United States Patent [19]

Roth et al.

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[54] **ANTIHYPERLIPIDEMIC AND ANTIATHEROSCLEROTIC UREA AND CARBAMATE COMPOUNDS**

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[21] Appl. No.: **359,830**

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Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 282,167, Dec. 9, 1988, abandoned, which is a continuation-in-part of Ser. No. 147,037, Feb. 5, 1988, abandoned, which is a continuation-in-part of Ser. No. 57,576, Jun. 2, 1987, abandoned.

[51] **Int. Cl.**[5] **A61K 31/17;** C07C 275/28; C07C 275/30; C07C 275/32

[52] **U.S. Cl.** **514/247;** 514/255; 514/256; 514/307; 514/311; 514/357; 514/367; 514/372; 514/374; 514/378; 514/381; 514/383; 514/400; 514/406; 514/415; 514/427; 514/438; 514/443; 514/469; 514/471; 514/481; 514/488; 514/510; 514/513; 514/517; 514/542; 514/564; 514/585; 514/586; 514/587; 514/595; 514/596; 514/597; 514/598; 544/224; 544/335; 544/336; 546/146; 546/175; 546/332; 548/178; 548/214; 548/236; 548/247; 548/262.8; 548/253; 548/342; 548/378; 548/469; 548/560; 564/26; 564/27; 564/28; 564/29; 564/48; 564/50; 564/52; 564/53; 564/54; 549/58; 549/77; 549/471; 549/496; 558/57; 558/234; 560/10; 560/13; 560/20; 560/21; 560/22; 560/23; 560/28; 560/29; 560/31; 560/32; 560/34; 562/427; 562/430; 562/435; 562/437; 562/439

[58] **Field of Search** 564/48, 26, 27, 28, 564/29, 50, 52, 53, 54; 514/596, 595, 597, 598, 247, 255, 256, 307, 311, 357, 367, 372, 374, 378, 381, 383, 400, 415, 427, 438, 443, 469, 471, 510, 517, 542, 564, 585, 586, 587; 544/224, 335, 336; 546/146, 175, 332; 548/178, 214, 236, 247, 262.8, 253, 342, 378, 469, 560; 549/58, 77, 471, 496; 558/57; 560/10, 13, 21, 22, 34; 562/427, 430, 435, 437, 439

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,852,343	12/1974	Krapcko	564/56
4,387,105	6/1983	DeVries et al.	564/498
4,397,868	8/1983	DeVries	564/48
4,410,697	10/1983	Torak et al.	564/48
4,623,662	11/1986	DeVries	514/596

FOREIGN PATENT DOCUMENTS

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154216	3/1982	German Democratic Rep. .

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[57] **ABSTRACT**

Certain substituted urea, thiourea, carbamate, and thiocarbamate compounds are potent inhibitors of the enzyme acyl-CoA: cholesterol acyltransferase and are thus useful agents for inhibiting the intestinal absorption of cholesterol, and for lowering blood plasma cholesterol.

31 Claims, No Drawings

ANTIHYPERLIPIDEMIC AND ANTIATHEROSCLEROTIC UREA AND CARBAMATE COMPOUNDS

CROSS-REFERENCE

This application is a continuation-in-part of co-pending application Ser. No. 282,167, filed Dec. 9, 1988, now abandoned, which is a continuation-in-part of co-pending application Ser. No. 147,037, filed Feb. 5, 1988, now abandoned, which is a continuation-in-part of co-pending application Ser. No. 057,576, filed June 2, 1987, now abandoned.

BACKGROUND OF THE INVENTION

This invention relates to chemical compounds having pharmacological activity, to pharmaceutical compositions which include these compounds, and to a pharmaceutical method of treatment. More particularly, this invention concerns certain substituted urea and carbamate compounds which inhibit the enzyme acyl-coenzyme A:cholesterol acyl-transferase (ACAT), pharmaceutical compositions containing these compounds, and a method of inhibiting intestinal absorption of cholesterol or of regulating cholesterol.

In recent years the role which elevated blood plasma levels of cholesterol plays in pathological conditions in man has received much attention. Deposits of cholesterol in the vascular system have been indicated as causative of a variety of pathological conditions including coronary heart disease.

