COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

CONVENTION APPLICATION FOR A STANDARD PATENT

We, ELI LILLY AND COMPANY, of Lilly Corporate Center, Indianapolis, Indiana, United States of America hereby apply for the grant of a standard patent for an invention entitled:

"A NOVEL CLASS OF HYPOGLYCEMIC AGENTS"

which is described in the accompanying complete specification.

DETAILS OF BASIC APPLICATION

Number of Basic Application: 670,776

Name of Convention Country in which Basic Application was filed:
United States of America

Date of Basic application: 13 November, 1984

Our address for service is:
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DATED this TWENTY-FOURTH day of OCTOBER 1985

ELI LILLY AND COMPANY

By:


TO: THE COMMISSIONER OF PATENTS
AUSTRALIA

SPRUSON & FERGUSON

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Sydney

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SBK/EGK/148T
In support of the Convention Application made for a patent for an invention entitled:
"A NOVEL CLASS OF HYPOGLYCEMIC AGENTS"
1. Mary Ann Tucker, Assistant Patent Counsel, Lilly Corporate Center, City of Indianapolis, State of Indiana 46285, United States of America, do solemnly and sincerely declare as follows:

1. I am authorized by ELI LILLY AND COMPANY, a corporation of the State of Indiana, United States of America, the applicant for the patent to make this declaration on its behalf.

2. (b) Samuel James Dominiani and Terence T.T. Yen of 6010 East 56th Street, Indianapolis, Indiana 46226 and 8704 Hunting Trail, Indianapolis, Indiana 46217 both in the United States of America respectively is/are the actual inventor(s) of the invention and the facts upon which the applicant(s) is/are entitled to make the application are as follows:

The applicant company is assignee of the inventor(s) by virtue of a deed of assignment dated: 09 November 1984

3. the basic application(s) as defined by Section 141 of the Act was/were made in United States of America on 13 November 1984

by Samuel James Dominiani and Terence T.T. Yen

4. The basic application(s) referred to in paragraph 3 of this Declaration was/were the first application(s) made in a Convention country in respect of the invention(s) the subject of the application.

DECLARED at Indianapolis, Indiana this 19th day of September 1985

ELI LILLY AND COMPANY

TO: THE COMMISSIONER OF PATENTS AUSTRALIA
Compounds of formula (I) are revealed, as well as their preparation.

Claim

1. A method for lowering blood glucose levels in a mammal which comprises administering to said mammal a compound of formula (I):

\[
\text{(I)}
\]

in which:

- \( R^1 \) is \( C_1-C_4 \) alkyl;
- \( R^2 \) and \( R^3 \), independently, are hydrogen or \( C_1-C_4 \) alkyl;
- each \( R^4 \), independently is, \(-OR^5, -NR^6R^7, C_1-C_4\) alkyl, \(C_1-C_4\) alkoxy, trifluoromethyl, or \(C_1-C_4\) alkylthio;
R^5 is hydrogen or -C-R^8;

R^6 is hydrogen, C_1-C_4 alkyl, or -C-R^8;

R^7 is hydrogen or C_1-C_4 alkyl;

each R^8, independently, is C_1-C_4 alkyl or phenyl;

Z is oxygen or sulfur;

X is a therapeutically acceptable anion; and

m is 0, 1 or 2.

12. A process for preparing a compound of Formula (II), as defined in claim 9, which comprises:

(a) reacting a 1-alkyl-imidazole of formula (III):

   \[ R^1-N-C-N \]

   (III)

with a phenacyl compound of formula (IV):

   \[ \begin{array}{c}
   \text{X} \\
   \text{R^2} \\
   \text{R^3} \\
   \text{R^4} \\
   \text{m} \end{array} \]

   (IV)

   to produce a compound of Formula (II) in which X, R^2, R^3, R^4, X and m are as defined in claim 9 and Z is oxygen;
(b) reacting a 1-phenacylimidazole of formula (V):

\[
\text{(V)}
\]

with an alkylating agent of formula (VI):

\[
\text{(VI)}
\]

\( R^1 X \)

to produce a compound of Formula (II) in which \( R^1, R^2, R^3, R^4, X \) and \( m \) are as defined in claim 9 and \( Z \) is oxygen; or

(c) oxidizing a compound of formula (VII):

\[
\text{(VII)}
\]

\( R^1-N \)

to the formula (II) compound in which \( R^1, R^2, R^3, R^4, X \) and \( m \) are as defined in claim 9 and \( Z \) is oxygen; and, if desired,

(d) reacting the product of any of steps (a), (b) or (c) with a thiating agent to prepare a corresponding compound of formula (II), as defined in claim 9, in which \( Z \) is sulfur.
A novel class of hypoglycemic agents

The following statement is a full description of this invention, including the best method of performing it known to us.
Abstract

The invention relates to imidazolium salts which are effective in lowering blood glucose levels in mammals. In particular, there is provided a compound of Formula (I) which is useful in lowering blood glucose levels:

\[
\begin{align*}
R^1 & \quad N \quad R^2 \\
& \quad Z \quad R^3 \\
& \quad X^- 
\end{align*}
\]

in which:

\[R^1\] is \(C_1-C_4\) alkyl;  
\[R^2\] and \[R^3\], independently, are hydrogen or \(C_1-C_4\) alkyl;  
each \[R^4\], independently is, \(-OR^5\), \(-NR^6R^7\), \(C_1-C_4\) alkyl, \(C_1-C_4\) alkoxy, trifluoromethyl, or \(C_1-C_4\) alkylthio;  
\[R^5\] is hydrogen or \(-C-R^8\);  
\[R^6\] is hydrogen, \(C_1-C_4\) alkyl, or \(-C-R^8\);  
\[R^7\] is hydrogen or \(C_1-C_4\) alkyl;  
each \[R^8\], independently, is \(C_1-C_4\) alkyl or phenyl;  
\[Z\] is oxygen or sulfur;  
\[X\] is a therapeutically acceptable anion; and  
\[m\] is 0, 1 or 2.
Diabetes mellitus is a systemic disease characterized by disorders in the metabolism of insulin, carbohydrates, fats, and proteins, and in the structure and function of blood vessels. The disease has several causes including a large genetic component as well as a relationship to the type and amount of physical exercise and diet of the individual. The primary symptom of acute diabetes mellitus is hyperglycemia, often accompanied by glycosuria, the presence in urine of abnormal amounts of glucose, and polyuria, the excretion of large volumes of urine. Additional symptoms arise in chronic or long-standing diabetes and include degeneration of the walls of blood vessels. Although many different organs are affected by these vascular changes, the eyes appear to be the most susceptible. As such, long-standing diabetes mellitus, even when treated with insulin, is a leading cause of blindness.

There are two recognized types of diabetes. Juvenile onset, or ketosis-prone, diabetes develops early in life with much more severe symptoms, and has a near-certain prospect of later vascular involvement. Control of this type of diabetes is often difficult. The second type of diabetes is adult onset, or ketosis-resistant, diabetes. This form develops later in life, is milder and has a more gradual onset.

