BENZOTHIAZINE DIOXIDES AS LIPID REGULATING AGENTS

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Field of Search 424/246; 260/243

ABSTRACT

Certain 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide and 3-oxo-2H-1,2-benzothiazine-4-carboxamide-1,1-dioxide compounds effective as lipid regulating agents are disclosed.

36 Claims, No Drawings
BENZOTHIAZINE DIOXIDES AS LIPOID REGULATING AGENTS

BACKGROUND OF THE INVENTION

This invention relates generally to a method of regulating lipid metabolism in humans. More particularly, it is concerned with 2H-1,2-benzothiazine-1,1-dioxide derivatives, and with the effectiveness of said derivatives as lipid regulating agents. What is meant by the term "regulating lipid metabolism" is the ability to depress triglycerides, free fatty acids, cholesterol, lipoproteins, phospholipids, etc. in human and animal blood.

SUMMARY OF THE INVENTION

In accordance with the present invention, it has been found that various novel 2H-1,2-benzothiazine-1,1-dioxide compounds are surprisingly useful when employed in the field of drug therapy as lipid regulating agents. The novel compounds of this invention are 2H-1,2-benzothiazine-1,1-dioxides of the formula:

and the base salts thereof with pharmacologically acceptable cations, wherein X and Y are each a member selected from the group consisting of hydroxyl, fluorine, chlorine, bromine, nitro, alkyl and alkoxy having from one to five carbon atoms and trifluoromethyl; R is a member selected from the group consisting of —OR and —NHR wherein R is alkyl having from one to twelve carbon atoms or phenylalkyl having up to three carbon atoms in the alkyl moiety, and R₂ is chosen from the group consisting of hydrogen, alkyl having from one to eight carbon atoms; alkenyl having up to six carbon atoms, cycloalkyl having up to eight carbon atoms, phenylalkyl having up to three carbon atoms in the alkyl moiety, nitrophenyl, napththyl, phenyl, pyridyl, 3-methyl-2-pyridyl, 4-methyl-2-pyridyl, 5-methyl-2-pyridyl, 6-methyl-2-pyridyl, 4,6-dimethyl-2-pyridyl, 5-chloro-2-pyridyl, 5-nitro-2-pyridyl, 3-hydroxy-2-pyridyl, 5-carboxamido-2-pyridyl, 2-pyrrazinyl, 2-pyrimidinyl, 4,5-dimethyl-2-pyrimidyl, 4-pyrimidinyl, 5-methyl-3-pyrazidinyl, 6-methoxy-3-pyrazidinyl, 1-phenyl-3-pyrazolonyl, 2-thiazolyl, 4-methyl-2-thiazolyl, 4,5-dimethyl-2-thiazolyl, 4-phenyl-2-thiazolyl, 5-bromo-2-thiazolyl, 3-isothiazolyl, 2-benzothiazolyl, 6-methyl-2-benzothiazolyl, 4-chloro-2-benzothiazolyl, 4-bromo-2-benzothiazolyl, 5-chloro-2-benzoxazolyl, 1,3,4-thiadiazolyl, 5-methyl-1,3,4-thiadiazolyl, 1,2,4-thiazole, 6-phenyl-1,2,4-triazole, 7-индазолyl and mono- and di-substituted phenyl wherein each substituent is halogen, hydroxy, alkyl or thioalkoxy having up to three carbon atoms, alkyl having up to four carbon atoms, trifluoromethyl, acetyl, methylsulfinyl or methylsulfonyl; R₃ is a member selected from the group consisting of hydrogen, alkyl having from one to six carbon atoms, trifluoromethyl, acetyl, methylsulfinyl or methylsulfonyl having up to six carbon atoms in the alkyl moiety and Z is oxygen or sulfur, except when R is OR when it is oxygen.

Of special interest in this connection are those compounds where X and Y are hydrogen, Z is oxygen, R is —NH₂ wherein R₂ is a member selected from the group consisting of phenyl, nitrophenyl, pyridyl, 3-methyl-2-pyridyl, 2-pyrimidyl, 2-thiazolyl, 4,5-dimethyl-2-thiazolyl, 3-isothiazolyl, 2-benzothiazolyl, 7-indazolyl and mono- and di-substituted phenyl wherein each substituent is halogen, hydroxy, alkyl or thioalkoxy having up to three carbon atoms, alkyl having up to four carbon atoms, trifluoromethyl, acetyl, methylsulfinyl or methylsulfonyl; R₃ having from one to six carbon atoms, and Z is oxygen or sulfur. Typical member compounds em...
time or divided dosages can be taken at different times during the day. On a body weight basis, a dosage of about 73 to about 440 mg/kg. per day is appropriate.