Initially, studies of this problem were directed toward finding therapeutic agents which would be effective in lowering total serum cholesterol levels. It is now known that cholesterol is transported in the blood in the form of complex particles consisting of a core of cholesterol esters plus triglycerides and an exterior consisting primarily of phospholipids and a variety-of types of protein which are recognized by specific receptors. For example, cholesterol is carried to the sites of deposit in blood vessels in the form of low density lipoprotein cholesterol (LDL cholesterol) and away from such sites of deposit by high density lipo-protein cholesterol (HDL cholesterol).

Following these discoveries, the search for therapeutic agents which control serum cholesterol turned to finding compounds which are more selective in their action; that is, agents which are effective in elevating the blood serum levels of HDL cholesterol and/or lowering the levels of LDL cholesterol. While such agents are effective in moderating the levels of serum cholesterol, they have little or no effect on controlling the initial absorption of dietary cholesterol in the body through the intestinal wall.

In intestinal mucosal-cells, dietary cholesterol is absorbed as free cholesterol which must be esterified by the action of the enzyme acyl-CoA: cholesterol acyltransferase (ACAT) before it can be packaged into the chylomicrons which are then released into the blood stream. Thus, therapeutic agents which effectively inhibit the action of ACAT prevent the intestinal absorption of dietary cholesterol into the blood stream or the reabsorption of cholesterol which has been previously released into the intestine through the body's own regulatory action.

INFORMATION DISCLOSURE

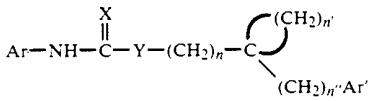
U.S. Pat. No. 4,397,868 (De Vries) discloses phenylurea compounds useful in reducing cholesterol wherein one of the nitrogen atoms is disubstituted with, e.g., aliphatic, alicyclic or aromatic groups.

U.S. Pat. No. 4,410,697 (Torok) discloses an improved process for preparing phenylurea compounds which are useful as herbicides, rodenticides, bacteriostatic agents, coccidiostatic agents and antiseptic agents. The non-aniline nitrogen in these compounds can be mono- or di-substituted with alkyl, cycloalkyl, alkoxy or phenyl which groups may be further substituted.

U.S. Pat. No. 4,623,662 (De Vries) discoses phenylurea and phenylthiourea compounds useful in treating atherosclerosis wherein the non-aniline nitrogen is disubstituted with aliphatic, cycloalkylalkyl, aralykyl groups wherein the aryl moiety may be substituted and wherein the aniline phenyl moiety is substituted with a wide variety of groups.

SUMMARY OF THE INVENTION

The present invention provides a class of compounds with ACAT inhibitory activity having the structure



wherein Ar is phenyl or naphthyl. The phenyl or naphthyl group is unsubstituted, or may be optionally substituted with alkyl of from one to six carbon atoms, hydroxy, phenoxy, alkoxy of from one to six carbon atoms, fluorine, chlorine, bromine, nitro, trifluoromethyl, —COOH, —COO-alkyl (where alkyl is from one to four carbon atoms), or $—NR_1R_2$ in which R_1 and R_2 are independently hydrogen or alkyl of from one to six carbon atoms.

The atom X is oxygen or sulfur, Y is oxygen or —NH—, n is zero or is an integer of from one to three, n′ is an integer of from two to six, and n″ is zero, one, or two.

Ar′ is selected from phenyl, naphthyl, or a 5- or 6-membered monocyclic or fused bicyclic heterocycle. Ar′ is unsubstituted, or may be optionally substituted with alkyl of from one to six carbon atoms; hydroxy; alkoxy of from one to six carbon atoms;. benzyloxy; fluorine; chlorine; bromine; nitro; trifluoromethyl; —NH—$COCH_3$; —$CONH_2$; —COOH; —COO-alkyl (where alkyl is from one to four carbon atoms); —CH_2COOH; —CH_2CONH_2; $—NR_1R_2$ in which R_1 and R_2 are independently hydrogen, alkyl of from one to six carbon atoms which terminal carbon may contain an OR_3 group where R_3 is hydrogen, alkyl of from one to six carbon atoms, alkanoyl having from two to five carbon atoms, benzoyl, or when joined together form a 5- or 6-membered ring optionally interrupted by an oxygen atom or $—NR_3'$ wherein R_3 is as defined above; $—CH_2NR_1R_2$ where R_1 and R_2 are as defined above: $—CH_2OR_3$ where R_3 is as defined above; —COO-alkyl where alkyl is from one to six carbons which terminal carbon may contain an OR_3 group or NR_1R_2 where R_1, R_2, and R_3 are as defined above; —NH—(CH_2)—COO-alkyl (where alkyl is from one to four carbon atoms); $—SO_2NR_1R_2$ where R_1 and R_2 are as defined above; $—SO_2OR_3$ where R_3 is as defined above, or —N-

H—SO_2R_4 where R_4 is alkyl of one to four carbon atoms or phenyl.