One of the most significant advancements in the history of medical science came in 1922 when Banting and Best demonstrated the therapeutic affects of insulin.
in diabetic humans. However, even today, a clear picture of the basic biochemical defects of the disease is not known, and diabetes is still a serious health problem. It is believed that two percent or more of the population of the United States is afflicted with some form of diabetes.

The introduction of orally effective hypoglycemic agents was also an important development in the treatment of diabetes mellitus. Hypoglycemic agents are useful in the treatment of hyperglycemia by lowering blood glucose levels. The term "hyperglycemia" refers to a clinical condition resulting from an abnormally high blood glucose level. Oral hypoglycemic agents are normally used in the treatment of adult onset diabetes since older individuals have a better chance of recovery than an individual afflicted with juvenile onset diabetes.

The present invention relates to a new class of orally active hypoglycemic agents capable of lowering blood glucose levels in mammals with adult onset diabetes.

In accordance with the invention, there is provided a method for lowering blood glucose levels in mammals which comprises administering to said mammal a compound of formula (I):

\[ R^1 \begin{array}{c} \text{X} \\ \text{R}^2 \end{array} \]

(II)
in which:

R^1 is C_1-C_4 alkyl;
R^2 and R^3, independently, are hydrogen or C_1-C_4 alkyl;

each R^4, independently is, -OR^5, -NR^6R^7, C_1-C_4 alkyl, C_1-C_4 alkoxy, trifluoromethyl or C_1-C_4 alkylthio;

R^5 is hydrogen or -C-R^8;

R^6 is hydrogen, C_1-C_4 alkyl, or -C-R^8;
R^7 is hydrogen or C_1-C_4 alkyl;

each R^8, independently, is C_1-C_4 alkyl or phenyl;

Z is oxygen or sulfur;

X is a therapeutically-acceptable anion; and

m is 0, 1 or 2.

An important class of these compounds is that in which each R^4 is, independently, -OR^5, -NR^6R^7, C_1-C_4 alkyl, C_1-C_4 alkoxy, or C_1-C_4 alkylthio.

The present invention also provides a pharmaceutical formulation comprising a compound of formula (I) and a pharmaceutically acceptable carrier, diluent or excipient therefor.

The present invention also provides a compound of formula (II):

(II)
in which:

- $R^1$ is $C_1$-$C_4$ alkyl;
- $R^2$ and $R^3$, independently, are hydrogen or $C_1$-$C_4$ alkyl;
- each $R^4$, independently, is -OR$^5$, NR$^6$R$^7$, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, trifluoromethyl or $C_1$-$C_4$ alkylthio;
- $R^5$ is hydrogen or -C-R$^8$;
- $R^6$ is hydrogen, $C_1$-$C_4$ alkyl, or -C-R$^8$;
- $R^7$ is hydrogen or $C_1$-$C_4$ alkyl;
- each $R^8$, independently, is $C_1$-$C_4$ alkyl or phenyl;
- $Z$ is oxygen or sulfur;
- $X$ is a therapeutically acceptable anion; and
- $m$ is 0, 1 or 2;

with the provisos that when $R^1$ is methyl, $R^2$ and $R^3$ are hydrogen and $Z$ is oxygen, $m$ is other than 0; and

when $R^1$ is methyl, $R^2$ and $R^3$ are hydrogen, $Z$ is oxygen, $X$ is bromine, and $m$ is 1, $R^4$ is other than 4-methoxy or 4-methyl.

An important class of compounds of formula (II) is that in which $R^4$, independently, is -OR$^5$, NR$^6$R$^7$, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, or $C_1$-$C_4$ alkylthio.

Further, there is provided a process for preparing a compound of formula (II) which comprises:

(a) reacting a 1-alkyl-imidazole of formula (III):
with a phenacyl compound of formula (IV):

![Diagram of formula (IV)](image)

(IV)

to produce a compound of Formula (II) in which $R^1$, $R^2$, $R^3$, $R^4$, $X$ and $m$ are as defined above and $Z$ is oxygen;

(b) reacting a 1-phenacylimidazole of formula (V):

![Diagram of formula (V)](image)

(V)

with an alkylating agent of formula (VI):

$$R^1X$$

(VI)

to produce a compound of Formula (II) in which $R^1$, $R^2$, $R^3$, $R^4$, $X$ and $m$ are as defined above and $Z$ is oxygen; or
(c) oxidizing a compound of formula (VII):

\[
\text{R}^1 \text{R}^2 \text{N} \text{R}^3 \text{R}^4 \text{OH}
\]

(VII)

to the formula (I) compound in which \( R^1, R^2, R^3, R^4, X \) are as defined above and Z is oxygen; and, if desired,

(d) reacting the product of any of steps (a), (b) or (c) with a thiating agent to prepare a corresponding compound of formula (II), as defined above, in which Z is sulfur.

All temperatures stated are in degrees Celsius and all units of measurement are in weight units except for liquids, which are in volume units.

As used "C\(_1\)-C\(_4\) alkyl" represents a straight or branched alkyl chain having from one to four carbon atoms. Typical C\(_1\)-C\(_4\) alkyl groups may include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.-butyl, isobutyl or t-butyyl.

"C\(_1\)-C\(_4\) alkoxy" represents a straight or branched alkoxy chain having from one to four carbon atoms. Typical C\(_1\)-C\(_4\) alkoxy groups may include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy or t-butoxy.

"C\(_1\)-C\(_4\) alkylthio" represents a straight or branched alkylthio chain having from one to four carbon atoms.
atoms. Typical C\textsubscript{1}-C\textsubscript{4} alkythio groups may include, for example, methylthio, ethylthio, n-propylthio, or sec-butylthio.

The compounds employed in this invention are imidazolium salts and as such require a "therapeutically acceptable anion", defined in the above formula by "X". A therapeutically-acceptable anion is any suitable anion which, when coordinated together with the imidazolium cation, forms a "therapeutically-acceptable" salt. A "therapeutically-acceptable salt" is a salt useful in the therapy of a warm-blooded animal. Commonly used anions may include chloride, bromide, iodide, sulfonate, p-toluenesulfonate, methanesulfonate, p-bromophenylsulfonate, phosphate, carbonate, oxalate, succinate, citrate, benzoate, acetate, and the like. A preferred and commonly used anion is bromide. Another preferred anion is chloride.

The following list of imidazolium salts illustrates the type of compounds comprehended by the present invention:

1-Ethyl-3-[2-(4-methylphenyl)-2-oxoethyl]lH-imidazolium bromide
1-Methyl-3-[2-(2,4-dimethylphenyl)-2-oxoethyl]lH-imidazolium chloride
1-Methyl-3-[2-(2-ethyl-4-methoxyphenyl)-2-oxoethyl]lH-imidazolium bromide
1-Methyl-3-[2-(4-methoxyphenyl)-2-oxoethyl]lH-imidazolium chloride
1-Methyl-3-[2-(3-methoxyphenyl)-2-oxoethyl]lH-imidazolium chloride
1-sec-Butyl-3-(2-phenyl-2-oxoethyl)lH-imidazolium bromide
1-Methyl-3-[2-(3-methoxyphenyl)-2-oxoethyl]-1H-imidazolium iodide
1-n-Propyl-3-[2-(4-methylphenyl)-2-oxoethyl]-1H-imidazolium bromide
5 1-Methyl-3-[2-(4-methylphenyl)-2-oxoethyl]-1H-imidazolium sulfonate
1-Methyl-3-[2-(4-methylphenyl)-2-oxoethyl]-1H-imidazolium methanesulfonate
1-Methyl-3-[2-(3-methoxyphenyl)-2-oxoethyl]-1H-imidazolium phosphate
10 1H-imidazolium phosphate
1-Methyl-3-[2-(4-n-butylyphenyl)-2-oxoethyl]-1H-imidazolium iodide
1-sec-Butyl-3-[2-(3,5-ditethoxyphenyl)-2-oxoethyl]-1H-imidazolium chloride
15 1-Methyl-3-[2-(4-hydroxyphenyl)-2-oxoethyl]-1H-imidazolium bromide
1-Methyl-3-[2-(3,4-dihydroxyphenyl)-2-oxoethyl]-1H-imidazolium bromide
1-t-Butyl-3-[2-(4-aminophenyl)-2-oxoethyl]-1H-imidazolium chloride
20 1-Methyl-3-[(1-n-propyl-2-phenyl-2-oxoethyl)]-1H-imidazolium bromide
1-Methyl-3-[2-(4-n-propoxophenyl)-2-oxoethyl]-1H-imidazolium bromide
25 1-Methyl-3-[1-methyl-2-(4-methylphenyl)-2-oxoethyl]-1H-imidazolium succinate
1-Methyl-3-[2-(4-methylphenyl)-2-thioxoethyl]-1H-imidazolium bromide
1-Methyl-3-[2-(2,6-dimethylphenyl)-2-oxoethyl]-1H-imidazolium iodide
30 1H-imidazolium iodide
While all combinations of variables listed in the above formulae provide compounds which lower blood glucose in mammals, there are preferred compounds for such use. For example, $R^1$ is preferably methyl and $R^2$ and $R^3$ are preferably methyl or hydrogen. Especially preferred is that $R^2$ and $R^3$ are both hydrogen. Other preferred aspects of the compounds employed in the present invention will be noted later.

A preferred procedure used to prepare the compounds of this invention involves reacting a 1'-alkyl-imidazole of formula III with a phenacyl derivative of formula IV. This reaction may be represented by the following scheme:

in which $R^1$, $R^2$, $R^3$, $R^4$, $Z$, $X$ and $m$ are as defined above.
This process is carried out by simply combining an appropriate phenacyl derivative with an equimolar or slight excess amount of a 1-alkylimidazole in a mutual solvent. Typical solvents suitable for use in this process should be aprotic and may include tetrahydronfuran, dimethylsulfoxide, dimethylformamide, sulfolane, 1,2-dimethoxyethane, diethyl ether or preferably, acetonitrile. The reaction is substantially complete after about 1 to 72 hours when conducted at a temperature in the range of about 0°C to about 150°C. The reaction is preferably conducted at a temperature in the range of about 20°C to about 35°C for about 1 to 24 hours. The product may be isolated by procedures well known in the art. The precipitated solid may be collected by filtration or the reaction solvents may be removed by evaporation or decantation. The product may be purified further, if desired, by common techniques such as crystallization or chromatography over solid supports such as silica gel or alumina.

Thioxoethyl imidazolium compounds, defined by the above general formulae in which Z is sulfur, form another important group of compounds that are orally active hypoglycemic agents and are a further embodiment of this invention. The thioxoethyl compounds of the invention preferably are prepared by thiating the corresponding phenacyl derivative according to the following scheme:
in which \( R^1, R^2, R^3, R^4, X \) and \( m \) are as defined above.

Any of several thiation agents can be employed in this reaction including phosphorous pentasulfide. Another preferred thiation agent is Lawesson's Reagent, which is 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide. This thiating agent and its general uses are described in detail in *Tetrahedron Letters*, 21, 4061 (1980). The thiation reaction preferably is carried out by combining approximately equimolar quantities of the phenacyl compound and Lawesson's Reagent in a mutual organic solvent such as toluene or dioxane. The reaction is generally complete within about 1 hour to about 10 hours when carried out at a temperature of about 50°C to about 150°C. The compound formed can be isolated and purified by usual methods such as crystallization and the like.
The compounds employed in the present invention may be prepared by alternative syntheses as well. For example, an appropriate 1-phenacyl imidazole derivative may be reacted with an alkyl halide to afford the corresponding 1-alkyl-3-phenacyl imidazolium derivative. Also, compounds of formula (I) in which Z is oxygen may be prepared readily by treating imidazole with a phenyl epoxide to give the corresponding 1-(2-hydroxy-2-phenyl-ethyl)imidazole. This compound then may be oxidized either to the ketone and reacted with an alkyl halide, or reacted with an alkyl halide and then oxidized to the ketone to provide the corresponding 1-alkyl-3-phenacyl imidazolium salt of the invention. Each of the above described procedures may be conducted by standard procedures well known to one of ordinary skill in the art.

Compounds in which R is hydroxy preferably are prepared by first protecting the substituent, for example with an alkyl group to afford an alkoxy moiety, and then removing the protecting group, for example with a strong acid such as hydrogen bromide, or with a milder reagent such as iodosotrimethylsilane.

Similarly, any other reactive moiety on any of the starting or final reagents, which may interfere with the progress of the reaction, may be protected by protecting groups familiar to those skilled in the art. See, for example, "Protective Groups in Organic Chemistry", McOmie, ed., Plenum Press, N.Y., N.Y. (1973) or "Protective Groups in Organic Synthesis", Greene, John Wiley & Sons, N.Y., N.Y. (1981).
Compounds of formula (I) in which the hydroxy or amino substituent on the phenyl ring contains an acyl or benzoyl moiety also are prepared by general processes. The acylated compounds are prepared by standard acylation conditions at any of the stages in the synthesis of the final products according to the procedures described above.

The therapeutically acceptable anion associated with the imidazolium cationic portion of the salts employed in this invention is defined in the above formula by $X^-$. The particular anion, forming a part of any salt of this invention, is not of a critical nature, as long as the salt, as a whole, is pharmacologically acceptable and as long as the anionic moiety does not contribute numerous undesired qualities to the salt as a whole. Preferred anions to be utilized are the halides, and whenever a halide such as chloride or bromide is the anion portion of the salt, it can, if desired for any reason, be readily replaced by a different anion. Such replacement can be effected either directly, by metathesis, i.e., by double decomposition either in solution or by employing anion exchange resin, or alternatively, by conversion of the quaternary salt to the corresponding hydroxide, and then neutralization of the hydroxide by reaction with the appropriate acid. For example, an imidazolium halide can be passed over a hydroxide ion exchange resin, or reacted with aqueous silver oxide, to form the corresponding imidazolium hydroxide. Reaction of the hydroxide with an acid such as methanesulfonic acid, formic acid, butyric acid, nitric acid, phosphoric acid or the like, then provides
the imidazolium salt having an anion corresponding to the acid utilized.

The starting materials used to prepare the compounds employed in the present invention are either commercially available or readily prepared by known processes. For example, the phenacyl starting materials in which X is halide may be synthesized readily by treating an acetophenone derivative with a halogenating agent, such as bromine or iodine, in methylene chloride and acetic acid at a temperature in the range of about 0°C to about 25°C.

The following non-limiting Examples are provided to further illustrate specific aspects of the present invention.

Example 1

1-Methyl-3-[2-(4-methylphenyl)-2-oxoethyl]-1H-imidazolium bromide

To a solution of 10.6 g (0.05 mol) of 1-bromo-2-(4-methylphenyl)-2-oxoethane in 150 ml of diethyl ether was added 4.18 g (0.051 mol) of 1-methylimidazole (Aldrich Chemical Company, Milwaukee, Wisconsin). The reaction mixture was stirred for approximately 3 hours at room temperature and the precipitated solid was collected by filtration. The resulting hygroscopic solid was recrystallized from methanol/ethyl acetate to afford 4.82 g of 1-methyl-3-[2-(4-methylphenyl)-2-oxoethyl]-1H-imidazolium bromide as a solid. A second crop was obtained from the filtrate to provide an additional 5.8 g of product. (72% yield) mp = 148°-151°C.
Analysis calculated for C\textsubscript{13}H\textsubscript{15}BrN\textsubscript{2}O\textsubscript{2}

Theory: C, 52.90; H, 5.12; N, 9.49;
Found: C, 52.73; H, 4.95; N, 9.26.

Example 2

1-Methyl-3-[2-(3-methoxyphenyl)-2-oxoethyl]-1H-imidazolium bromide

A solution of 4.58 g (0.01 mol) of 1-bromo-2-(3-methoxyphenyl)-2-oxoethane in 10 ml of diethyl ether was filtered, and the filtrate was treated with 1.82 g (0.01 mol) of 1-methylimidazole. The resulting reaction mixture was stirred at room temperature for approximately 15 hours whereupon the solution was decanted and the residue was washed with diethyl ether. The residue was dissolved in hot acetonitrile and, upon cooling, dark needles precipitated out of solution. The resulting solid was collected and recrystallized twice from acetonitrile/ethyl acetate to afford 2.1 g of 1-methyl-3-[2-(3-methoxyphenyl)-2-oxoethyl]-1H-imidazolium bromide as white needles. (34% yield) mp = 167°-171°C

Analysis calculated for C\textsubscript{13}H\textsubscript{15}BrN\textsubscript{2}O\textsubscript{2}

Theory: C, 50.18; H, 4.86; N, 9.00; Br, 25.68;
Found: C, 49.89; H, 4.75; N, 8.98; Br, 25.56.
Example 3

1-Methyl-3-[2-(3-ethoxyphenyl)-2-oxoethyl]-1H-imidazolium bromide

A solution of 2.9 g (0.012 mol) of 1-bromo-2-(3-ethoxyphenyl)-2-oxoethane in 20 ml of acetonitrile was combined with 1.03 g (0.013 mol) of 1-methylimidazole and the resulting mixture was stirred at room temperature for approximately 18 hours. The mixture was diluted with methanol and the volatiles were evaporated under reduced pressure to a volume of approximately 15 ml. This solution was diluted with ethyl acetate and the precipitated brown solid was collected by filtration. The collected solid was washed with ethyl acetate and dissolved in hot acetonitrile. The mixture was purified with charcoal and upon cooling the solid was collected. The solid was recrystallized from acetonitrile/diethyl ether to provide two crops which were combined and recrystallized three times from isopropyl alcohol to afford 0.27 g of 1-methyl-3-[2-(3-ethoxyphenyl)-2-oxoethyl]-1H-imidazolium bromide as pale yellow flakes. (7% yield) mp = 137°-138°C

Analysis calculated for C_{14}H_{17}BrN_{2}O_{2}

Theory:  C, 51.71; H, 5.27; N, 8.61; Br, 24.57;
Found:  C, 51.54; H, 5.01; N, 8.40; Br, 24.80.
Example 4

1-Methyl-3-(1,1-dimethyl-2-phenyl-2-oxoethyl)-1H-imidazolium bromide

A solution of 4.6 g (0.02 mol) of α-bromo-isobutyrophenone and 1.8 g (0.022 mol) of 1-methyl-imidazole in 30 ml of diethyl ether was stirred at room temperature for approximately 48 hours. The solvent was decanted and the resulting oil was slurried in ethyl acetate. The solvent was again decanted and the residue was dissolved in acetonitrile prior to adding a small portion of ethyl acetate. A white precipitate was collected by filtration and recrystallized from methanol/ethyl acetate to afford 3.88 g of 1-methyl-3-(1,1-dimethyl-2-phenyl-2-oxoethyl)-1H-imidazolium bromide as glittering white flakes. (63% yield) mp = 137°-140°C

Analysis calculated for C_{14}H_{17}BrN_{2}O

Theory: C, 54.38; H, 5.54; N, 9.06; Br, 25.84;

Found: C, 54.25; H, 5.82; N, 8.87; Br, 25.67.

Example 5

1-Methyl-3-[2-(4-ethylphenyl)-2-oxoethyl]-1H-imidazolium bromide

A solution of 4.41 g (0.019 mol) of 1-bromo-2-(4-ethylphenyl)-2-oxoethane and 1.65 g (0.02 mol) of
1-methylimidazole in 40 ml of diethyl ether was stirred at room temperature for approximately 18 hours. The reaction solvent was decanted, and the residue was washed with diethyl ether and dissolved in a small amount of acetonitrile. The resulting solution was diluted with a small amount of ethyl acetate, whereupon a brown precipitate formed. The solid was collected and recrystallized from acetonitrile/ethyl acetate to provide 2.26 g of 1-methyl-3-[2-(4-ethylphenyl)-2-oxoethyl]-1H-imidazolium bromide as fine yellow brown needles. (38% yield) mp = 177°-179°C

Analysis calculated for C_{14}H_{17}BrN_{2}O

Theory:  C, 54.38; H, 5.54; N, 9.06;
         Br, 25.84;

Found:   C, 54.13; H, 5.81; N, 9.04;
         Br, 26.05.

Example 6

1-Methyl-3-[2-(2-methylphenyl)-2-oxoethyl]-1H-imidazolium bromide

A solution of 4.22 g (0.02 mol) of 1-bromo-2-
(2-methylphenyl)-2-oxoethane, 2.64 g (0.032 mol) of
1-methylimidazole and 60 ml of diethyl ether was stirred at room temperature for approximately 17 hours. The reaction solvent was decanted and the residue was washed with diethyl ether. The residue was dissolved in hot acetonitrile, and the resulting solution was cooled and diluted with diethyl ether. The solid was collected and recrystallized twice from acetonitrile/diethyl ether to
afford 1.99 g of 1-methyl-3-[2-(2-methylphenyl)-2-oxoethyl]-1H-imidazolium bromide as white needles. (34% yield) mp = 152°-154°C

Analysis calculated for C_{13}H_{15}BrN_{2}O

Theory: C, 52.90; H, 5.12; N, 9.49;
Br, 27.07;

Found: C, 52.82; H, 5.28; N, 9.54;
Br, 27.14.

Example 7

1-Methyl-3-(1-methyl-2-phenyl-2-oxoethyl)-1H-imidazolium bromide

A solution of 8 ml (0.047 mol) of 90% pure 1-phenyl-1-oxo-2-bromopropane and 4.25 g (0.052 mol) of 1-methylimidazole in 100 ml of diethyl ether was stirred at room temperature for approximately 24 hours. The precipitated solid was collected by filtration, washed with diethyl ether and dissolved in methanol. This solution was diluted with diethyl ether and the resulting white solid was collected by filtration. This solid was recrystallized from methanol/diethyl ether to afford 7.65 g of 1-methyl-3-(1-methyl-2-phenyl-2-oxoethyl)-1H-imidazolium bromide as white crystals. (55% yield) mp = 167°-170°C

Analysis calculated for C_{13}H_{15}BrN_{2}O

Theory: C, 52.90; H, 5.12; N, 9.49;
Found: C, 52.73; H, 4.95; N, 9.26;
Example 8

1-Methyl-3-[1-methyl-2-(4-methylphenyl)-2-oxoethyl]-1H-imidazolium bromide

A solution of 2.24 g (0.01 mol) of 1-(4-methylphenyl)-1-oxo-2-bromopropane and 0.9 g (0.011 mol) of 1-methylimidazole in 50 ml of diethyl ether was stirred at room temperature for approximately 18 hours. The reaction solvent was decanted, and the residue was washed with diethyl ether and dissolved in acetonitrile. The resulting solution was diluted with diethyl ether and the precipitated solid was collected by filtration. The solid was recrystallized from acetonitrile/diethyl ether to afford 0.33 g of 1-methyl-3-[1-methyl-2-(4-methylphenyl)-2-oxoethyl]-1H-imidazolium bromide as a solid. (11% yield) mp = 175°C-177°C

Analysis calculated for C_{17}H_{17}BrN_{2}O
Theory: C, 54.38; H, 5.54; N, 9.06;
Found: C, 54.09; H, 5.54; N, 9.17.

A second crop was obtained from the filtrate to provide an additional 0.4 g of the title product. mp = 174°C-178°C

Example 9

1-Methyl-3-[2-(2,4-dimethylphenyl)-2-oxoethyl]-1H-imidazolium bromide

A solution of 4.76 g (0.021 mol) of 1-bromo-2-(2,4-dimethylphenyl)-2-oxoethane and 1.76 g (0.021 mol...
mol) of 1-methylimidazole in 50 ml of diethyl ether was stirred at room temperature for approximately 21 hours. The reaction solvent was decanted and the residue was washed with diethyl ether. The residue was recrystallized from acetonitrile/ethyl acetate to afford 3.32 g of the title product as white crystals. (51% yield) mp = 179°-181°C.

Analysis calculated for C₁₄H₁₇BrN₂O
Theory:  C, 54.38; H, 5.54; N, 9.09;
Br, 25.84;
Found:  C, 54.18; H, 5.46; N, 8.86;
Br, 25.96.

Example 10

1-Methyl-3-[2-(3-methylphenyl)-2-oxoethyl]-1H-imidazolium bromide

A solution of 5.16 g (0.024 mol) of 1-bromo-2-(3-methylphenyl)-2-oxoethane and 2.15 g (0.026 mol) of 1-methylimidazole in approximately 30 ml of diethyl ether was stirred at room temperature for about 19 hours. The reaction solvent was decanted and the resulting brown residue was washed with diethyl ether. The residue was washed with hot acetonitrile and recrystallized twice from acetonitrile/diethyl ether to afford 1.74 g of 1-methyl-3-[2-(3-methylphenyl)-2-oxoethyl]-1H-imidazolium bromide as white needles. (25% yield) mp = 185°-187°C
Analysis calculated for C_{13}H_{15}BrN_{2}O

Theory:  C, 52.90;  H, 5.12;  N, 9.49;
                   Br, 27.07;
Found:  C, 53.11;  H, 5.08;  N, 9.43;
                   Br, 26.96.

The following Examples illustrate additional compounds employed in the present invention and were prepared by the general procedures outlined above.

**Example 11**

1-Methyl-3-[2-(2,5-dimethoxyphenyl)-2-oxoethyl]-1H-imidazolium bromide, mp = 207°-210°C dec.

Analysis calculated for C_{14}H_{17}BrN_{2}O_{3}

Theory:  C, 49.28;  H, 5.02;  N, 8.21;  Br, 23.42;
Found:  C, 49.05;  H, 4.98;  N, 8.08;  Br, 23.14.

**Example 12**

1-n-Propyl-3-(2-phenyl-2-oxoethyl)-1H-imidazolium chloride, mp = 143°-150°C

Analysis calculated for C_{14}H_{17}ClN_{2}O

Theory:  C, 63.51;  H, 6.47;  N, 10.58;
Found:  C, 64.81;  H, 6.77;  N, 9.86.

**Example 13**

1-Methyl-3-[2-(2-methoxyphenyl)-2-oxoethyl]-1H-imidazolium bromide, mp = 165°-167°C

Analysis calculated for C_{13}H_{15}BrN_{2}O_{2}

Theory:  C, 50.18;  H, 4.86;  N, 9.00;  Br, 25.61;
Found:  C, 49.95;  H, 4.97;  N, 8.78;  Br, 25.92.

Table 1

Blood Glucose Levels in Obese-Diabetic Mice
Example 14

1-Methyl-3-[2-(3,5-dimethoxyphenyl)-2-oxoethyl]-1H-imidazolium bromide, mp = 239°-241°C dec.
Analysis Calculated for C_{14}H_{17}BrN_{2}O_{3}
  Theory: C, 49.28; H, 5.02; N, 8.21; Br, 23.42;
  Found: C, 49.33; H, 4.98; N, 7.97; Br, 23.34.

Example 15

1-Methyl-3-[2-(4-ethoxyphenyl)-2-oxoethyl]-1H-imidazolium bromide, mp = 143°-146°C
Analysis calculated for C_{14}H_{17}BrN_{2}O_{2}
  Theory: C, 51.71; H, 5.27; N, 8.61; Br, 24.57;
  Found: C, 51.49; H, 5.39; N, 8.42; Br, 24.45.

Example 16

1-Methyl-3-[2-(3,4-dimethylphenyl)-2-oxoethyl]-1H-imidazolium bromide, mp = 163°-165°C
Analysis calculated for C_{14}H_{17}BrN_{2}O
  Theory: C, 54.38; H, 5.54; N, 9.09; Br, 25.84;
  Found: C, 54.61; H, 5.49; N, 9.17; Br, 25.90.

