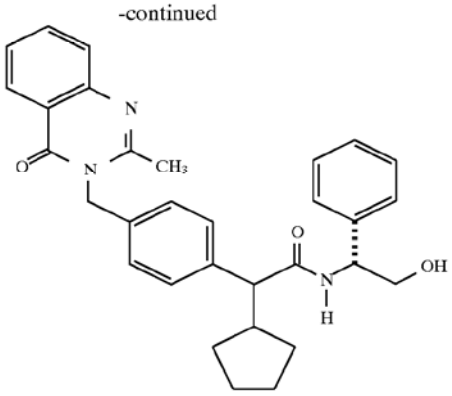


Suitable solvents here are inert organic solvents which do not change under the reaction conditions. These include ethers, such as diethyl ether or tetrahydrofuran, halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride, 1,2-dichloroethane, trichloroethane, tetrachloroethane, 1,2-dichloroethane or trichloroethylene, hydrocarbons, such as benzene, xylene, toluene, hexane, cyclohexane or petroleum fractions, nitromethane, dimethylformamide, acetone, acetonitrile or hexamethylphosphoric acid triamide. It is also possible to employ mixtures of the solvents. Methylene chloride, tetrahydrofuran, toluene or dimethylformamide are particularly preferred.

Inorganic or organic bases can in general be employed as bases for the process according to the invention. These include, preferably, alkali metal hydroxides, such as, for example, sodium hydroxide or potassium hydroxide, alkaline earth metal hydroxides, such as, for example, barium hydroxide, alkali metal carbonates, such as sodium carbonate or potassium carbonate, alkaline earth metal carbonates, such as calcium carbonate, or alkali metal or alkaline earth metal alcoholates, such as sodium or potassium methanolate, sodium or potassium ethanolate or potassium tert-butylate, or organic amines (trialkyl($C_1$–$C_6$)amines), such as triethylamine, or heterocyclic compounds, such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU), pyridine, diaminopyridine, methylpiperidine or morpholine. It is also possible to employ alkali metals, such as sodium, and hydrides thereof such as sodium hydride, as bases. Sodium carbonate, potassium carbonate and triethylamine are preferred.

The base is employed in an amount of 1 mol to 5 mol, preferably 1 mol to 3 mol, per mole of the compound of the general formula (II).

Dehydrating reagents are also suitable auxiliaries. These include, for example, carbodiimides, such as diisopropylcarbodiimide, dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, or carbonyl compounds, such as carbonyldiimidazole, or 1,2-oxazolium compounds, such as 2-ethyl-5-phenyl-1,2-oxazolium 3-sulphonate, or propanephosphoric anhydride or iso-butyl chloroform ate or benzotriazolyloxy-tris-(dimethylamino)phosphonium hexafluorophosphate or phosphonic acid diphenyl esteramide or methanesulphonyl chloride, if appropriate in the presence of bases, such as triethylamine or N-ethylmorpholine or N-methylpiperidine or dicyclohexylcarbodiimide and N-hydroxysuccinimide.

The reaction is in general carried out in a temperature range from 0° C. to 150° C., preferably from +20° C. to +110° C.

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