DETAILED DESCRIPTION

The compounds of the present invention form a class of substituted ureas, thioureas, carbamates, and thiocarbamates having potent activity as inhibitors of the enzyme acyl CoA: cholesterol acyltransferase (ACAT). Preferred compounds of the present invention are the urea and thiourea compounds, with the urea compounds being most preferred.

In the urea compounds of the present invention, the first nitrogen atom is monosubstituted by an aromatic ring system selected from phenyl or naphthyl. The phenyl ring is unsubstituted or, alternatively, is substituted with one, two, or three groups selected independently from alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, —COOH, —COO-alkyl (where alkyl is from one to four carbon atoms), or —NR_1R_2 in which R_1 and R_2 are independently hydrogen or alkyl of from one to six carbon atoms. Preferred compounds are those in which the aromatic ring system is phenyl or substituted phenyl.

In the urea and thiourea compounds of this invention, the second nitrogen atom is substituted with an aryl-substituted cycloalkyl ring which may be attached directly to the nitrogen atom, or may separated from the nitrogen atom by a bridging group of up to three methylene (i.e. —CH_2—) groups. The cycloalkyl ring is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, with cyclopentyl and cyclohexyl being preferred.

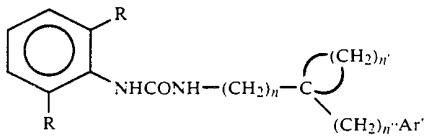
The cycloalkyl ring is further substituted, at the same atom of attachment to the nitrogen of the urea moiety or the same atom of attachment to the methylene bridge, by an aryl group. This aryl group is unsubstituted phenyl, naphthyl, or a 5- or 6-membered monocyclic or fused bicyclic heterocycle or, alternatively, one of these aromatic rings may optionally be substituted by one, two, or three groups independently selected from alkyl of from one to six carbon atoms; alkoxy of from one to six carbon atoms; benzyloxy; hydroxy; fluorine; chlorine;

35 bromine; nitro; trifluoromethyl; —NH—$COCH_3$; —$CONH_2$; —COOH; —CH_2COOH; —CH_2CONH_2; —NR_1R_2 in which R_1 and R_2 are independently hydrogen, alkyl of from one to six carbon atoms which terminal carbon may contain an OR_3 group where R_3 is hydrogen or alkyl of-from one to six carbon atoms, or when joined together form a 5- or 6-membered ring optionally interrupted by an oxygen atom or —NR_3; —$CH_2NR_1R_2$ where R_1 and R_2 are as defined above; —CH_2OR_3 where R_3 is as defined above; —COO-alkyl where alkyl is from one to six carbons which terminal carbon may optionally be substituted with an OR_3 group or NR_1R_2 where R_1, R_2, and R_3 are as defined above; —NH—(CH_2)—COO-alkyl (where alkyl is from one to four carbon atoms); —$SO_2NR_1R_2$ where R_1 and R_2 are as defined above; —SO_2OR_3 where R_3 is as defined above, or —NH—SO_2R_4 where R_4 is alkyl of one to four carbon atoms or phenyl.

A 5- or 6-membered monocyclic or fused bicyclic heterocycle is a monocyclic or fused bicyclic aromatic ring containing at least one to four hetero atoms in at least one ring, such as nitrogen, oxygen or sulfur or a combination thereof. Such a heterocycle group includes, for example, thienyl, benzothienyl, furanyl, benzofuranyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, pyrrazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, imidazolyl, benzothiazolyl, indolyl, quinolinyl, isoquinolinyl, or N-oxides of a heterocycle containing a nitrogen atom.