Example 17

1-Methyl-3-[2-(4-methoxyphenyl)-2-oxoethyl]-1H-imidazolium bromide, mp = 156°-159°C
Analysis calculated for C_{13}H_{15}BrN_{2}O_{2}
  Theory: C, 50.18; H, 4.86; N, 9.00; Br, 25.68;
  Found: C, 49.98; H, 5.11; N, 8.82; Br, 25.95.
Example 18

1-Methyl-3-(2-phenyl-2-oxoethyl)-1H-imidazolium chloride, mp = 104°-108°C

Analysis calculated for C_{12}H_{13}ClN_{3}O
Theory: C, 60.89; H, 5.53; N, 11.84; Cl, 14.98;
Found: C, 59.63; H, 5.35; N, 11.37; Cl, 14.33.

Example 19

1-(1-Methylethyl)-3-[2-(3-methoxyphenyl)-2-oxoethyl]-1H-imidazolium bromide

The titled compound was made by the following procedure:
A stirred solution of 1-(3-methoxyphenacyl) imidazole (1.08 g) in 20 ml of acetonitrile was treated with 2-bromopropane, at room temperature for 7-days. The solvent was removed in vacuo and the residue, a brown glass, was triturated with tetrahydrofuran, providing an off-white powder. Recrystallization of the powder from methanol-tetrahydrofuran provided the product as fine white needles, mp = 177-179°C (dec.)

Analysis calculated for C_{15}H_{19}N_{2}O_{2}Br
Theory: C, 53.11; H, 5.65; N, 8.26;
Found: C, 52.91; H, 5.39; N, 8.35.

Following this procedure, the products of Example 20 and 21 were prepared.
Example 20

1-Methyl-3-[2-(3-hydroxyphenyl)-2-oxoethyl]-1H-imidazolium 4-methylbenzenesulfonate, mp 96-98°C (dec.)

Analysis calculated for C_{19}H_{20}N_{5}O_{5}
Theory: C, 58.75; H, 5.19; N, 7.21; S, 8.25;
Found: C, 58.54; H, 4.91; N, 7.22; S, 8.02.

Example 21

1-Methyl-3-[2-(3-trifluoromethylphenyl)-2-oxoethyl]-1H-imidazolium iodide, mp 184-186°C (dec.)

Analysis calculated for C_{13}H_{12}N_{2}O_{3}I
Theory: C, 39.41; H, 3.05; N, 7.07;
Found: C, 39.65; H, 3.26; N, 7.02.

Following the procedure outlined in Examples 1 to 10, the following compound was prepared:

Example 22

1-Methyl-3-[2-(3-acetaminophenyl)-2-oxoethyl]-1H-imidazolium bromide

Analysis calculated for C_{14}H_{16}N_{2}O_{3}Br
Theory: C, 49.72; H, 4.77; N, 12.42;
Found: C, 49.48; H, 4.74; N, 12.21.

The present invention provides a method for lowering blood glucose levels in mammals comprising administering to said mammal an effective amount of an
imidazolium compound of formula (I). The term "effective amount" means the amount of compound necessary to provide a hypoglycemic effect following administration, preferably to a mammal susceptible to adult onset diabetes.

The active compounds are effective over a wide dosage range. For example, dosages per day normally will fall within the range of about 0.5 to about 500 mg/kg of body weight. In the treatment of adult humans, the range of about 1.0 to about 100 mg/kg, in single or divided doses, is preferred. However, those skilled in the art will understand that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances including the condition to be treated, the choice of compound to be administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the chosen route of administration; therefore, the above dosage ranges are not intended to limit the scope of the invention in any way. While the present compounds preferably are administered orally to reduce blood glucose levels in mammals, the compounds also may be administered by a variety of other routes such as the transdermal, subcutaneous, intranasal, intramuscular and intravenous routes.

The compounds employed in the present invention function differently than sulfonylureas and are believed to improve insulin resistance. Therefore, the present compounds are particularly well suited for Type II, or adult onset, diabetics since many of these individuals have sufficient circulating insulin but are
resistant to insulin itself. However, the precise mechanism by which the present compounds function is not yet known, and the present invention is not limited by any mode of operation.

As noted above, the compounds of the present invention preferably are administered orally to the subject in question. While it is possible to administer a compound of the invention directly without any formulation, the compounds are employed preferably in the form of a pharmaceutical formulation comprising a pharmaceutically acceptable carrier, diluent or excipient and a compound of the invention. Such compositions will contain from about 0.1 percent to about 90 percent of a present compound.

In making the compositions of the present invention the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the composition can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, emulsions, solutions, syrups, suspensions, aerosols (as a solid or in a liquid medium), and soft and hard gelatin capsules.

Examples of suitable carriers, excipients, and diluents may include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl-
hydroxybenzoates, talc, magnesium stearate, water, and mineral oil. The formulations also may include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient, after administration to the patient, by employing procedures well known in the art.

For oral administration, a compound of this invention ideally can be admixed with carriers and diluents and molded into tablets or enclosed in gelatin capsules.

The compositions preferably are formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg, more usually about 5 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

In order to more fully illustrate this aspect of the invention, the following non-limiting formulation examples are provided. The examples are illustrative only and are not intended to limit the scope of the invention. The formulations may employ as active compounds any of the pharmaceutical compounds of formula (I).
Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

<table>
<thead>
<tr>
<th>Amount Per Capsule</th>
<th>Concentration by Weight (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Methyl-3-[2-(4-methylphenyl)-2-oxoethyl]-1H-imidazolium bromide</td>
<td>250 mg 55.0</td>
</tr>
<tr>
<td>Starch dried</td>
<td>200 mg 43.0</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>10 mg  2.0</td>
</tr>
<tr>
<td></td>
<td>460 mg 100.0</td>
</tr>
</tbody>
</table>

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

Capsules each containing 20 mg of medicament are made as follows:

<table>
<thead>
<tr>
<th>Amount Per Capsule</th>
<th>Concentration by Weight (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Methyl-3-[2-(3-methoxyphenyl)-2-oxoethyl]-1H-imidazolium bromide</td>
<td>20 mg 10.0</td>
</tr>
<tr>
<td>Starch</td>
<td>89 mg 44.5</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>89 mg 4.5</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2 mg  1.0</td>
</tr>
<tr>
<td></td>
<td>200 mg 100.0</td>
</tr>
</tbody>
</table>

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve and filled into a hard gelatin capsule.
Formulation 3

Capsules each containing 100 mg of active ingredient are made as follows:

<table>
<thead>
<tr>
<th>Amount Per Capsule</th>
<th>Weight (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Methyl-3-[2-(3-ethoxyphenyl)-2-oxoethyl]-1H-imidazolium bromide</td>
<td>100 mg 28.57</td>
</tr>
<tr>
<td>Polyoxylethylene-sorbitan monoglucone</td>
<td>50 mcg 0.014</td>
</tr>
<tr>
<td>Starch powder</td>
<td>250 mg 71.418</td>
</tr>
<tr>
<td></td>
<td>350.05 mg 100.00</td>
</tr>
</tbody>
</table>

The above ingredients are thoroughly mixed and placed in an empty gelatin capsule.

Formulation 4

Tablets each containing 10 mg of active ingredient are made up as follows:

...
The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granule so produced is dried at 50°-60°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granule which, after mixing, is compressed on a tablet machine to yield a tablet weighing 100 mg.
Formulation 5

A tablet formula may be prepared using the ingredients below:

<table>
<thead>
<tr>
<th>Amount Per Tablet</th>
<th>Concentration by Weight (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Methyl-3-[2-(4-ethyl-phenyl)-2-oxoethyl]-1H-imidazolium bromide</td>
<td>250 mg</td>
</tr>
<tr>
<td>Cellulose microcrystalline</td>
<td>400 mg</td>
</tr>
<tr>
<td>Silicon dioxide fumed</td>
<td>10 mg</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>5 mg</td>
</tr>
<tr>
<td></td>
<td>665 mg</td>
</tr>
</tbody>
</table>

The components are blended and compressed to form tablets each weighing 665 mg.

Formulation 6

Suspensions each containing 5 mg of medicament per 5 ml dose are made as follows:

<table>
<thead>
<tr>
<th>per 5 ml of suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Methyl-3-[2-(2-methylphenyl)-2-oxoethyl]-1H-imidazolium bromide</td>
</tr>
<tr>
<td>Sodium carboxymethyl cellulose</td>
</tr>
<tr>
<td>Syrup</td>
</tr>
<tr>
<td>Benzoic acid solution</td>
</tr>
<tr>
<td>Flavor</td>
</tr>
<tr>
<td>Color</td>
</tr>
<tr>
<td>Water</td>
</tr>
</tbody>
</table>
The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethylcellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color is diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

**Formulation 7**

An aerosol solution is prepared containing the following components:

<table>
<thead>
<tr>
<th>Component</th>
<th>Concentration by Weight (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Methyl-3-(1-methyl-2-oxo-2-phenylethyl)-1H-imidazolium bromide</td>
<td>0.25</td>
</tr>
<tr>
<td>2. Ethanol</td>
<td>29.75</td>
</tr>
<tr>
<td>20. Propellant 22 (Chlorodifluoromethane)</td>
<td>70.00</td>
</tr>
</tbody>
</table>

The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted further with the remaining amount of propellant. The valve units are then fitted to the container.
The hypoglycemic activity of the present compounds was determined by testing the efficacy of formulations of the compounds in vivo in viable yellow obese-diabetic mice. The test procedure is described in detail below.

**Experiment**

Test formulations were prepared by dissolving the test compound in a saline solution containing 2% Emulphor (a polyoxyethylated vegetable oil surfactant from GAF Corp.) to provide a dose level of 100 mg/kg. Each test formulation was administered to six viable yellow obese-diabetic mice by gavage. Evaluations of the blood glucose level were recorded at 0, 2 and 4 hours following administration. A mean was taken of the 6 values and the data is reported in Table 1:
### Table 1

Blood Glucose Levels in Obese-Diabetic Mice

<table>
<thead>
<tr>
<th>Example No. of Compound Tested</th>
<th>Hours after administration</th>
<th>Percent Blood Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>80±3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>88±2</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>63±4</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>76±4</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>66±9</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>89±4</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>84±5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>78±8</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>77±5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>88±6</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>93±6</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>95±6</td>
</tr>
</tbody>
</table>
### Table 1

Blood Glucose Levels in Obese-Diabetic Mice

<table>
<thead>
<tr>
<th>Example No. of Compound Tested</th>
<th>Hours after administration</th>
<th>Percent Blood Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>80 ± 3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>88 ± 0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>63 ± 4</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>76 ± 4</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>66 ± 9</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>89 ± 4</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>84 ± 5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>78 ± 8</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>77 ± 5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>88 ± 6</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>93 ± 6</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>95 ± 0</td>
</tr>
<tr>
<td>Mice</td>
<td>Q/en</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>80±3</td>
<td></td>
</tr>
<tr>
<td>88±8</td>
<td>63±4</td>
<td></td>
</tr>
<tr>
<td>76±4</td>
<td>66±9</td>
<td></td>
</tr>
<tr>
<td>99±4</td>
<td>84±5</td>
<td></td>
</tr>
<tr>
<td>78±8</td>
<td>77±5</td>
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<tr>
<td>88±5</td>
<td>95±6</td>
<td></td>
</tr>
<tr>
<td>92±6</td>
<td>95±6</td>
<td></td>
</tr>
</tbody>
</table>
Table 1 (continued)

Blood Glucose Levels in Obese-Diabetic Mice

<table>
<thead>
<tr>
<th>Example No.</th>
<th>Hours after administration</th>
<th>Percent Blood Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>70±6</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>61±7</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>75±5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>69±8</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>77±4</td>
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<td></td>
<td>4</td>
<td>76±5</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>78±5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>73±7</td>
</tr>
<tr>
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Certain of the compounds also were tested in Type II diabetic rats and were found to have the ability to lower blood glucose levels in these animals as well.
The claims defining the invention are as follows:

1. A method for lowering blood glucose levels in a mammal which comprises administering to said mammal a compound of formula (I):

   ![formula](I)

   in which:
   - \( R^1 \) is \( \text{C}_1-\text{C}_4 \) alkyl;
   - \( R^2 \) and \( R^3 \), independently, are hydrogen or \( \text{C}_1-\text{C}_4 \) alkyl;
   - each \( R^4 \), independently is, \(-\text{OR}^5\), \(-\text{NR}^6\text{R}^7\), \( \text{C}_1-\text{C}_4 \) alkyl, \( \text{C}_1-\text{C}_4 \) alkoxy, trifluoromethyl, or \( \text{C}_1-\text{C}_4 \) alkylthio;
   - \( \text{R}^5 \) is hydrogen or \(-\text{C}-\text{R}^6\);
   - \( \text{R}^6 \) is hydrogen, \( \text{C}_1-\text{C}_4 \) alkyl, or \(-\text{C}-\text{R}^8\);
   - \( \text{R}^7 \) is hydrogen or \( \text{C}_1-\text{C}_4 \) alkyl;
   - each \( \text{R}^8 \), independently, is \( \text{C}_1-\text{C}_4 \) alkyl or phenyl;
   - \( Z \) is oxygen or sulfur;
   - \( X \) is a therapeutically acceptable anion; and
   - \( m \) is 0, 1 or 2.

2. A method as claimed in claim 1 in which in the compound of formula (I), each \( R^4 \), independently, is \(-\text{OR}^5\), \(-\text{NR}^6\text{R}^7\), \( \text{C}_1-\text{C}_4 \) alkyl, \( \text{C}_1-\text{C}_4 \) alkoxy, or \( \text{C}_1-\text{C}_4 \) alkylthio.
3. A method as claimed in claim 2 in which in the compound of Formula (I), $R^2$ is methyl, and both $R^2$ and $R^3$ are hydrogen.

4. A method as claimed in claim 2 or 3 in which the compound of Formula (I) is: 1-methyl-3-[2-(4-methylphenyl)-2-oxoethyl]imidazolium bromide, 1-methyl-3-[2-(3-methoxyphenyl)-2-oxoethyl]-1H-imidazolium bromide, 1-methyl-3-[2-(3-ethoxyphenyl)-2-oxoethyl]-1H-imidazolium bromide, 1-methyl-3-[2-(4-ethylphenyl)-2-oxoethyl]-1H-imidazolium bromide, 1-methyl-3-[2-(2-methylphenyl)-2-oxoethyl]-1H-imidazolium bromide, 1-methyl-3-[2-(2,4-dimethylphenyl)-2-oxoethyl]-1H-imidazolium bromide, 1-methyl-3-[2-(3-methylphenyl)-2-oxoethyl]-1H-imidazolium bromide, or 1-methyl-3-[2-(2,5-dimethoxyphenyl)-2-oxoethyl]-1H-imidazolium bromide.

5. A method as claimed in claim 2 in which in the compound of Formula (I), $R^2$ or $R^3$ is hydrogen or methyl, and $R^1$ is methyl.

6. A pharmaceutical formulation which comprises as an active ingredient a compound of formula (I):
in which:

- $R^1$ is $C_1-C_4$ alkyl;
- $R^2$ and $R^3$, independently, are hydrogen or $C_1-C_4$ alkyl;
- each $R^4$, independently, is $\text{OR}^5$, $\text{NR}^6R^7$, $C_1-C_4$ alkyl, $C_1-C_4$ alkoxy, trifluoromethyl, or $C_1-C_4$ alkylthio;
- $R^5$ is hydrogen or $-\text{C}R^8$;
- $R^6$ is hydrogen, $C_1-C_4$ alkyl, or $-\text{C}R^8$;
- $R^7$ is hydrogen or $C_1-C_4$ alkyl;
- each $R^8$, independently, is $C_1-C_4$ alkyl or phenyl;
- $Z$ is oxygen or sulfur;
- $X$ is a therapeutically-acceptable anion; and
- $m$ is 0, 1 or 2, associated with one or more pharmaceutically-acceptable carriers, diluents or excipients therefor.

7. A pharmaceutical formulation, as defined in claim 6, in which each $R^4$ of the formula (I) compound, independently, is $\text{OR}^5$, $\text{NR}^6R^7$, $C_1-C_4$ alkyl, $C_1-C_4$ alkoxy, or $C_1-C_4$ alkylthio.

8. A compound of formula (II):

\[
\begin{align*}
R^1 & \quad \text{Cyclic Structure} \\
R^2 & \quad \text{Cyclic Structure} \\
R^3 & \quad \text{Cyclic Structure} \\
R^4 & \quad \text{Cyclic Structure} \\
X & \quad \text{Cyclic Structure} \\
\end{align*}
\]

in which:

- $R^1$ is $C_1-C_4$ alkyl;
- $R^2$ and $R^3$, independently, are hydrogen or $C_1-C_4$ alkyl;
each \( R^4 \), independently, is \(-\text{OR}^5\), \(-\text{NR}^6\text{R}^7\), \( \text{C}_1\text{-C}_4 \) alkyl, \( \text{C}_1\text{-C}_4 \) alkoxy, trifluoromethyl, or \( \text{C}_1\text{-C}_4 \) alkylthio; each \( R^5 \), independently, is \(-\text{OR}^6\); each \( R^6 \), independently, is \( \text{C}_1\text{-C}_4 \) alkyl or phenyl; each \( R^7 \), independently, is \( \text{C}_1\text{-C}_4 \) alkyl or \( \text{C}_1\text{-C}_4 \) alkoxy; each \( R^8 \), independently, is \( \text{C}_1\text{-C}_4 \) alkyl or phenyl; each \( R^9 \), independently, is \( \text{C}_1\text{-C}_4 \) alkyl or \( \text{C}_1\text{-C}_4 \) alkoxy; each \( R^{10} \), independently, is \( \text{C}_1\text{-C}_4 \) alkyl or phenyl; each \( R^{11} \), independently, is \( \text{C}_1\text{-C}_4 \) alkyl or \( \text{C}_1\text{-C}_4 \) alkoxy; with the provisos that when \( R^1 \) is methyl, \( R^2 \) and \( R^3 \) are hydrogen; when \( R^1 \) is methyl, \( R^2 \) and \( R^3 \) are hydrogen, \( Z \) is oxygen or sulfur; when \( R^1 \) is methyl, \( R^2 \) and \( R^3 \) are hydrogen, \( Z \) is oxygen, \( X \) is bromine, \( m \) is 0, 1 or 2; 9. A compound of formula (II), as defined in claim 8, in which each \( R^4 \), independently, is \(-\text{OR}^5\), \(-\text{NR}^6\text{R}^7\), \( \text{C}_1\text{-C}_4 \) alkyl, \( \text{C}_1\text{-C}_4 \) alkoxy, or \( \text{C}_1\text{-C}_4 \) alkylthio. 10. A compound of Formula (II), as defined in claim 9, in which \( R^1 \) and \( R^2 \) are methyl. 11. 1-methyl-3-[2-(3-methoxyphenyl)-2-oxoethyl]-1H-imidazolium bromide, 1-methyl-3-[2-(3-ethoxyphenyl)-2-oxoethyl]-1H-imidazolium bromide, 1-methyl-3-[2-(4-ethylphenyl)-2-oxoethyl]-1H-imidazolium bromide, 1-methyl-3-[2-(2-methylphenyl)-2-oxoethyl]-1H-imidazolium bromide,
12. A process for preparing a compound of Formula (II), as defined in claim 9, which comprises:
(a) reacting a 1-alkyl-imidazole of formula (III):

![Chemical Structure](image)

(III)

with a phenacyl compound of formula (IV):

![Chemical Structure](image)

(IV)

to produce a compound of Formula (II) in which \( R^1, R^2, R^3, R^4, X \), and \( m \) are as defined in claim 9 and \( Z \) is oxygen;
(b) reacting a 1-phenacylimidazole of formula (V):

with an alkylating agent of formula (VI):

\[ R'X \]  

(VI)

to produce a compound of Formula (II) in which \( R^1, R^2, R^3, R^4, X \) and \( m \) are as defined in claim 9 and \( Z \) is oxygen; or

(c) oxidizing a compound of formula (VII):

\[ R^1 \]

(VII)

to the formula (II) compound in which \( R^1, R^2, R^3, R^4, X \) and \( m \) are as defined in claim 9 and \( Z \) is oxygen; and, if desired,

(d) reacting the product of any of steps (a), (b) or (c) with a thiating agent to prepare a corresponding compound of formula (II), as defined in claim 9, in which \( Z \) is sulfur.

13. A compound of formula (II), as defined in claim 9, whenever prepared according to a process of claim 12.
14. A method for lowering blood glucose levels, as defined in claim 1 or 2, substantially as hereinbefore described.

15. A pharmaceutical formulation, substantially as hereinbefore described, with reference to any one of the Examples.

16. A compound of Formula (II), substantially as hereinbefore described, with reference to any one of the Examples.

17. A process for preparing a compound of Formula (II), substantially as hereinbefore described, with reference to any one of the Examples.

DATED this TWENTY-FOURTH day of OCTOBER, 1985

ELI LILLY AND COMPANY

Patent Attorneys for the Applicant
SPRUSON & FERGUSON