The physician will determine the dosage which will be most suitable for an individual patient and it will with the age, the weight, and response of the particular patient. The above dosages are exemplary of the average host. There can, of course, be individual cases where higher or lower dosage ranges are merited, and such are within the scope of this invention.

The term lipids is used here in the broad sense, covering triglycerides, cholesterol, phospholipids and free fatty acids. It is generally accepted that abnormalities in lipid metabolism, frequently indicated by elevated blood lipid levels, are closely associated with atherosclerosis, with cardiovascular disease, and with derangements of carbohydrate metabolism, e.g. diabetes. Drugs which will lower lipid levels can therefore be expected to be useful in the treatment of these diseases, and of others in which lipid metabolism is abnormal.

The products of this invention are tested in vivo for hypolipemic activity by measuring their ability to lower the blood lipid level of mammals. This property can be demonstrated in rats. Groups, each comprising 4 animals, normal Sprague-Dawley (Charles River) male rats weighing from 160-220 grams, are fed rat chow containing 0.25 percent of the compounds described herein for two overnight feeding periods. On the morning of the third day the animals are anesthetized and bled from the abdominal aorta. The total plasma cholesterol is then determined by the method of J.J. Carr and I.J. Dekker reported in Clin. Chem., 2, 355 (1956).

The plasma cholesterol level of the treated animals is found to be significantly reduced when compared to animals not receiving the test compound.

The following examples are provided by way of illustration, and should not be interpreted as limiting the invention, many variations of which are possible without departing from the spirit or scope thereof.

EXAMPLE I

A dry solid pharmaceutical composition is prepared by blending the following materials together in the proportions by weight specified below:

<table>
<thead>
<tr>
<th>Compound</th>
<th>% Cholesterol Fall</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2-dihydro-4-hydroxy-2-methyl-1,2-benzothiazine-3-carboxanilide-1,1-dioxide</td>
<td>11</td>
</tr>
<tr>
<td>3',4'-dichloro-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxanilide-1,1-dioxide</td>
<td>22</td>
</tr>
<tr>
<td>2'-chloro-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxanilide-1,1-dioxide</td>
<td>13</td>
</tr>
<tr>
<td>4'-bromo-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxanilide-1,1-dioxide</td>
<td>22</td>
</tr>
<tr>
<td>2-methyl-3'-chloro-4-hydroxy-2H-1,2-benzothiazine-3-o-toluidine-1,1-dioxide</td>
<td>19</td>
</tr>
<tr>
<td>4'-acetyl-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxanilide-1,1-dioxide</td>
<td>13</td>
</tr>
<tr>
<td>2',5'-trimethyl-4'-nitro-4-hydroxy-2H-1,2-benzothiazine-3-carboxanilide-1,1-dioxide</td>
<td>37</td>
</tr>
<tr>
<td>2',4'-trichloro-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxanilide-1,1-dioxide</td>
<td>19</td>
</tr>
<tr>
<td>N-(5-methyl-1,3,4-thiadiazol-2-yl)-4'-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxanilide-1,1-dioxide</td>
<td>19</td>
</tr>
<tr>
<td>N-(4-methyl-2-pyridyl)-4'-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxanilide-1,1-dioxide</td>
<td>14</td>
</tr>
<tr>
<td>N-(5-bromo-2-pyridyl)-4'-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxanilide-1,1-dioxide</td>
<td>14</td>
</tr>
<tr>
<td>N-(4-methyl-2-pyridyl)-4'-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxanilide-1,1-dioxide</td>
<td>14</td>
</tr>
<tr>
<td>N-(6-bromo-2-benzothiazolyl)-4'-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxanilide-1,1-dioxide</td>
<td>41</td>
</tr>
<tr>
<td>N-(3,4-dihydro-2-methyl-3-oxo-2H-1,2-benzothiazine-4-carboxanilide-1,1-dioxide</td>
<td>19</td>
</tr>
<tr>
<td>N-(3,4-dihydro-2-methyl-3-oxo-2H-1,2-benzothiazine-4-carboxanilide-1,1-dioxide</td>
<td>31</td>
</tr>
<tr>
<td>N-(3,4-dihydro-2-methyl-N-(1-naphthyl)-3-oxo-2H-1,2-benzothiazine-4-carboxanilide-1,1-dioxide</td>
<td>20</td>
</tr>
<tr>
<td>N-(3,4-dihydro-2-methyl-3-oxo-2H-1,2-benzothiazine-4-carboxanilide-1,1-dioxide</td>
<td>24</td>
</tr>
<tr>
<td>5',3',4',dichloro-3,4-dihydro-3-methyl-3-oxo-2H-1,2-benzothiazine-4-carboxanilide-1,1-dioxide</td>
<td>37</td>
</tr>
<tr>
<td>2-benzylo-4-chloro-3,4-dihydro-3-oxo-2H-1,2-benzothiazine-4-carboxanilide-1,1-dioxide</td>
<td>23</td>
</tr>
<tr>
<td>3,4-dihydro-2-methyl-3-trifluoromethyl-3-oxo-2H-1,2-benzothiazine-4-carboxanilide-1,1-dioxide</td>
<td>15</td>
</tr>
<tr>
<td>2-benzyl-2',4'-dichloro-3,4-dihydro-3-oxo-2H-1,2-benzothiazine-4-carboxanilide-1,1-dioxide</td>
<td>23</td>
</tr>
<tr>
<td>3',4'-dichloro-3,4-dihydro-2,4'-dimethyl-3-oxo-1,2-benzothiazine-4-carboxanilide-1,1-dioxide</td>
<td>18</td>
</tr>
<tr>
<td>4'-acetyl-3,4-dihydro-2-methyl-3-oxo-2H-1,2-benzothiazine-4-carboxanilide-1,1-dioxide</td>
<td>14</td>
</tr>
<tr>
<td>4'-bromo-3,4-dihydro-2,7-dimethyl-3-oxo-1,2-benzothiazine-4-carboxanilide-1,1-dioxide</td>
<td>41</td>
</tr>
</tbody>
</table>