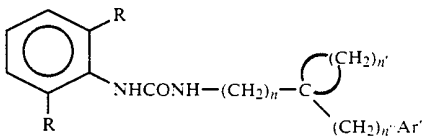
More specifically, such a heterocycle may be 2- or 3-thienyl; 2- or 3-furanyl; 2-, 3-, or 4-pyridyl or or 3-thienyl; 2- or 3-furanyl; 2-, 3-, or 4-pyridyl or -pyridyl-N-oxide; 2, 4, or 5-pyrimidinyl; 3- or 4-pyradazinyl; 2-pyrazinyl; 2- or 3-pyrrolyl; 3-, 4-, or 5-pyrrazolyl, 3-, 4-, or 5-isoxazolyl; 3-, 4- or 5-oxazolyl; 3-, 4-, or 5-isothiazolyl; 5-tetrazolyl; 3- or 5-(1,2,4-)triazolyl; 4- or 5-(1,2,3-)triazolyl; 2-, 4-, or 5-imidazolyl; 2-, 3-, 4-, 5-, 6-, or 7-indolyl; 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl; 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl; 2-, 4-, 5-, 6-, or 7-benzothiazolyl; or 2-, 3-, 4-, 5-, 6-, or 7-benzothienyl.

A preferred class of urea compounds is represented by a compound of the formula



where R is alkyl of one to four carbon atoms, especially isopropyl or otherwise referred to as 1-methylethyl; n is 0 or 1, especially 1; n′ is an integer from 2 to 6, especially 4 or 5; n″ is 0 or 1, especially 0, and Ar′ is phenyl or phenyl substituted by alkyl of from one to six carbon atoms; hydroxy; alkoxy of from one to six carbon atoms; benzyloxy; fluorine; chlorine; bromine; nitro; trifluoromethyl; —NH—$COCH_3$; —$CONH_2$; —COOH; —COO-alkyl (where alkyl is from one to four carbon atoms); —CH_2COOH; —CH_2CONH_2; —NR_1R_2 in which R_1 and R_2 are independently hydrogen, alkyl of from one to six carbon atoms which terminal carbon may contain an OR_3 group where R_3 is hydrogen or alkyl of from one to six carbon atoms, or when joined together form a 5- or 6-membered ring optionally interrupted by an oxygen atom or —NR_3; —$CH_2NR_1R_2$ where R_1 and R_2 are as defined above; —CH_2OR_3 where R_3 is as defined above; —COO-alkyl where alkyl is from one to six carbons which terminal carbon may contain an OR_3 group or NR_1R_2 where R_1, R_2, and R_3 are as defined above; —NH—(CH_2)—COO-alkyl (where alkyl is from one to four carbon atoms); —$SO_2NR_1R_2$ where R_1 and R_2 are as defined above; —SO_2OR_3 where R_3 is as defined above, or —NH—SO_3R_4 where R_4 is alkyl of one to four carbon atoms or phenyl. Especially preferred is a compound as defined above where Ar′ is phenyl or phenyl substituted by alkyl, hydroxy, alkoxy, fluorine, chlorine, nitro, trifluoromethyl, or —NR_1R_2.

A particularly valuable class of urea compounds having a heterocyclic group defined above is a compound of the formula



where R is alkyl of one to four carbon atoms, especially isopropyl or otherwise referred to as 1-methylethyl; n is

0 or 1, especially 1; n′ is an integer from 2 to 6, especially 4 or 5; n″ is 0 or 1, especially 0, and Ar′ is a 5- or 6-membered monocyclic or fused bicyclic heterocycle defined above.

Preferred compounds of this invention are those in which the aromatic ring system attached to the cycloalkyl ring is thienyl, tetrazolyl, isoxazolyl, triazolyl, pyrazolyl, pyridyl, pyridyl-N-oxide, unsubstituted phenyl, or unsubstituted naphthyl.

Examples of compounds contemplated as falling within the scope of the invention are the following:

N-(2,6-Dimethylphenyl)-N′-(1-phenylcycopentyl)urea.
N-(2,6-Diethylphenyl)-N′-(1-phenylcyclobutyl)urea.
N-(2,6-Diethylphenyl)-N′-(1-phenylcyclopentyl)urea.
N-(2,6-Diethylphenyl)-N′-(1-phenylcyclopropyl)methyl]urea.
N-(1-Phenylcyclopentyl)-N′-(2,4,6-trimethoxyphenyl-)urea.
N-(2,6-Dimethylphenyl)-N′-[1-(2-thienyl)cyclohexyl-]urea.
N-(2,6-Diethylphenyl)-N′-[1-(2-thienyl)cyclohexyl-]urea.
N-[2,6-bis(1-Methylethyl)]-N′-[1-(2-thienyl)cyclohexyl-]urea.
N-(2,6-Diethylphenyl)-N′-[(1-phenylcyclohexyl)methyl]urea.
N-(2,6-Dimethylphenyl)-N′-(1-phenylcyclopentyl)methyl]urea.
N-(2,6-Dimethylphenyl)-N′-[(1-phenylcyclohexyl)methyl]urea.
N-(2,6-Diethylphenyl)-N′-[(1-phenylcyclopentyl)methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-(1-phenylcyclopentyl)methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[(1-phenylcyclohexyl)methyl]urea.
N-[2-Methyl-6-(1-methylethyl)phenyl]-N′-1-(2-thienyl)-cyclohexyl]urea.
N-[2-(1,1-Dimethylethyl)-6-methylphenyl]-N′-[1-(2-thienyl)cyclohexyl]urea.
N-[2-Methyl-6-(1-methylethyl)phenyl]-N′-[(1-phenylcyclohexyl)methyl]urea.
N-[2-(1,1-Dimethylethyl)-6-methylphenyl]-N′-[(1-phenylcyclohexyl)methylurea.
N-[2-Ethyl-6-(1-methylethyl)phenyl]-N′-[(1-phenylcyclohexyl)methyl]urea.
N-[2-Methyl-6-(1-methylethyl)phenyl]-N′-[(1-phenylcyclopentyl)methyl]urea.
N-[2-(1,1-Dimethylethyl)-6-methylphenyl]-N′-[(1-phenylcyclopentyl)methyl]urea.
N-[2-Ethyl-6-(1-methylethyl)phenyl]-N′-[(1-phenylcyclopentyl)methyl]urea.
N-(2,4-Difluorophenyl)-N′-[1-(2-thienyl)-cyclohexyl-]urea.
N-(2,4-Difluorophenyl)-N′-[(1-phenylcyclopentyl)methyl]urea.
N-(2,4-Difluorophenyl)-N′-[(1-phenylcyclohexyl)methyl]urea.
N-(2,6-Dibromo-4-fluorophenyl)-N′-[(1-phenylcyclohexyl)methyl]urea.
N-(2,4-Dimethylphenyl)-N′-[(1-phenylcyclohexyl)methyl]urea.
2-[[[[(1Phenylcyclohexyl)methyl]amino]carbonyl-]amino]benzoic acid, butyl ester.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[1-(2-naphthalenyl)cyclobutylmethyl]urea.
N-(2,5-Dimethylphenyl)-N′-(1-phenylcyclohexyl)methyl]urea.
N-(2,3-Dichlorophenyl)-N′-[(1-phenylcyclohexyl)methyl]urea.
N-(3,4-Dichlorophenyl)-N′-[(1-phenylcyclohexyl)methyl]urea.
N-[4-(1-Methylethyl)phenyl]-N′-[(1-phenylcyclohexyl)methyl]urea.
N-(4-Bromophenyl)-N′-(1-phenylcyclohexyl)methyl-]urea.
N-(4-Butoxyphenyl)-N′-(1-phenylcyclohexyl)methyl-]urea.
N-(4-Phenoxyphenyl)-N′-[(1-phenylcyclohexyl)methyl]urea.
N-(4-Nitrophenyl)-N′-[(1-phenylcyclohexyl)methyl-]urea.
N-(4-Methoxyphenyl)-N′-[(1-phenylcyclohexyl)methyl]urea.
N-(4-Ethoxyphenyl)-N′-[(1-phenylcyclohexyl)methyl-]urea.
N-(4-Acetylphenyl)-N′-[(1-phenylcyclohexyl)methyl-]urea.
4-[[[(1-Phenylcyclohexyl)methyl]amino]carbonyl-]amino]benzoic acid, ethyl ester.
N-(4-Methylphenyl)-N′-[(1-phenylcyclohexyl)methyl-]urea.
N-(4-Ethylphenyl)-N′-[(1-phenylcyclohexyl)methyl-]urea.
N-(3-Methoxyphenyl)-N′-[(1-phenylcyclohexyl)methyl]urea.
N-[(1-1,1′-Biphenyl]-4-ylcyclobutyl)methyl]N′-[2.6-bis(1-methylethyl)phenyl]urea.
N-(4-Chlorophenyl)-N′-(1-phenylcyclohexyl)methyl-]urea.
N-(4-Iodophenyl)-N′-[(1-phenylcyclohexyl)methyl-]urea.
N-(2-Methylphenyl)-N′-[(1-phenylcyclohexyl)methyl-]urea.
N-(3-Methylphenyl)-N′-(1-phenylcyclohexyl)methyl-]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[[1-4-(trifluoromethyl)phenyl]cyclobutyl]methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[[1-(4-methylphenyl)cyclobutyl]methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[1-(2-methylphenyl)cyclobutyl]methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[1-(1-naphthalenyl)cyclobutyl]methylurea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[1-(3-methylphenyl)cyclobutyl]methyl]urea.
N-[(1-Phenylcyclohexyl)methyl]-N′-3-(trifluoromethyl)phenylurea.
N-[2-Chloro-5-(trifluoromethyl)phenyl]-N′-(1-phenylcyclohexyl)methyl]urea.
N-(5-Chloro-2-methoxyphenyl)-N′-(1-phenylcyclohexyl)methyl]urea.
N-(4-Chloro-2-methylphenyl)-N′-[(1-phenylcyclohexyl)methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N,-[[1-(3,4,5-trimethoxyphenyl)cyclobutyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[[1-[3-(trifluoromethyl)phenyl]cyclobutyl]methyl]urea.
2-[[[[(1-Phenylcyclohexyl)methyl]amino]carbonyl-]amino]benzoic acid, methyl ester.
2-[[[[(1-Phenylcyclohexyl)methyl]amino]carbonyl-]amino]benzoic acid, ethyl ester.
N-Phenyl-N′-(1-phenylcyclohexyl)methyl]urea.
N-(2,5-Dimethoxyphenyl)-N′-(1-phenycyclohexyl)methyl]urea.

N-[2,6-bis(1-Methylethyl)phenyl]-N′-[1-2-(trifluoromethyl)phenyl]cyclobutyl]methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[[1-(4-methylphenyl)cyclopentyl]methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[1-[4-(1-methylethyl)phenyl]cyclopentyl]methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[1-(2-methylphenyl)cyclopentylmethyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-(1-phenylcyclopropyl)methyl]urea.
N-(5-Chloro-2-methylphenyl)-N′-[(1-phenylcyclohexyl)methyl]urea.
N-(2,5-Dichlorophenyl)-N′-[(1-phenylcyclohexyl)methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[[1-(4-methoxyphenyl)cyclopentyl]methylurea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[(1-phenylcyclobutyl)methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[1-(2-naphthalenyl)cyclopentyl]methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[1-(2-naphthalenyl)cyclobutyl]methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[[1-[3-(phenylmethoxy)phenyl]cyclopentyl]methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[[1-(4-fluorophenyl)cyclopentyl]methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[[1-[4-(phenylmethoxy)phenyl]cyclopentyl]methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[[1-[4-(trifluoromethyl)phenyl]cyclopentyl]methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[[1-(2,6-dichlorophenyl)cyclobutyl]methyl]urea,
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[[1-[3,5-bis(trifluoromethyl)phenyl]cyclopentyl]-methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[1-[2-(trifluoromethyl)phenyl]cyclopentyl]methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[[1-(4-chlorophenyl)cyclopentyl]methyl]urea.
N-[2,6-bis(1-Methylethyl)phenyl]-N′-[[1-(4-nitrophenyl)cyclopentyl]methyl]urea.
N-[1-(4-Aminophenyl)cyclopentyl]methyl]-N′-[2,6-bis(1-methylethyl)phenyl]urea.
N-[4-[1-[[[[[2,6-bis(1-Methylethyl)phenyl]amino]carbonyl]amino]methyl]cyclopentyl]phenyl]acetamide.
N-[2,6-bis(1-Methylethyl)phenYl]-N′-[[1-(4-dimethylaminophenyl)cyclopentyl]methyl]urea or its hydrochloride salt.
N-[2,6-bis(1-methylethyl)phenyl]-N′-[1-(4-dimethylaminophenyl)cyclohexyl]methyl]urea.
N-[2,6-bis(1-methylethylphenyl]-N′-[[1-(4-diethylaminophenyl)cyclopentyl]methyl]urea.
N-[2,6-bis(1-methylethyl)phenyl]-N′-[[[1-4-(2-hydroxyethyl)amino]phenyl]cyclopentyl]methyl]urea.
N′-[[1-[4-[-bis(2-hydroxyethylamino]phenyl]cyclopentyl]methyl]-N-[2,6-bis(1-methylethyl)phenyl]urea.
N-[2,6-bis(1-methylethyl)phenyl]-N′-[[[1-(2-trifluoromethyl-4-dimethylamino)phenyl]cyclopentyl]-methyl]urea.
N-[2,6-bis(1-methylethyl)phenyl]-N′-[[[1-(2-trifluoromethyl-4-methylamino)phenyl]cyclopentyl]-methyl]urea.

Additional examples of compounds contemplated as falling within the scope of the invention are the following N-(2,6-bis(1-methylethyl)-N′-[1-heterocyclecyclopentyl)methyl]ureas

where the heterocycle is:
5-(1-methyltetrazolyl),
5-(1-H-tetrazolyl),
4-(2,5-dimethylisoxazolyl),
4-[(1-benzyl-5-(N,N-dimethylamino)]-1,2,3-triazolyl],
4-[1-methyl-5-(N,N-dimethylamino)-1,2,3-triazolyl],
4-(1,3,5-trimethylpyrazolyl),
4-(1-H,-3,5-dimethylpyrazolyl), and
3-pyridyl-N-oxide.

By the term "lower alkyl" or "alkyl" as used throughout this specification and the appended claims is meant a branched or unbranched hydrocarbon grouping derived from a saturated hydrocarbon of from one to six carbon atoms by removal of a single hydrogen atom. Examples of alkyl groups contemplated as falling within the scope of this invention include methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, and 1,1-dimethylethyl.

By the term "alkoxy" is meant a lower alkyl group, as defined above, attached to the parent molecular moiety through an oxygen atom.

In those instances where the compounds of the present invention bear a basic nitrogen atom as, for example, when Ar or Ar′ is substituted by amino, alkylamino, or dialkylamino, or when Ar′ is pyridyl, the compounds are capable of forming acid addition salts. These acid addition salts are also contemplated as falling within the scope of this invention.

While the acid addition salts may vary from the free base form of the compounds in certain properties such as melting point and solubility, they are considered equivalent to the free base forms for the purposes of this invention.

The acid addition salts may be generated from the free base forms of the compounds by reaction of the latter with one equivalent of a suitable non-toxic, pharmaceutically acceptable acids followed by evaporation of the solvent employed for the reaction and recrystallization of the salt, if required. The free base may be recovered from the acid addition salt by reaction of the salt with a water solution of the salt with a suitable base such as sodium carbonate, sodium bicarbonate, potassium carbonate, sodium hydroxide, and the like.

Suitable acids for forming acid addition salts of the compounds of this invention include, but are not necessarily limited to acetic, benzoic, benzenesulfonic, tartaric, hydrobromic, hydrochloric, citric, fumaric, gluconic, glucuronic, glutamic, lactic, malic, maleic, methanesulfonic, pamoic, salicylic, stearic, succinic, sulfuric, and tartaric acids. The class of acids suitable for the formation of non-toxic, pharma-ceutically acceptable salts is well known to practi-tioners of the pharmaceutical formulation arts. (See, for example, Stephen N. Berge, et al. *J. Pharm. Sciences*, 66:1–19 (1977).

In those instances where the compounds of the present invention bear a basic nitrogen atom in a heterocyclic group as, for example, when Ar′ is pyridyl, the compounds are capable of forming N-oxides. These N-oxides are also contemplated as falling within the scope of this invention.

The N-oxides may be prepared from the free base forms of the compounds by reaction of the latter with an oxidizing agent, such as, for example, hydrogen peroxide, peracetic acid or perbenzoic acid in a suitable solvent.

Further, the compounds of this invention may exist in unsolvated as well as solvated forms with pharma-ceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

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