The remaining compounds of this invention cause a drop in plasma cholesterol levels in a comparable percentage range.

What is claimed is:
1. A method of lowering lipid levels in a human which comprises the oral or parenteral administration to a human in need...
of said treatment an effective amount for lowering lipid levels of a compound selected from the group consisting of

or the base salts thereof with pharmaceutically-acceptable cations, wherein X and Y are each a member selected from the group consisting of hydrogen, fluorine, chlorine, bromine, nitro, alkyl and alkoxy having from one to five carbon atoms, and trifluoromethyl; R is a member selected from the group consisting of —OR, and —NHR, wherein R1 is alkyl having from one to twelve carbon atoms or phenylalkyl having up to three carbon atoms in the alkyl moiety, and R2 is chosen from the group consisting of hydrogen, alkyl having from one to eight carbon atoms, alkanyl having up to six carbon atoms, cycloalkyl having up to eight carbon atoms, phenylalkyl having up to three carbon atoms in the alkyl moiety, phenyl, nitrophenyl, naphthyl, pyridyl, 3-methyl-2-pyridyl, 4-methyl-2-pyridyl, 5-methyl-2-pyridyl, 6-methyl-2-pyridyl, 4,6-dimethyl-2-pyridyl, 5-chloro-2-pyridyl, 2-bromo-2-pyridyl, 5-nitro-2-pyridyl, 3-hydroxy-2-pyridyl, 5-carboxamido-2-pyridyl, 2-pyrazinyl, 2-pyrimidyl, 4,5-dimethyl-2-pyrimidyl, 4-pyrimidyl, 5-methyl-3-pyridazinyl, 6-methoxy-3-pyridazinyl, 1-phenyl-3-pyrazolonyl, 2-thiazolyl, 4-methyl-2-thiazolyl, 4-phenyl-2-thiazolyl, 5-bromo-2-thiazolyl, 4,5-dimethyl-2-thiazolyl, 5-iodothiazolyl, 2-benzothiazolyl, 6-methyl-2-benzothiazolyl, 4-chloro-2-benzothiazolyl, 6-bromo-2-benzothiazolyl, 5-chloro-2-benzoxazolyl, 1,3,4-thiadiazolyl, 5-methyl-1,3,4-thiadiazolyl, 1,2,4-triazolyl, 6-phenyl-1,2,4-triazolyl, 7-indazolyl, mono- and di-substituted phenyl wherein each substituent is halogen, hydroxy, alkyl or alkoxy having up to three carbon atoms, alkyl having up to four carbon atoms, trifluoromethyl, acetyl, methylsulfinyl or methylsulfonyl; R3 is a member selected from the group consisting of hydrogen, alkyl having from one to six carbon atoms, alkanyl having up to four carbon atoms and phenylalkyl having up to three carbon atoms in the alkyl moiety; and Z is oxygen or sulfur, except when R is —OR, when it is oxygen.

2. The method of claim 1 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide having the first formula wherein R is —NHR.

3. The method of claim 2 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is phenyl and R2 is alkyl of from one to six carbon atoms.

4. The method of claim 2 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is sulfur, R1 is phenyl and R2 is alkyl of from one to six carbon atoms.

5. The method of claim 2 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is chlorophenyl and R2 is alkyl of from one to six carbon atoms.

6. The method of claim 2 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is phenylalkyl having up to three carbon atoms in the alkyl moiety and R2 is alkyl of from one to six carbon atoms.

7. The method of claim 2 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is alkylalkyl having up to six carbon atoms and R2 is alkyl of from one to six carbon atoms.

8. The method of claim 2 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is cycloalkyl having up to eight carbon atoms and R2 is alkyl of from one to six carbon atoms.

9. The method of claim 2 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is dichlorophenyl and R2 is alkyl of from one to six carbon atoms.

10. The method of claim 2 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is pyridyl and R2 is alkyl of from one to six carbon atoms.

11. The method of claim 2 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is pyridyl and R2 is alkyl of from one to six carbon atoms.

12. The method of claim 2 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is pyridyl and R2 is alkyl of from one to six carbon atoms.

13. The method of claim 2 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is monomethyl 2-pyridyl and R2 is alkyl of from one to six carbon atoms.

14. The method of claim 2 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is monomethyl 2-pyridyl and R2 is alkyl of from one to six carbon atoms.

15. The method of claim 2 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is alkyl having from one to twelve carbon atoms and R2 is alkyl of from one to six carbon atoms.

16. The method of claim 2 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is alkyl having from one to twelve carbon atoms and R2 is alkyl of from one to six carbon atoms.

17. The method of claim 2 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide having the second formula wherein R is —OR, and Z is oxygen.

18. The method of claim 17 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is phenyl and R2 is alkyl of from one to six carbon atoms.

19. The method of claim 17 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is chlorophenyl and R2 is alkyl of from one to six carbon atoms.

20. The method of claim 17 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is pyridyl and R2 is alkyl of from one to six carbon atoms.

21. The method of claim 17 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is dichlorophenyl and R2 is alkyl having from one to six carbon atoms.

22. The method of claim 17 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is bromophenyl and R2 is alkyl of from one to six carbon atoms.

23. The method of claim 17 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is naphthyl and R2 is alkyl of from one to six carbon atoms.

24. The method of claim 17 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R1 is alkyl having from one to eight carbon atoms and R2 is alkyl of from one to six carbon atoms.

25. The method of claim 17 wherein said compound is a 3,4-dihydro-4-oxo-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is alkyl having from one to five carbon atoms, Z is oxygen, R1 is dichlorophenyl and R2 is alkyl of from one to six carbon atoms.
26. The method of claim 17 wherein said compound is a 3,4-dihydro-3-oxo-2H-1,2-benzothiazine-4-carboxamide-1,1-dioxide wherein X is hydrogen, Y is alkyl having from one to five carbon atoms, Z is oxygen, R₂ is bromophenyl and R₃ is alkyl of from one to six carbon atoms.

27. The method of claim 17 wherein said compound is a 3,4-dihydro-3-oxo-2H-1,2-benzothiazine-4-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R₂ is phenyl and R₃ is phenylalkyl having up to three carbon atoms in the alkyl moiety.

28. The method of claim 17 wherein said compound is a 3,4-dihydro-3-oxo-2H-1,2-benzothiazine-4-carboxamide-1,1-dioxide wherein X and Y are each hydrogen, Z is oxygen, R₂ is 2-thiazolyl and R₃ is alkyl of from one to six carbon atoms.

29. The method of claim 1 wherein said compound is a 3,4-dihydro-3-oxo-2H-1,2-benzothiazine-4-carboxylate-1,1-dioxide having the second formula wherein R is OR₁ and Z is oxygen.

30. The method of claim 29 wherein said compound is a 3,4-dihydro-3-oxo-2H-1,2-benzothiazine-4-carboxylate-1,1-dioxide wherein X and Y are each hydrogen, R₂ is alkyl having from one to 12 carbon atoms and R₃ is alkyl of from one to six carbon atoms.

31. The method of claim 17 wherein said compound is 3,4-dihydro-4'-ethoxy-2-methyl-3-oxo-2H-1,2-benzothiazine-4-carboxanilide-1,1-dioxide.

32. The method of claim 17 wherein said compound is 2-benzyl-4'-chloro-3,4-dihydro-3-oxo-2H-1,2-benzothiazine-4-carboxanilide-1,1-dioxide.

33. The method of claim 2 wherein said compound is 2,2',5'-trimethyl-4'-nitro-4-hydroxy-2H-1,2-benzothiazine-3-carboxanilide-1,1-dioxide.

34. The method of claim 17 wherein said compound is 2-benzyl-2',4'-dichloro-3,4-dihydro-3-oxo-2H-1,2-benzothiazine-4-carboxanilide-1,1-dioxide.

35. The method of claim 2 wherein said compound is 4-hydroxy-2-methyl-N-(6-methyl-2-benzothiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,4-dioxide.

36. The method of claim 2 wherein said compound is N-(6-bromo-2-benzothiazolyl)-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide.