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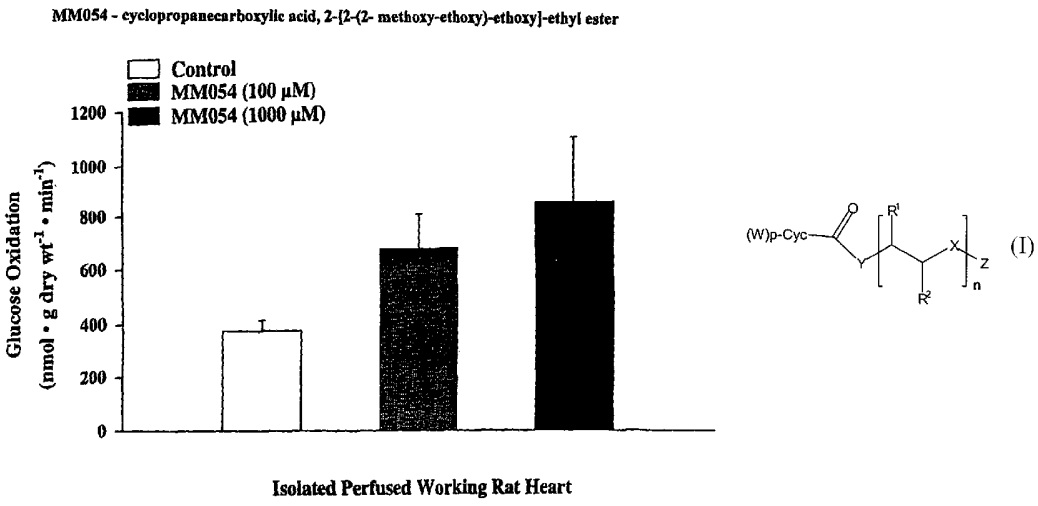
(54) Title: COMPOUNDS THAT STIMULATE GLUCOSE UTILIZATION AND METHODS OF USE



(57) Abstract: The invention provides novel compounds of the Formula (I) that stimulate rates of glucose oxidation in myocardial cells wherein W, Cyc, p, , X, Z, R, K-, R, R^1, R^2, R^3,R^4, I and n are as defined for Formula (I) herein. The invention also relates to pharmaceutical compositions comprising compounds capable of stimulation of glucose Oxidation, methods for increasing glucose oxidation rates in myocardial cells, and methods of treatment of myocardial ischemia.

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COMPOUNDS THAT STIMULATE GLUCOSE UTILIZATION AND METHODS OF USE

This Patent Application is a continuation-in-part of United States Serial No. 10/181,274 which is a United States National filing under 35 U.S.C. 371 which is based on PCT/IB02/02525, filed April 1, 2002, now withdrawn, the entirety of the disclosure of each of these applications which is hereby incorporated into the present application by reference.

FIELD OF THE INVENTION

The invention relates to novel compounds that stimulate rates of glucose oxidation in myocardial cells. The invention also relates to pharmaceutical compositions comprising compounds capable of stimulating glucose oxidation, methods for increasing glucose oxidation rates in myocardial cells, and methods of treatment of myocardial ischemia.

BACKGROUND OF THE INVENTION

Myocardial ischemia is a common clinical pathology that occurs in the setting of angina pectoris, acute myocardial infarction, or during cardiac surgery. Myocardial ischemia is a major clinical problem, with its complications being the major cause of mortality and morbidity in Western society.

It has been reported that stimulating glucose oxidation both during and following ischemia can benefit the ischemic heart . *Br J Pharmacol* 128: 197-205, 1999, *Am J Physiol* 275: H1533-41, 1998. *Biochimica et Biophysica Acta* 1225: 191-9, 1994, *Pediatric Research* 34: 735-41, 1993, *Journal of*

Biological Chemistry 270: 17513-20, 1995. *Biochimica et Biophysica Acta* 1301: 67-75, 1996, *Am J Cardiol* 80: 11A-16A, 1997, *Molecular & Cellular Biochemistry* 88: 175-9, 1989, *Circ Res* 65: 378-87, 1989, *Circ Res* 66: 546-53, 1990, *American Journal of Physiology* 259: H1079-85, 1990, *American Journal of Physiology* 261: H1053-9, 1991, *Am J Physiol Heart Circ Physiol* 280: H1762-9., 2001, *J Am Coll Cardiol* 36: 1378-85., 2000.

To meet the high energy demands of the contracting muscle, the heart must produce a constant and plentiful supply of the free energy carrier, adenosine triphosphate (ATP). This energy is produced by the metabolism of a variety of carbon substrates, including carbohydrates such as glucose. The metabolism of fatty acid is the other major source of energy for the heart.

Glucose metabolism in the heart consists of two important pathways, namely glycolysis and glucose oxidation.

It has been shown that during ischemia (such as that produced by angina pectoris, myocardial infarction or heart surgery) the levels of circulating fatty acids in the plasma can be dramatically elevated. *Am Heart J* 128: 61-7, 1994. As a result, during ischemia and reperfusion the heart is exposed to high levels of fatty acids, which results in the preferential use of fatty acids as an oxidative substrate over glucose. It further has been reported that this over-reliance on fatty acids as a major source of ATP contributes to fatty acid-induced ischemic damage. This observation has sparked numerous approaches directed at switching substrate utilization back to glucose in an attempt to protect the heart from fatty acid-induced ischemic damage. *J Cardiovasc Pharmacol* 31: 336-44., 1998, *Am Heart J* 134: 841-55., 1997,

Am J Physiol 273: H2170-7., 1997, *Cardiovasc Drugs Ther* 14: 615-23., 2000, *Cardiovasc Res* 39: 381-92., 1998, *Am Heart J* 139: S115-9., 2000, *Coron Artery Dis* 12: S8-11., 2001, *Am J Cardiol* 82: 14K-17K., 1998, *Molecular & Cellular Biochemistry* 172: 137-47, 1997, *Circulation* 95: 313-5., 1997, *Gen Pharmacol* 30: 639-45., 1998, *Am J Cardiol* 82: 42K-49K., 1998, *Coron Artery Dis* 12: S29-33., 2001, *Coron Artery Dis* 12: S3-7., 2001, *J Nucl Med* 38: 1515-21., 1997. Current approaches that are used to manipulate myocardial energy metabolism involve either stimulating glucose metabolism directly or indirectly (i.e., inhibiting fatty acid metabolism).

Since high fatty acid oxidation rates markedly decrease glucose oxidation, one approach to increasing glucose oxidation is to inhibit fatty acid oxidation. This has proven effective both during and following ischemia, and this pharmacological approach is starting to see clinical use. Although a number of pharmacological agents designed to inhibit fatty acid oxidation have recently been developed, the direct ß-oxidation inhibitor, trimetazidine, was the first anti-anginal agent widely used that has a mechanism of action that can be attributed to an optimization of energy metabolism *Circulation Research*. 86: 580-8, 2000 .

Trimetazidine is reported to primarily act by inhibiting fatty acid oxidation, thereby stimulating glucose oxidation in the heart.

A second clinically effective agent that is reported to switch energy metabolism from fatty acid to glucose oxidation is ranolazine. It has been reported that this agent stimulates glucose oxidation secondary to an

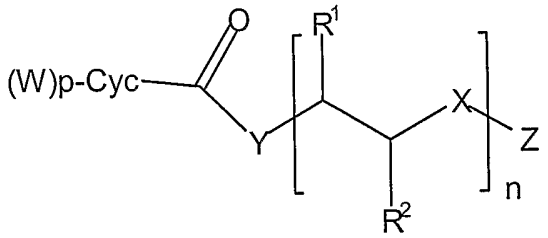
inhibition of fatty acid oxidation *Circulation* 93: 135-42., 1996.

The detrimental effects of fatty acids on mechanical function during and following ischemia may also be attenuated by agents that increase glucose oxidation directly. Numerous experimental studies have reported that stimulation of glucose oxidation by using dichloroacetate (DCA) following ischemia (at the expense of fatty acids) can benefit the ischemic heart. *Am Heart J* 134: 841-55, 1997. Although DCA is an effective compound designed to stimulate glucose oxidation, it has a short biological half-life.

Therefore, there is need to develop novel class of compounds and to identify compounds that can stimulate glucose oxidation, have long biological life, and be effective in treatment or prevention of myocardial ischemia

SUMMARY OF THE INVENTION

In one aspect, the present invention is directed to novel compounds represented by Formula (I):



Formula (I)

wherein

W is C_1-C_6 alkyl, halogen, or aryl;

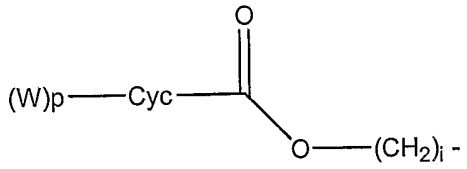
Cyc is C_3 or C_4 cycloalkyl;

p is an integer from 0 to 3 when Cyc is C_4 cycloalkyl, and p is an integer from 0 to 2 when Cyc is C_3 cycloalkyl;

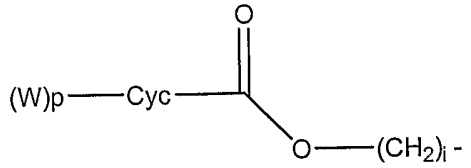
Y is O, S, or NR;

X is O, S, NR, or CR^3R^4;

Z is H, alkyl, cycloalkyl, aryl or (cyclo)alkylcarbonyl or

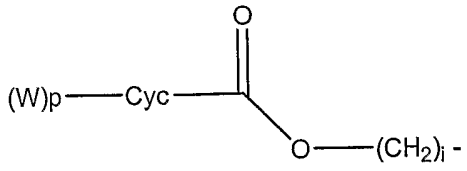


if X is NR and R is



;

R is H, alkyl, aryl, or



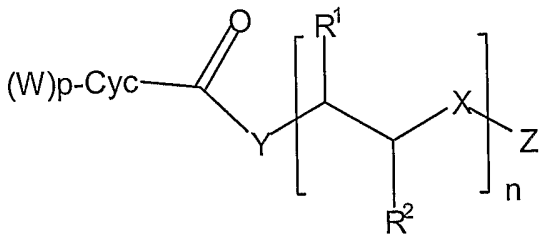
where i is an integer from 2 to 4;

R^1 is H, alkyl, aryl or O;

R^2 is H, alkyl or aryl;

R^3 and R^4 are independently H, alkyl or aryl; and n is an integer from 1 to 10; or a pharmaceutically acceptable salt, ester or prodrug thereof.

In one alternate preferred aspect, the present invention is directed to novel compounds of Formula (I) which are represented by Formula (Ia):



Formula (Ia)

wherein

W is C_1-C_6 alkyl, halogen, or aryl;

Cyc is C_3 or C_4 cycloalkyl;

p is an integer from 0 to 3 when Cyc is C_4 cycloalkyl, and p is an integer from 0 to 2 when Cyc is C_3 cycloalkyl;

Y is O, S, or NR;

X is O, S, NR, or CR^3R^4;

Z is H, alkyl, cycloalkyl, aryl or (cyclo)alkylcarbonyl;

R is H, alkyl or aryl;

R^1 is H, alkyl, aryl or O;

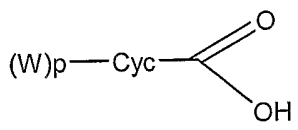
R^2 is H, alkyl or aryl;

R^3 and R^4 are independently H, alkyl or aryl; and

n is an integer from 1 to 10;

or a pharmaceutically acceptable salt, ester or prodrug thereof.

According to one aspect, the present invention is further directed to methods for increasing or improving glucose utilization in myocardial or other types of cells, tissue or organs of warm blooded animals, especially those which are capable of high glucose metabolism (e.g., heart and other muscles). The method comprises treating cells, tissue or organs with substituted or unsubstituted cyclopropane carboxylic acid or cyclobutane carboxylic acid represented by the Formula (II):



Formula (II)

wherein W, Cyc and p are as defined in connection with Formula (I), or a cyclopropane carboxylic acid or cyclobutane carboxylic derivative of Formula (I).

According to an alternate aspect, the present invention is also directed to pharmaceutical compositions comprising a compound according to the Formula (I) and suitable pharmaceutical carriers, excipients or fillers.

According to a further aspect, the present invention is directed to a method of treating physiological conditions or disorders that may be effectively treated by increasing of cell glucose utilization. According to one embodiment, such method comprises administering to a patient in need of such treatment an effective amount of a pharmaceutical composition comprising substituted or unsubstituted cyclopropane carboxylic acid or cyclobutane carboxylic acid according to Formula (II) or a cyclopropane carboxylic acid or cyclobutane carboxylic acid derivative of Formula (I).

The present invention is further directed to kits including a pharmaceutical composition according to the present invention.

The methods of the present invention are applicable for treating warm blooded animal subjects, such as mammals, including humans, primates, etc.

Definitions

As used herein, the term "alkyl" means straight or branched alkane chain, which may be, optionally substituted with, for example, halogens, cyclic or aromatic substituents.

As used herein, the terms "aryl" or "aromatic" refer to mono- and bi-cyclic structures comprising 5 to 12 carbon

atoms, preferably monocyclic rings containing six carbon atoms. The ring may be optionally substituted with alkyl, alkenyl, halogen, alkoxy, or haloalkyl substituents.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph which depicts glucose oxidation in an isolated perfused working rat heart model at the indicated concentrations of cyclopropanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester (MM054) as compared to a control.

Figure 2 is a graph which depicts glucose oxidation in an isolated perfused working rat heart model at the indicated concentrations of cyclobutanecarboxylic acid, 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester (MM056) as compared to a control.

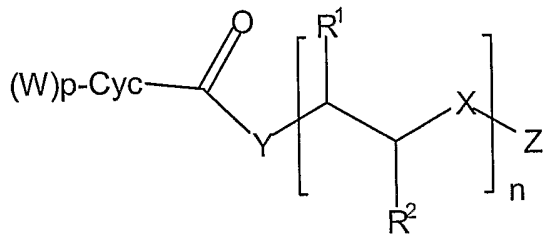
Figure 3 is a graph which depicts glucose oxidation in an isolated perfused working rat heart model at increasing concentrations of cyclopropanecarboxylic acid, 2-isopropoxy-ethyl ester (MM070) as compared to a control.

Figure 4 is a graph which depicts glucose oxidation in an isolated perfused working rat heart model at increasing concentrations of cyclopropanecarboxylic acid (MM001) as compared to a control.

DETAILED DESCRIPTION OF THE INVENTION

According to one aspect, the present invention provides novel compounds which are derivatives of a cyclopropane carboxylic acid or a cyclobutane carboxylic acid. These compounds exhibit glucose oxidation stimulating activity in myocardial cells and other types of cells. The compounds

according to the present invention are represented by the Formula (I):



Formula (I)

wherein

W is C_1-C_6 alkyl, halogen, or aryl;

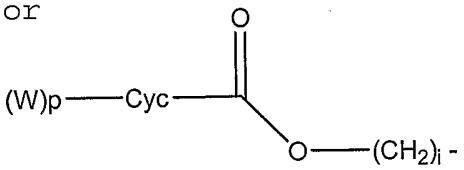
Cyc is C_3 or C_4 cycloalkyl;

p is an integer from 0 to 3 when Cyc is C_4 cycloalkyl, and p is an integer from 0 to 2 when Cyc is C_3 cycloalkyl;

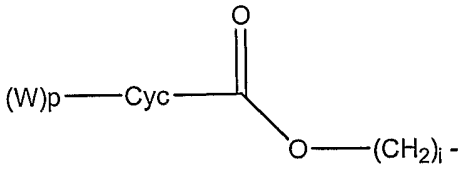
Y is O, S, or NR,

X is O, S, NR, or CR^3R^4;

Z is H, alkyl, cycloalkyl, aryl or (cyclo)alkyl carbonyl or

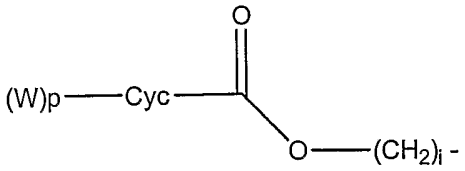


if X is NR and R is



;

R is H, alkyl, aryl or



where i is an integer from 2 to 4;

R^1 is H, alkyl or aryl;

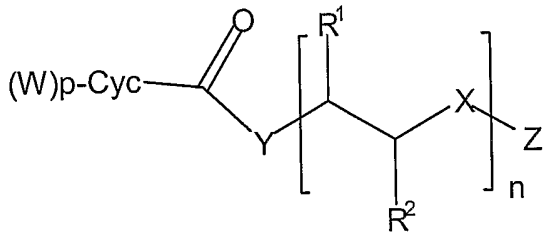
R^2 is H, alkyl, aryl or O;

R^3 and R^4 are independently H, alkyl or aryl and

n is an integer from 1 to 10;

or a pharmaceutically acceptable salt, ester or prodrug thereof.

According to an alternate aspect, the present invention provides novel compounds of Formula (I) according to the present invention which are represented by Formula (Ia):



Formula (Ia)

wherein

W is C_1-C_6 alkyl, halogen, or aryl;

Cyc is C_3 or C_4 cycloalkyl;

p is an integer from 0 to 3 when Cyc is C_4 cycloalkyl, and p is an integer from 0 to 2 when Cyc is C_3 cycloalkyl;

Y is O, S, or NR,

X is O, S, NR, or CR^3R^4;

Z is H, alkyl, cycloalkyl, aryl or (cyclo)alkyl carbonyl or

R is H, alkyl or aryl;

R^1 is H, alkyl or aryl;

R^2 is H, alkyl, aryl or O;

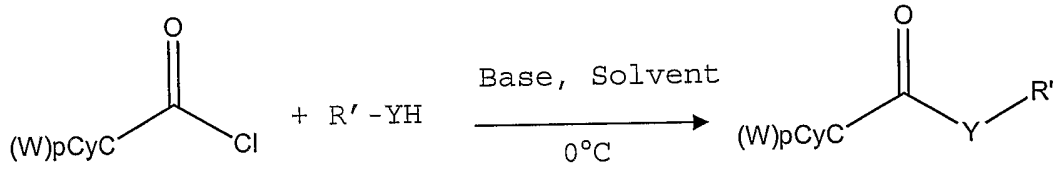
R^3 and R^4 are independently H, alkyl or aryl and

n is an integer from 1 to 10;

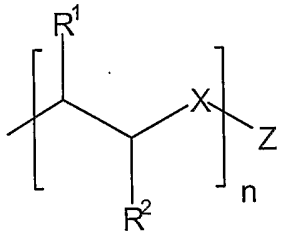
or a pharmaceutically acceptable salt, ester or prodrug thereof.

Certain compounds according to the present invention may be conveniently prepared from the appropriate

substituted or unsubstituted cyclopropane carbonyl chloride or cyclobutane carbonyl chloride according to the following reaction scheme:



wherein W, Cyc, and p are as defined in connection with Formula (I), Y is O such that R'YH is an alcohol and

R' is 

where R^1, R^2, X, Z and n are as defined in connection with Formula (Ia).

Other compounds of Formula (I) may be prepared by methods similar to those described in Example 23 and using the appropriate starting materials.

Suitable solvents include inert organic solvents such as dichloromethane and suitable base catalysts include triethylamine and pyridine.

Reaction conditions may be varied depending on the starting materials and the desired end product. Optimization of the reaction conditions would be apparent for one of ordinary skill.

Preferred compounds have unsubstituted cycloalkyl rings (p is 0).

According to a preferred embodiment Y is O, and X is NR or O, n is 1 to 4, p is 0, R^1, R^2, R^3 and R^4 are hydrogen, and

Z is lower alkyl, cycloalkyl or phenyl; or Y is NR, and X is O, n is 1 or 2, p is 0, R^1, R^2, R^3 and R^4 are hydrogen, and Z is hydrogen.

The compounds according to the present invention are exemplified by the following compounds:

cyclopropanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester;

cyclobutanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester;

(cyclobutanecarbonyl-amino)-acetic acid;

cyclopropanecarboxylic acid 2-(2-benzyloxy-ethoxy)-ethyl ester;

2-(cyclopropanecarbonyl-amino)-propionic acid;

cyclobutanecarboxylic acid 2-(2-benzyloxy-ethoxy)-ethyl ester;

cyclobutanecarboxylic acid, 2-(2-butoxy-ethoxy)-ethyl ester;

cyclobutanecarboxylic acid, 2-(2-ethoxy-ethoxy)-ethyl ester;

cyclopropanecarboxylic acid 2-(2-dimethylamino-ethoxy)-ethyl ester;

cyclobutanecarboxylic acid 2-(2-dimethylamino-ethoxy)-ethyl ester;

cyclopropanecarboxylic acid 2-(2-hexyloxy-ethoxy)-ethyl ester;

cyclobutanecarboxylic acid 2-(2-hexyloxy-ethoxy)-ethyl ester;

cyclopropanecarboxylic acid 2-(2-methoxy-ethoxy)-ethyl ester;

cyclobutanecarboxylic acid 2-(2-methoxy-ethoxy)-ethyl ester;

cyclopropanecarboxylic acid 2-ethoxy-ethyl ester;

cyclobutanecarboxylic acid 2-ethoxy-ethyl ester;

cyclopropanecarboxylic acid 2-isopropoxy-ethyl ester;

cyclobutanecarboxylic acid 2-isopropoxy-ethyl ester;

cyclopropanecarboxylic acid, 2-(2-cyclopropanecarbonyloxy-ethoxy)-ethyl ester;

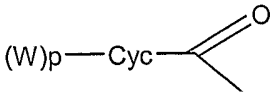
cyclobutanecarboxylic acid, 2-(2-cyclobutanecarbonyloxy-ethoxy)-ethyl ester;

cyclopropanecarboxylic acid, 2-[2-(2-cyclopropanecarbonyloxy-ethoxy)-ethoxy]-ethyl ester; and

cyclobutanecarboxylic acid, 2-[2-(2-cyclobutanecarbonyloxy-ethoxy)-ethoxy]-ethyl ester.

The invention further provides a method for increasing the rate of glucose oxidation and improving glucose utilization in myocardial and other cells, tissue or organs of humans and animals. It has been discovered that substituted or unsubstituted cyclopropanecarboxylic acid and cyclobutanecarboxylic acid, cyclopropanecarboxylic acid and cyclobutanecarboxylic acid represented by the Formula (II) and cyclopropanecarboxylic acid and cyclobutanecarboxylic acid derivatives, such as cyclopropanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester and cyclobutanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester and other compounds represented by the Formula (I) can increase glucose utilization in myocardial an other types of cells, tissue or organs of warm blooded animals, including humans.

Compounds of Formula II have the structure:



Formula (II)

Wherein

W is C_1-C_6 alkyl, halogen, or aryl;

Cyc is C_3 or C_4 cycloalkyl; and

p is an integer from 0 to 3 when Cyc is C_4 cycloalkyl, or p is an integer from 0 to 2 when Cyc is C_3 cycloalkyl;

According to one embodiment, the method according to the present invention comprises treating cells, tissue or organs of an animal with at least one compound represented by Formula (I) or Formula (II) in an amount effective to stimulate glucose utilization. The compounds of the Formula (I) or Formula (II) may be delivered to the cells, tissues or organs by conventional means of administrating pharmaceutical compositions such as oral administration, injection or infusion, etc., of the compounds of the Formula (I) or (II) to the animal.

The invention further provides pharmaceutical compositions comprising, as its active component, at least one compound according to the Formulas (I) or (II) or their pharmaceutically acceptable salts, esters or prodrugs. Pharmaceutical compositions comprising more than one compound according to the Formulas (I) or (II), their various mixtures and combinations are also contemplated to be within the scope of the present invention.

Pharmaceutical compositions or formulations include compositions and formulations conventionally used in the pharmaceutical arts and may comprise carriers and excipients compatible with oral, intravenous, intramuscular, intraarterial, intracranial, and/or intracavity administration. Suitable pharmaceutical compositions and/or

formulations may further compose colloidal dispersion systems, or lipid formulations (e.g., cationic or anionic lipids), micelles, microbeads, etc.

As noted, pharmaceutical compositions of the present invention may comprise pharmaceutically acceptable and physiologically acceptable carriers, diluents or excipients. Examples of suitable carriers, diluents and excipients include solvents (aqueous or non-aqueous), solutions, emulsions, dispersion media, coatings, isotonic and absorption promoting or delaying agents, compatible with pharmaceutical administration, and other commonly used carriers known in the art.

Pharmaceutical compositions may also include carriers to protect the composition against rapid degradation or elimination from the body, and, thus may comprise a controlled release formulation, including implants and microencapsulated delivery systems. For example, a time delay material such as glyceryl monostearate or glyceryl stearate alone, or in combination with a wax, may be employed.

Pharmaceutical compositions can be formulated to be compatible with a particular route of administration. For oral administration, a composition can be incorporated with excipients and used in the form of tablets, pills or capsules, e.g., gelatin capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included in oral formulations. The tablets, pills, capsules, etc., can contain any of the following ingredients, or similar compounds: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent

such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; or a flavoring or sweetening agent.

Pharmaceutical compositions for parenteral, intradermal, or subcutaneous administration can include a sterile diluent, such as water, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose.

Pharmaceutical compositions for injection include sterile aqueous solutions (where water-soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). Antibacterial and antifungal agents include, for example, parabens, chlorobutanol, phenol, ascorbic acid and thimerosal. Isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride may be included in the composition. Including an agent which delays absorption, for example, aluminum monostearate and gelatin can prolong absorption of injectable compositions.

The pharmaceutical formulations can be packaged in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to

physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the pharmaceutical carrier or excipient.

The compositions can be administered by any route compatible with a desired outcome. Thus, routes of administration include oral (e.g., ingestion or inhalation), intraperitoneal, intradermal, subcutaneous, intravenous, intraarterial, intracavity, intracranial, and parenteral. The compositions can also be administered using implants and microencapsulated delivery systems.

Compositions, including pharmaceutical formulations can further include particles or a polymeric substance, such as polyesters, polyamine acids, hydrogel, polyvinyl pyrrolidone, ethylene-vinylacetate, methylcellulose, carboxymethylcellulose, protamine sulfate, or lactide/glycolide copolymers, polylactide/glycolide copolymers, or ethylenevinylacetate copolymers. Cyclopropanecarboxylic acid, cyclopropanecarboxylic acid and derivatives and modified forms thereof can be entrapped in microcapsules, for example, by the use of hydroxymethylcellulose or gelatin-microcapsules, or poly (methylmethacrolate) microcapsules, respectively, or in a colloid drug delivery system.

In instances where cell, tissue or organ targeting is desired, a composition of the invention can of course be delivered to the target cell, organ or tissue by injection or infusion or the like. Targeting can be achieved by injection or infusion in practicing the methods of the invention. Targeting can also be achieved by using proteins

that bind to a cell surface protein (e.g., receptor or matrix protein) present on the cell or population of cell types. For example, antibodies or antibody fragments (e.g., Fab region) that bind to a cell surface protein can be included in the delivery systems in order to facilitate cell, tissue or organ targeting. Viral coat proteins that bind particular cell surface proteins can be used for targeting. For example, naturally occurring or synthetic (e.g. recombinant) retroviral envelope proteins with known cell surface protein binding specificity can be employed in the liposomes in order to intracytoplasmically deliver cyclopropanecarboxylic acid, cyclopropanecarboxylic acid and derivatives and modified forms thereof into target cells, tissue or organs. Thus, delivery vehicles, including colloidal dispersion systems, can be made to have a protein coat in order to facilitate targeting or intracytoplasmic delivery of cyclopropanecarboxylic acid, cyclopropanecarboxylic acid and derivatives and modified forms thereof.

The invention further provides a method for prophylactic and therapeutic treatments of various physiological condition or disorder treatable by increasing or improving glucose utilization in cells, tissue or organs of a patient by administering to the patient in need of such treatment, effective amounts of pharmaceutical compositions comprising substituted or unsubstituted cyclopropanecarboxylic acid, cyclopropanecarboxylic acid and cyclobutanecarboxylic acid derivative compounds represented by the Formulas (I) and (II).

Disorders or conditions that can be treated with a method according to the present invention include, for

example, ischemic/reperfusion injury, post myocardial infarction, angina, heart failure, a cardiomyopathy, peripheral vascular disease, diabetes, and lactic acidosis, or symptoms or side effects associated with heart surgery (e.g., open heart surgery, bypass surgery, heart transplant).

The method according to the present invention includes administering a pharmaceutical compositions comprising effective amounts of substituted or unsubstituted cyclopropanecarboxylic acid, cyclopropanecarboxylic acid and cyclobutanecarboxylic acid derivative compounds represented by the Formulas (I) and (II) in a single daily dose, or the total daily dosage may be administered in divided doses several times daily. Furthermore, the pharmaceutical compositions may be administered as a single dose or over a period of time.

Patients that can be treated with the method according to the present invention include all known kind of mammals, including non human primates (apes, gibbons, chimpanzees, orangutans, macaques), companion animals (dogs and cats), farm animals (horses, cows, goats, sheep, pigs), experimental animals (mouse, rat, rabbit, guinea pig), and humans.

The dosage regiment utilizing the pharmaceutical compositions according to the present invention is selected based on various factors such as type of physiological condition to be treated, age, weight, sex of the patient, severity of the conditions to be treated, the route of administration, and particular compound contained in the pharmaceutical composition. A physician or veterinarian of ordinary skill can readily determine and prescribed the

effective amount of the pharmaceutical composition to prevent or to treat the specific physiological condition.

The daily dosage may be varied over wide range and can be such that the amount of the active compound selected from substituted or unsubstituted cyclopropanecarboxylic acid, cyclopropanecarboxylic acid and cyclobutanecarboxylic acid derivative compounds represented by the Formulas (I) and/or Formula (II) is sufficient to increase glucose utilizationin a cell, tissue or organ of a warm blooded animal and to achieve the desired effect of alleviating or preventing fatty acid-induced ischemic damage.

The invention provides kits containing substituted or unsubstituted cyclopropanecarboxylic acid, cyclopropanecarboxylic acid and derivatives and modified forms thereof represented by the Formulas (I) and Formula (II), including pharmaceutical formulations, packaged into a suitable set. A kit typically includes a label or packaging insert including instructions for use, in vitro, in vivo, or ex vivo, of the components therein.

The term "packaging material" refers to a physical structure housing the components of the kit, such as cyclopropanecarboxylic acid, cyclopropanecarboxylic acid or derivatives or modified forms thereof. The packaging material can maintain the components sterilely, and can be made of material commonly used for such purposes (e.g., paper, corrugated fiber, glass, plastic, foil, ampules, etc.). The label or packaging insert can include appropriate written instructions, for example, practicing a method of the invention.

Kits of the invention therefore can additionally include instructions for using the kit components in a

method of the invention. Instructions can include instructions for practicing any of the methods of the invention described herein. Thus, for example, a kit can include a cyclopropanecarboxylic acid, cyclopropanecarboxylic acid or a derivative or modified form thereof in a pharmaceutical formulation in a container, pack, or dispenser together with instructions for administration to a human subject. Instructions may additionally include indications of a satisfactory clinical endpoint or any adverse symptoms that may occur, or any additional information required by the Food and Drug Administration for use in humans.

A kit may include instructions for increasing or improving glucose utilization in vitro, ex vivo or in vivo. In other embodiments, a kit includes instructions for treating a disorder associated with deficient or inefficient glucose utilization. In one aspect, the instructions comprise instructions for treating a subject having or at risk of having ischemic/reperfusion injury, post myocardial infarction, angina, heart failure, a cardiomyopathy, peripheral vascular disease, diabetes, or lactic acidosis. In another aspect, the instructions comprise instructions for treating a subject having or at risk of having heart surgery (e.g., open heart surgery, bypass surgery, heart transplant and angioplasty).

The instructions may be on "printed matter," e.g., on paper or cardboard within the kit, or on a label affixed to the kit or packaging material, or attached to a vial or tube containing a component of the kit. Instructions may additionally be included on a computer readable medium, such as a disk (floppy diskette or hard disk), optical CD such as

CD- or DVD-ROM/RAM, magnetic tape, electrical storage media such as RAM and ROM and hybrids of these such as magnetic/optical storage media.

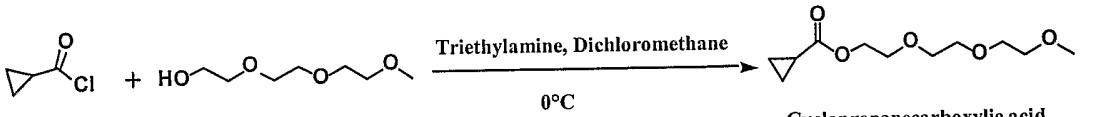
Kits can additionally include a buffering agent, a preservative, or a stabilizing agent. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package.

The present invention is further illustrated in the following examples wherein all parts, percentages, and ratios are in equivalents, all temperatures are in °C, and all pressures are atmospheric unless otherwise indicated:

EXAMPLES

EXAMPLE 1

Preparation of Cyclopropanecarboxylic acid, 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester



Cyclopropanecarboxylic acid 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester

Triethylene glycol monomethyl ether (1.1 eq, 5.26 mmol, 0.84 ml) and triethylamine (1.1 eq, 5.26 mmol, 0.73 ml) were taken in a 10 ml round bottom flask and dichloromethane (3 ml) was added. This mixture was cooled to 0°C and then cyclopropanecarbonyl chloride (4.78 mmol, 0.5 g, 0.43 ml) was added in a dropwise fashion maintaining the temperature at 0°C with constant stirring.

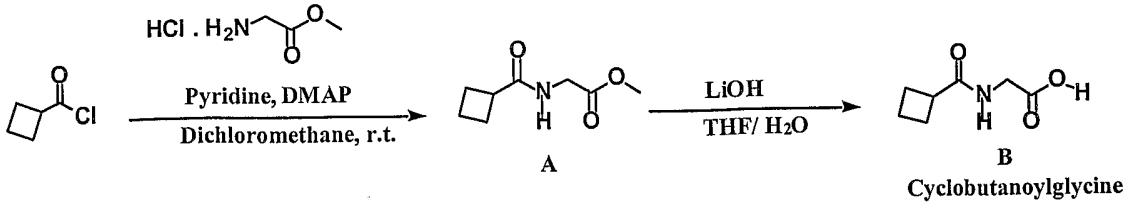
A yellowish-orange solid was observed after some time. Stirring was continued for 1 hour at 0°C. The reaction was monitored by thin layer chromatography, and then quenched

with saturated ammonium chloride solution. The mixture was then transferred to a separatory funnel, washed with 5% sodium bicarbonate (2 x 5 ml), 1:1 hydrochloric acid (2 x 5 ml) and then with brine (5 ml). The dichloromethane layer was separated from the aqueous layer, dried over anhydrous sodium sulphate, filtered, and evaporated *in vacuo* to give the title product as a pale yellow liquid. Purification was by flash chromatography and vacuum distillation (b.p. = 144°C, 3.0 mm of Hg) which afforded the pure product as a colorless liquid (527.0 mg, 48%).

The compound obtained was characterized by ^{1}H and ^{13}C NMR, IR, and mass spectroscopy:
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.2 (m, 2H), 3.68 (m, 2H), 3.64 (m, 6H), 3.52 (m, 2H), 3.36 (s, 3H), 1.62 (m, 1H), 0.99 (m, 2H), 0.84 (m, 2H); IR ($CHCI_3$) 2876.07, 1726.62, 1199.53, 1179.49, 1107.97 cm^{-1}; ^{13}C NMR (75.5 MHz, $CDCI_3$) δ 174.67, 71.80, 70.44, 69.06, 63.45, 58.84, 12.65, 8.35; MS (ES, MNa^{+}): calculated for $C_{11}H_{20}O_5Na$ 255.11, found 255.1.

EXAMPLE 2

Preparation of Cyclobutanoylglycine (Cyclobutanecarbonyl-amino)-acetic acid)



Methyl ester glycine hydrochloride (1 eq, 2.39 mmol, 300 mg) and pyridine (2 eq, 4.78 mmol, 0.39 ml) were suspended in (5 ml) of dichloromethane followed by addition

of DMAP (1.5 eq, 218.5 mg) in one portion; the reaction mixture was stirred for 30 minutes at room temperature. After 30 minutes, cyclobutanecarbonyl chloride (2 eq, 4.77 mmol, 0.54 ml) was added slowly and the reaction mixture was stirred for 4 hours at room temperature. The solvent was evaporated *in vacuo* and the residue extracted with ethyl acetate. The ethyl acetate layer was dried and concentrated to dryness. The crude material obtained was purified by flash chromatography to yield pure compound **A** (358 mg, 87%).

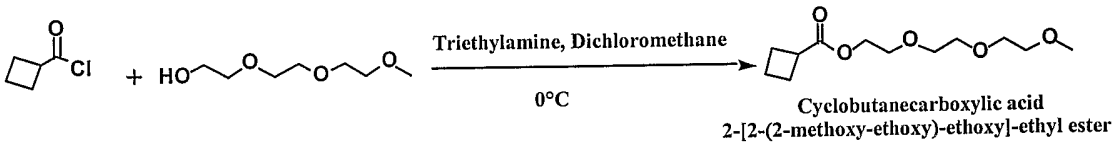
To a solution of **A** in (6 ml) THF, was added lithium hydroxide (1.1 eq, 2.3 mmol, 2.3 ml, 1M) at room temperature and the reaction mixture was stirred for 1.5 hours. The reaction mixture was then concentrated *in vacuo* and acidified to pH = 3 with 2N HCl. The crude product was then extracted with ethyl acetate and purified by recrystallization, using an ethyl acetate/hexane mixture. The product obtained after recrystallization was further purified by flash chromatography and again recrystallization to give the title compound **B** as a white solid (196 mg, 59%).

The compound obtained was characterized by ^{1}H and ^{13}C NMR, IR, and mass spectroscopy:

^{1}HNMR (300 MHz, CD_3OD) δ 3.87 (s, 2H), 3.14 (quintet, 1H), 1.84-2.2 (m, 6H); IR (USCOPE) 3313.01, 3098.14, 2986.18, 2940.41, 2525.15, 2469.13, 2435.25, 1738.49, 1620.96, 1566.87, 1486.61, 1346.65, 1264.23 cm^{-1}; ^{13}C NMR (75.5 MHz, CD_3OD) δ 178.20, 173.12, 41.69, 40.61, 26.12, 19.01; HRMS (ES, MNa^{+}): calculated for $C_7H_{11}NO_3Na$ 180.06311, found 180.06290.

EXAMPLE 3

Preparation of Cyclobutanecarboxylic acid, 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester



Cyclobutanecarboxylic acid 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester

Triethylene glycol monomethyl ether (1.1 eq, 4.64 mmol, 0.74 ml) and triethylamine (1.1 eq, 4.64 mmol, 0.65 ml) were taken in a 25 ml round bottom flask and dichloromethane (3 ml) was added. This mixture was cooled to 0°C and then cyclobutanecarbonyl chloride (4.22 mmol, 0.5 g, 0.48 ml) was added in a dropwise fashion maintaining the temperature at 0°C with constant stirring (vigorous reaction).

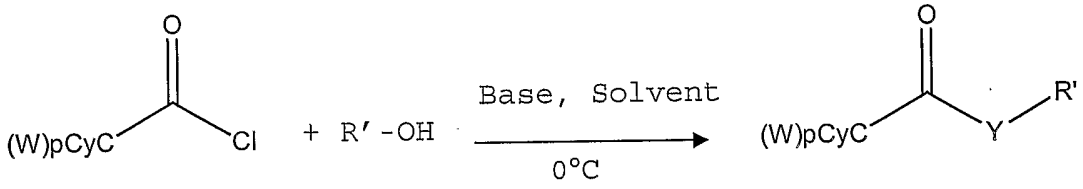
A pink colored solution was observed after some time. An extra 4 ml of dichoromethane was added to maintain proper stirring (the reaction mixture became thick). Stirring was continued for 1 hour at 0°C. The reaction was monitored by thin layer chromatography and then quenched with saturated ammonium chloride solution. The mixture was then transferred to a separatory funnel, washed with 5% sodium bicarbonate (2 x 5 ml), 1:1 hydrochloric acid (2 x 5 ml) and then with brine (5 ml). The dichloromethane layer was separated from the aqueous layer, dried over anhydrous sodium sulphate, filtered, and evaporated *in vacuo* to give the title product as a pale yellowish-pink liquid. The liquid was purified by flash chromatography and vacuum distillation (b.p. = 189°C, 3.0 mm of Hg) to yield the pure product as a colorless liquid (679.6 mg, 65.34%).

The product was characterized by ^{1}H and ^{13}C NMR, IR and mass spectroscopy:

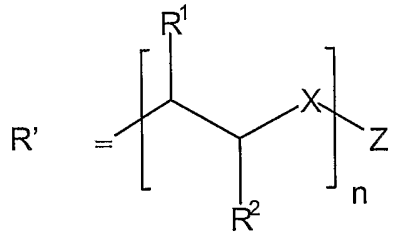
^{1}HNMR (300 MHz, $CDCl_3$) δ 4.18 (m, 2H), 3.4 (m, 2H), 3.6 (m, 6H), 3.5 (m, 2H), 3.32 (s, 3H), 3.1 (quintet, 1H), 2.2 (m, 4H), 1.86 (m, 2H); IR ($CDCI_3$) 2946.38, 2870.68, 1730.73, 1179.35, 1109.59 cm^{-1}; ^{13}C NMR (75.5 MHz, $CDCI_3$) δ 175.45, 71.93, 70.58, 69.21, 63.40, 59.01, 38.0, 25.24, 18.38; MS (ES, MNa^{+}): calculated for $C_{12}H_{22}O_5Na$ 269.13, found 269.1.

EXAMPLES 4, 6 to 14, 18 and 19

General Procedure for the preparation of certain cyclopropanecarboxylic acid and cyclobutanecarboxylic acid derivatives



where W, Cyc, and p are as defined for Formula (I) and Y is O such that R'-YH is an alcohol, where R' is:



where R^1, R^2, Z and n are defined in connection with Formula (Ia); using triethylamine or pyridine as a base and dichloromethane as a solvent.

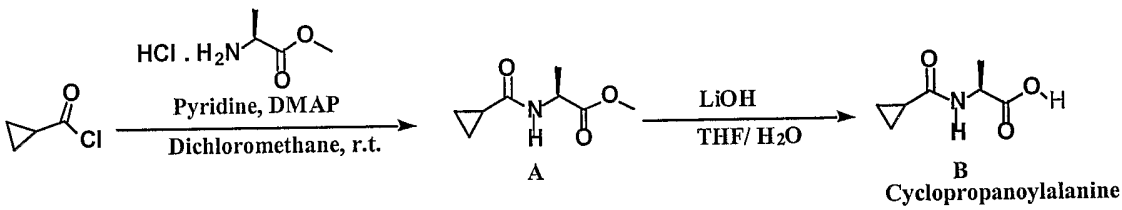
Following the procedures described in Example 1 and Example 3 and using the appropriate starting alcohol and cycloalkyl cyclopropane carboxylic acid chloride materials,

(the appropriate starting alcohols were used in place of triethylene glycol monomethyl ether), the noted cyclopropanecarboxylic acid and of cyclobutanecarboxylic acid derivatives respectively were prepared (see Table I). The compounds prepared, cycloalkyl carbonylchloride and alcohol starting materials used for their preparation and their molecular weights are summarized in Table 1.

The compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy.

EXAMPLE 5

Preparation of Cyclopropanoylalanine



The procedure of Example 2 was followed except that 2.5 equivalents of pyridine was used instead of 2 equivalents, cyclopropanecarbonyl chloride was used in place of cyclobutanecarbonylchloride and methyl ester alanine hydrochloride was used in place of methyl ester glycine hydrochloride.

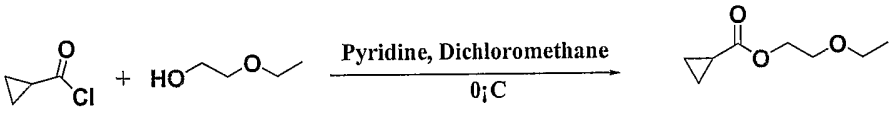
Purified compound **B** (321 mg, 87%) was characterized by ^{1}H and ^{13}C NMR, IR, and mass spectroscopy.

^{1}HNMR (300 MHz, CD_3OD) δ 8.25 (br s, 1H), 4.38 (m, 1H), 3.25 (s, 1H), 1.64 (m, 1H), 1.39 (dd, 3H), 0.7- 0.9 (m, 4H); IR (USCOPE) 3323.78, 3020.25, 2645.76, 1791.56, 1729.13, 1632.33, 1537.27, 1406.24, 1281.02 cm^{-1}; ^{13}C NMR (75.5 MHz, CD_3 OD) δ 176.28, 176.18, 49.38, 17.77, 14.59, 7.41, 7.33;

HRMS (ES, M): calculated for $C_7H_{12}NO_3$ 158.08117, found 158.08123.

EXAMPLE 15

Preparation of Cyclopropanecarboxylic acid 2-ethoxy-ethyl ester



Cyclopropanecarboxylic acid 2-ethoxy-ethyl ester

2-Ethoxy-ethanol (1.1 eq, 5.26 mmol, 0.47 g, 0.51 ml) and pyridine (1.1 eq, 5.26 mmol, 0.42 g, 0.43 ml) were taken in a 25 ml round bottom flask and dichloromethane (6 ml) was added. This mixture was cooled to 0°C and then cyclopropanecarbonyl chloride (4.78 mmol, 0.5 g, 0.43 ml) was added in a dropwise fashion maintaining the temperature at 0°C with constant stirring.

An orange-yellow colored solution was observed after sometime. Stirring was continued for 1 hour at 0°C. The reaction was monitored by thin layer chromatography and then quenched with saturated ammonium chloride solution. The mixture was then transferred to a separatory funnel, washed with 5% sodium bicarbonate (2 x 5 ml), 1:1 hydrochloric acid (2 x 5 ml), and then with brine (5 ml). The dichloromethane layer was separated from the aqueous layer, dried over anhydrous magnesium sulphate, filtered, and evaporated *in vacuo* to give the title product as a pale yellowish-orange liquid. Purification was by flash chromatography and vacuum

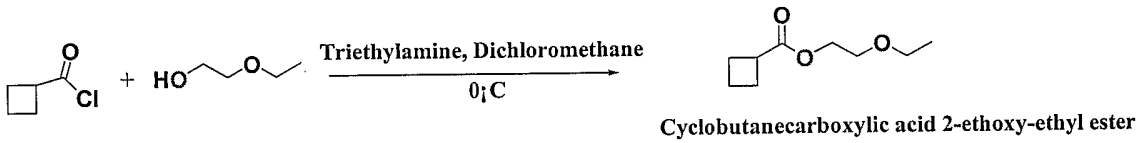
distillation (b.p. = 43°C, 2.8 mm of Hg) which afforded the pure product as a colorless liquid (515.8mg, 55.4 %).

Characterization was done by NMR (^{1}H and ^{13}C), IR, and mass spectroscopy:

^{1}HNMR (400 MHz, $CDCl_3$) δ 4.22 (m, 2H), 3.62 (m, 2H), 3.53 (q, 2H), 1.64 (m, 1H), 1.2 (t, 3H), 0.98 (m, 2H), 0.84 (m, 2H); MS (ES, M+Na): calculated for $C_8H_{14}O_3Na$ 181.19, found 181.1 ; IR (CH_2Cl_2) 2976.37, 2869.55, 1728.78, 1455.55, 1177.86 cm^{-1}; ^{13}CNMR (125 MHz, $CDCl_3$) δ 174.76, 68.39, 66.60, 63.73, 15.17, 12.91, 8.62.

EXAMPLE 16

Preparation of Cyclobutanecarboxylic acid 2-ethoxy-ethyl ester



Cyclobutanecarboxylic acid 2-ethoxy-ethyl ester

2-Ethoxy-ethanol (1.1eq, 4.64 mmol, 0.42 g, 0.45 ml) and triethylamine (1.1 eq, 4.64 mmol, 0.47 g, 0.65 ml) were taken in a 25 ml round bottom flask and dichloromethane (6 ml) was added. This mixture was cooled to 0°C and then cyclobutanecarbonyl chloride (4.22 mmol, 0.5 g, 0.48 ml) was added in a dropwise fashion maintaining the temperature at 0°C with constant stirring.

An orange-yellow colored solution was observed after sometime. Stirring was continued for 1 hour at 0°C. The reaction was monitored by thin layer chromatography and then quenched with saturated ammonium chloride solution. The

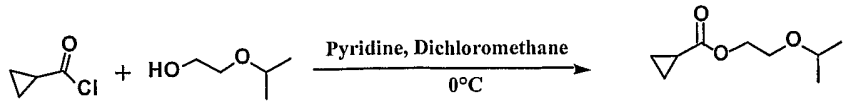
mixture was then transferred to a separatory funnel, washed with 5% sodium bicarbonate (2 x 5 ml), 1:1 hydrochloric acid (2 x 5 ml), and then with brine (5 ml). The dichloromethane layer was separated from the aqueous layer, dried over anhydrous magnesium sulphate, filtered, and evaporated *in vacuo* to give the title product as a pale yellow liquid. Purification was attempted by flash chromatography and vacuum distillation (b.p. = 48°C, 2.8 mm of Hg) which afforded the pure product as a colorless liquid (421.3 mg, 57.7 %).

Characterization was done by NMR (^{1}H and ^{13}C), IR, and mass spectroscopy:

^{1}HNMR (500 MHz, $CDCl_3$) δ 4.18 (m, 2H), 3.58 (m, 2H), 3.48 (q, 2H), 3.14 (m, 1H) 2.2 (m, 4H), 1.9 (m, 2H), 1.17 (t, 3H); MS (ES, M+Na): calculated for $C_9H_{16}O_3Na$ 195.11, found 195.1; IR (CH_2Cl_2) 2976.99, 2949.17, 1732.12, 1444.39, 1175.39 cm^{-1}; ^{13}CNMR (125 MHz, $CDCl_3$) δ 175.33, 68.38, 66.58, 63.51, 38.06, 25.32, 18.47, 15.16.

EXAMPLE 17

Preparation of cyclopropanecarboxylic acid 2-isopropoxy-ethyl ester



Cyclopropanecarboxylic acid 2-isopropoxy-ethyl ester

2-Isopropoxy-ethanol (1.1eq, 5.26 mmol 0.55 g, 0.61 ml) and pyridine (1.1 eq, 5.26 mmol, 0.42 g, 0.43 ml) were taken in a 25 ml round bottom flask and dichloromethane (6 ml) was added. This mixture was cooled to 0°C and then

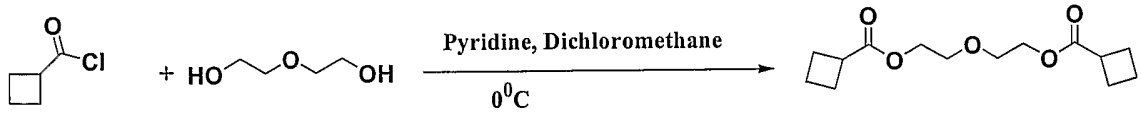
cyclopropanecarbonyl chloride (4.78 mmol, 0.5 g, 0.43 ml) was added in a dropwise fashion maintaining the temperature at 0°C with constant stirring.

An orange-yellow colored solution was observed after sometime. An extra 2 ml of dichoromethane was added to maintain proper stirring (reaction mixture becomes thick). Stirring was continued for 1 hour at 0°C. The reaction was monitored by thin layer chromatography and then quenched with saturated ammonium chloride solution. The mixture was then transferred to a separatory funnel, washed with 5% sodium bicarbonate (2 x 5 ml), 1:1 hydrochloric acid (2 x 5 ml), and then with brine (5 ml). The dichloromethane layer was separated from the aqueous layer, dried over anhydrous magnesium sulphate, filtered, and evaporated *in vacuo* to give the title product as a pale yellowish-orange liquid. Purification was by flash chromatography and vacuum distillation (b.p. = 33°C, 2.9 mm of Hg) which afforded the pure product as a colorless liquid (630.2 mg, 76.40%).

Characterization of the resulting compound was done by ^{1}H and ^{13}C NMR, IR, and mass spectroscopy:
^{1}HNMR (400 MHz, $CDCl_3$) δ 4.2 (m, 2H), 3.6 (m, 3H), 1.65 (m, 1H), 1.15 (d, 6H), 1.0 (m, 2H), 0.85 (m, 2H); IR (CH_2CI_2) 3015.93, 2972.88, 1729.05, 1454.97, 1177.85 cm^{-1}; ^{13}C NMR (125 MHz, $CDCI_3$) δ 174.72, 71.93, 65.95, 64.0, 22.06, 12.92, 8.54; MS (ES, MNa^+): calculated for $C_9H_{16}O_3Na$ 195.09, found 195.0

EXAMPLE 20

Preparation of Cyclobutanecarboxylic acid, 2-(2-cyclobutanecarbonyloxy-ethoxy)-ethyl ester



Diethylene glycol (0.5 eq, 1 mmol, 0.11 g) and pyridine (2.2 eq, 2.2 mmol, 0.174 g, 0.18 ml) were taken in a 10 ml round bottom flask and dichloromethane (4 ml) was added. This mixture was cooled to 0°C and then cyclobutanecarbonyl chloride (2.0 mmol, 0.24 g, 0.23 ml) was added in a dropwise fashion maintaining the temperature at 0°C with constant stirring.

A white thick suspension was observed after sometime. Stirring was continued for 1 hour at 0°C. The reaction was monitored by thin layer chromatography and then quenched with saturated ammonium chloride solution. The mixture was then transferred to a separatory funnel, washed with 5% sodium bicarbonate (2 x 5 ml), 1:1 hydrochloric acid (2 x 5 ml), and then with brine (5 ml). The dichloromethane layer was separated from the aqueous layer, dried over anhydrous magnesium sulphate, filtered, and evaporated *in vacuo* to give the title product as a pale yellowish liquid. Purification was by flash chromatography and vacuum distillation (b.p. = 113°C, 2.8mm of Hg) which afforded the pure product as a colorless liquid (130.0 mg, 46.42 %).

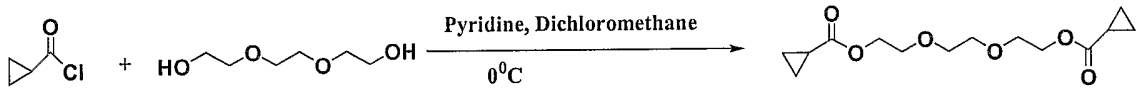
Characterization was done by NMR (^{1}H and ^{13}C), IR, and mass spectroscopy:

^{1}HNMR (500 MHz, $CDCl_3$) δ 4.2 (m, 4H), 3.63 (m, 4H), 3.14(m, 2H), 1.9 - 2.2(m, 12H); MS (ES, M+Na): calculated for $C_{14}H_{22}O_5Na$ 293.15, found 293.0; IR (CH_2Cl_2) 2949.36, 2869.67,

1731.42, 1445.39, 1174.72 cm^{-1}; ^{13}CNMR (125 MHz, $CDCl_3$) δ 175.26, 69.16, 63.32, 63.27, 38.05, 25.33, 18.49.

EXAMPLE 21

Preparation of Cyclopropanecarboxylic acid, 2-[2-(2-cyclopropanecarbonyloxy-ethoxy)-ethoxy]-ethyl ester



Triethylene glycol (1.6 mmol, 0.24 g) and pyridine (2.2 eq, 3.52 mmol, 0.28 g, 0.28 ml) were taken in a 10 ml round bottom flask and dichloromethane (5 ml) was added. This mixture was cooled to 0°C and then cyclopropanecarbonyl chloride (3.4 mmol, 0.36 g, 0.31 ml) was added in a dropwise fashion maintaining the temperature at 0°C with constant stirring.

A white, thick suspension was observed after sometime. Stirring was continued for 1 hour at 0°C. The reaction was monitored by thin layer chromatography and then quenched with saturated ammonium chloride solution. The mixture was then transferred to a separatory funnel, washed with 5% sodium bicarbonate (2 x 5 ml), 1:1 hydrochloric acid (2 x 5 ml), and then with brine (5 ml). The dichloromethane layer was separated from the aqueous layer, dried over anhydrous magnesium sulphate, filtered, and evaporated *in vacuo* to give the title product as a pale yellowish liquid. Purification was by flash chromatography and vacuum

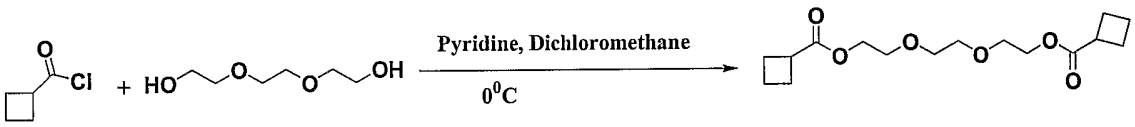
distillation (b.p. = 127°C, 2.8mm of Hg) which afforded the pure product as a colorless liquid (234.5 mg, 50.97 %).

Characterization was done by NMR (^{1}H and ^{13}C), IR, and mass spectroscopy:

^{1}HNMR (500 MHz, $CDCl_3$) δ 4.2 (m, 4H), 3.68 (m, 4H), 3.64(br s, 4H), 1.62(m, 2H), 0.97 (m,4H), 0.84 (m, 4H); MS (ES, M+Na): calculated for $C_{14}H_{22}O_6Na$ 309.14, found 309.0; IR (CH_2Cl_2) 3015.01, 2951.60, 2873.12, 1726.69, 1454.28, 1177.84 cm^{-1}; ^{13}CNMR (125 MHz, $CDCl_3$) δ 175.0, 70.0, 69.0, 63.0, 13.0, 8.0.

EXAMPLE 22

Preparation of Cyclobutanecarboxylic acid, 2-[2-(2-cyclobutanecarbonyloxy-ethoxy)- ethoxy]-ethyl ester



The procedure described in Example 21 was followed using the following amounts of these reagents: triethylene glycol (1.6 mmol, 0.24 g), pyridine (2.2 eq, 3.52 mmol, 0.28 g, 0.28 ml); and cyclobutanecarbonyl chloride (3.4 mmol, 0.40 g, 0.39 ml).

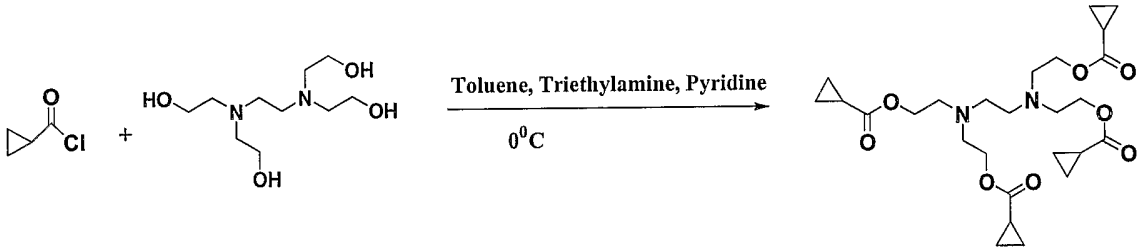
The compound was characterized by NMR (^{1}H and ^{13}C), IR and mass spectroscopy:

^{1}HNMR (500 MHz, $CDCl_3$) δ 4.2 (m, 4H), 3.68 (m, 4H), 3.62(br s, 4H), 3.14(m, 2H), 2.1-2.3 (m,8H), 1.8-2.0 (m, 4H); MS (ES, M+Na): calculated for $C_{16}H_{26}O_6Na$ 337.14, found 337.0; IR (CH_2Cl_2) 2948.71, 2869.27, 1731.17, 1445.80, 1175.60 cm^{-1};

^{13}CNMR (125 MHz, $CDCl_3$) δ 175.29, 70.59, 69.27, 63.39, 38.06, 25.33, 18.49.

EXAMPLE 23

Preparation of Cyclopropanecarboxylic acid 2-[{2-[bis(2-cyclopropanecarbonyloxy-ethyl)-amino]-ethyl}-(2-cyclopropanecarbonyloxy-ethyl)-amino]ethyl ester



A solution of the diamine tetra-ol (1 eq, 4.23 mmol, 1.0 g), pyridine (1.0 eq, 4.23 mmol, 0.33 g, 0.34 ml) and triethylamine (5.0 eq, 0.021 mol, 2.12 g, 2.90 ml) was taken in a 25 ml round bottom flask and toluene (10 ml) was added. This mixture was cooled to 0°C and then cyclopropanecarbonyl chloride (0.019 mol, 1.98 g, 1.72 ml) was added in one shot with vigorous stirring, maintaining the temperature at 0°C.

A yellowish-white thick suspension was observed after sometime. Stirring was continued for 15 minutes at 0°C. The reaction was monitored by thin layer chromatography and then quenched with saturated ammonium chloride solution. The mixture was then transferred to a separatory funnel, and extracted with ethyl acetate (2 x 25 ml). The ethyl acetate layer was washed with brine (1 x 20 ml), dried over anhydrous magnesium sulphate, filtered, and evaporated *in vacuo* to give the title product as a pale yellowish liquid.

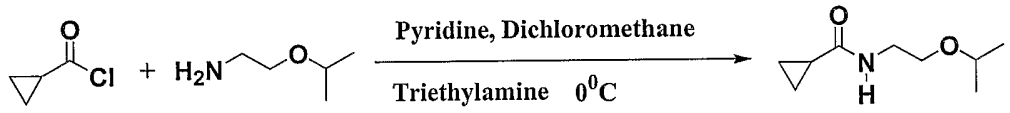
Purification was by flash chromatography which afforded the pure product as a colorless liquid (900.0 mg, 42.0 %).

Characterization was done by NMR (^{1}H and ^{13}C), IR, and mass spectroscopy:

^{1}HNMR (300 MHz, $CDCl_3$) δ 4.13 (t, 8H), 3.3 (m, 3H), 2.82 (t, 8H), 2.68 (s, 4H) 1.64 (m,4H), 0.88 (m, 16H); MS (ES, M+H): calculated for $C_{26}H_{40}N_2O_8$ +H 509.29, found 509.0; IR (CH_2Cl_2) 3014.69, 2958.19, 2826.89, 1725.90, 1452.31, 1173.00 cm^{-1}; ^{13}CNMR (125 MHz, $CDCl_3$) δ 174.59, 62.62, 53.55, 53.29, 12.92, 8.50.

EXAMPLE 24

Preparation of Cyclopropanecarboxylic acid (2-isopropoxy-ethyl)-amide



A solution of the amino ether (1.1 eq, 5.26 mmol, 0.54 g, 0.64 ml), pyridine (0.5 eq, 2.39 mmol, 0.19 g, 0.19 ml), triethylamine (1.1 eq, 5.26 mmol, 0.53 g, 0.73 ml) was taken in a 10 ml round bottom flask and dichloromethane (6 ml) was added. This mixture was cooled to 0°C and then cyclopropanecarbonyl chloride (4.78 mmol, 0.5 g, 0.43 ml) was added in a dropwise fashion, maintaining the temperature at 0°C.

A white precipitate was observed after sometime. Stirring was continued for 30 minutes at 0°C. The reaction was monitored by thin layer chromatography and then quenched with saturated ammonium chloride solution. The mixture was

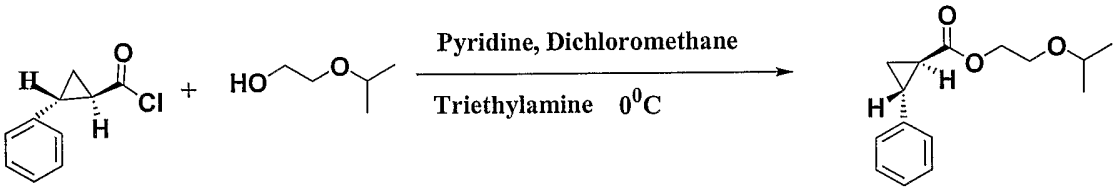
then transferred to a separatory funnel, washed with water (1 x 10 ml), brine (2 x 10 ml), dried over anhydrous magnesium sulphate, filtered, and evaporated *in vacuo* to give the title product as a colorless liquid. Purification was by flash chromatography and vacuum distillation (b.p. =106°C, 1.4 mm of Hg) which afforded the pure product as a colorless liquid (493.8 mg, 60.22 %).

Characterization was done by NMR (^{1}H and ^{13}C), IR, and mass spectroscopy:

^{1}HNMR (300 MHz, $CDCl_3$) δ 6.0 (br s, 1H), 3.57 (m, 1H), 3.44 (m, 4H), 1.32 (m, 1H) 1.14 (d, 6H), 0.94 (m, 2H), 0.7 (m, 2H); MS (EI, M^+): calculated for $C_9H_{17}NO_2$ 171.12, found 171.12; IR (CH_2Cl_2) 3299.39, 3092.61, 2971.98, 2868.14, 1644.61, 1552.31, 1197.34 cm^{-1}; ^{13}CNMR (125 MHz, $CDCl_3$) δ 173.41, 71.76, 66.68, 39.83, 22.10, 14.72, 7.07.

EXAMPLE 25

Preparation of
(±)-trans-2-Phenyl-cyclopropanecarboxylic acid
2-isopropoxy-ethyl ester



2-Isopropoxy-ethanol (1.1 eq, 3.04 mmol, 0.32 g, 0.35 ml), pyridine (0.5 eq, 1.38 mmol, 0.11 g, 0.11 ml), triethylamine (1.1 eq, 3.04 mmol, 0.31 g, 0.43 ml) were taken in a 10 ml round bottom flask and dichloromethane (6 ml) was added. This mixture was cooled to 0°C and then (±)-trans-2-phenyl-cyclopropanecarbonyl chloride (2.76 mmol, 0.5 g, 0.43 ml) was added in a dropwise fashion, maintaining the temperature at 0°C.

A white precipitate was observed after sometime. Stirring was continued for 30 minutes at 0°C. The reaction was monitored by thin layer chromatography and then quenched with saturated ammonium chloride solution. The mixture was then transferred to a separatory funnel, washed with 5% sodium bicarbonate (2 x 5 ml), 1:1 hydrochloric acid (2 x 5 ml), and then with brine (5 ml). The dichloromethane layer was separated from the aqueous layer, dried over anhydrous magnesium sulphate, filtered, and evaporated *in vacuo* to give the title product as a pale yellowish liquid. Purification was by flash chromatography which afforded the pure product as a colorless liquid (450.0 mg, 65.0 %). The

above compound is racemic as determined by chiral HPLC (chiralcel OJ column) 2% Isopropanol in hexane. UV λ_{max} = 278 nm (flow = 1 ml/ min).

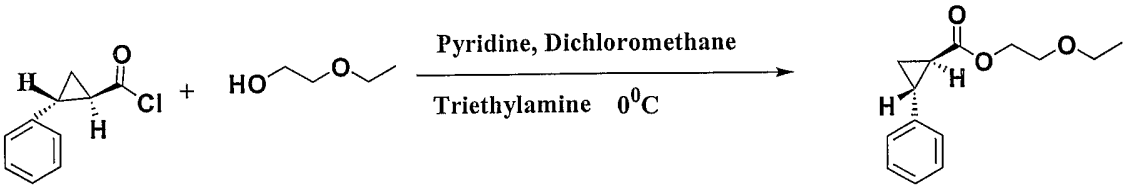
Characterization was done by NMR (^1H and ^{13}C), IR, and mass spectroscopy:

^{1}HNMR (300 MHz, $CDCl_3$) δ 7.07- 7.27 (m, 5H), 4.22 (m, 2H), 3.61 (m, 3H), 2.51 (m, 1H) 1.93 (m, 1H), 1.58 (m, 1H), 1.26 (m, 1H), 1.53 (d, 6H); MS (EI, M^+): calculated for $C_{15}H_{20}O_3$ 248.14, found 248.14; IR (CH_2Cl_2) 3063.09, 3030.28, 2971.95, 2867.20, 1727.02, 1151.71 cm^{-1}; ^{13}CNMR (125 MHz, $CDCl_3$) δ 173.27, 139.92, 128.36,126.39, 126.10, 72.01, 65.94, 64.33, 26.44, 24.17, 22.10, 17.26.

EXAMPLE 26

Preparation of (±)-trans-2-Phenyl-cyclopropanecarboxylic acid 2

MM079 **(±) - trans-2-Phenyl-cyclopropanecarboxylic acid 2-ethoxy-ethyl ester**



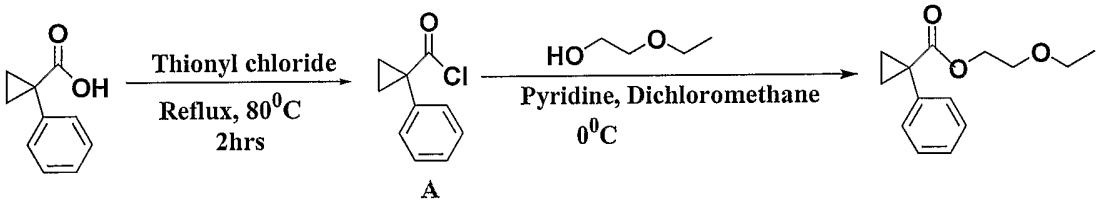
This compound was prepared using the procedure described in Example 25 and using the following reagents: 2-ethoxy-ethanol (1.1 eq, 3.05 mmol, 0.27 g, 0.30 ml) pyridine (0.5 eq, 1.39 mmol, 0.11 g, 0.11 ml), triethylamine (1.1 eq, 3.05 mmol, 0.31 g, 0.43 ml); and (±)-trans-2-phenyl- cyclopropanecarbonyl chloride (2.77 mmol, 0.5 g, 0.43 ml).

The compound was characterized by NMR (^{1}H and ^{13}C), IR and mass spectroscopy:

^{1}HNMR (300 MHz, $CDCl_3$) δ 7.06- 7.28 (m, 5H), 4.24 (m, 2H), 3.62 (m, 2H), 3.52 (q, 2H) 2.51 (m, 1H), 1.94 (m, 1H), 1.58 (m, 1H), 1.29 (m, 1H), 1.19 (t, 3H); MS (EI, M^+): calculated for $C_{14}H_{18}O_3$ 234.12, found 234.12; IR (CH_2Cl_2) 2975.07, 2868.63, 1726.37, 1175.66 cm^{-1}; ^{13}CNMR (125 MHz, $CDCl_3$) δ 173.26, 139.90, 128.37,126.40, 126.08, 68.36, 66.65, 64.04, 26.48, 24.13, 17.35, 15.2

EXAMPLE 27

Preparation of 1-Phenyl-cyclopropanecarboxylic acid 2-ethoxy-ethyl ester



1-Phenyl-cyclopropanecarboxylic acid (0.5 g, 3.1 mmol), was dissolved in thionyl chloride (10 eq, 0.031 mol, 3.68 g, 2.3 ml), and refluxed at 80°C for 1.5 hours. Then excess of thionyl chloride was evaporated on the rotary evaporator which yielded a dark- yellowish liquid (1-phenyl-cyclopropanecarbonyl chloride **A**), which was then cooled to 0°C, under argon.

2-Ethoxy-ethanol (1.1 eq, 3.41 mmol, 0.31 g, 0.33 ml) and pyridine (1.2 eq, 3.41 mmol, 0.27g, 0.28 ml) was taken in a 25 ml round bottom flask and dichloromethane (10 ml) was added. This mixture was cooled to 0°C and then **A** was

added in a dropwise fashion maintaining the temperature at 0°C. Stirring was continued for 30 minutes at 0°C. The reaction was monitored by thin layer chromatography and then quenched with saturated ammonium chloride solution. The mixture was then transferred to a separatory funnel, washed with 5% sodium bicarbonate (2 x 5 ml), 1:1 hydrochloric acid (2 x 5 ml), and then with brine (5 ml). The dichloromethane layer was separated from the aqueous layer, dried over anhydrous magnesium sulphate, filtered, and evaporated *in vacuo* to give the title product as a pale yellowish liquid. Purification was by flash chromatography and vacuum distillation (b.p. = 93°C, 2.4 mm of Hg), which afforded the pure product as a colorless liquid (437.7 mg, 60.62%)

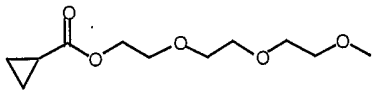
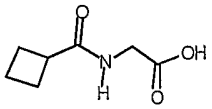
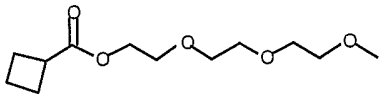
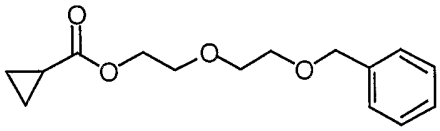
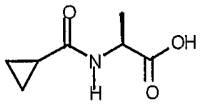
Characterization was done by NMR (^{1}H and ^{13}C), IR, and mass spectroscopy:

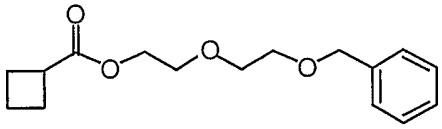
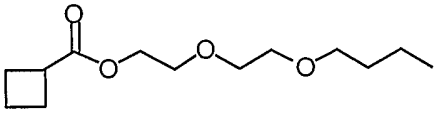
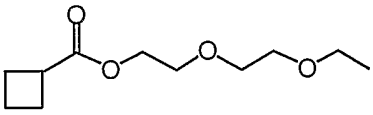
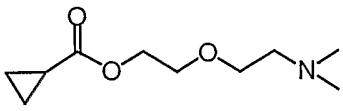
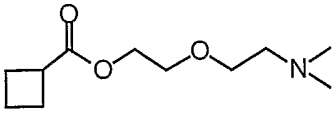
^{1}HNMR (300 MHz, $CDCl_3$) δ 7.2- 7.35 (m, 5H), 4.14 (m, 2H), 3.51 (m, 2H), 3.35 (q, 2H) 1.60 (dd, 2H), 1.18 (dd, 2H), 1.1 (t, 3H); MS (EI, M^+): calculated for $C_{14}H_{18}O_3$ 234.12, found 234.12; IR (CH_2Cl_2) 2958.04, 2837.41, 1676.09, 1600.65, 1288.07 cm^{-1}; ^{13}CNMR (125 MHz, $CDCl_3$) δ 174.28, 139.40, 130.41, 127.97, 127.00, 68.11, 66.57, 64.43, 29.19, 16.59, 15.23.

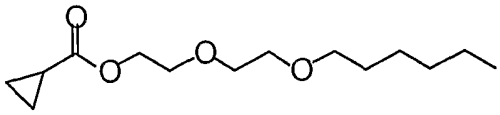
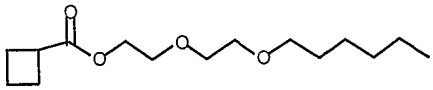
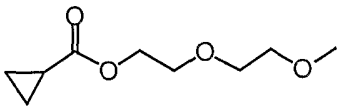
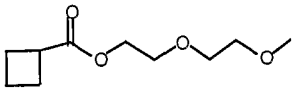
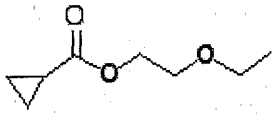
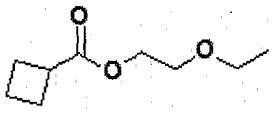
Note:

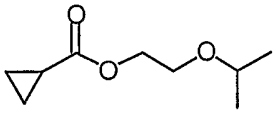
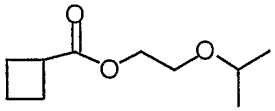
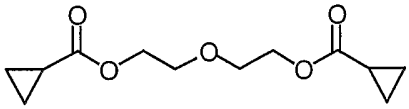
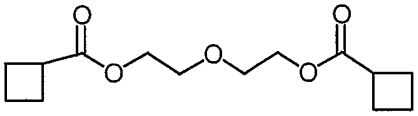
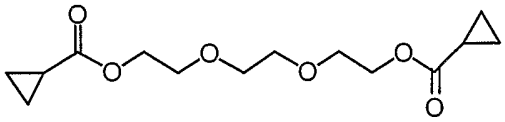
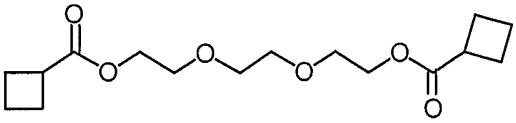
For the compounds of Examples 1 to 27, the solvent system used for flash chromatography was ethyl acetate/hexane, unless otherwise specified.

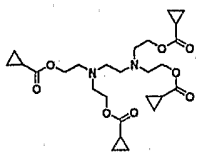
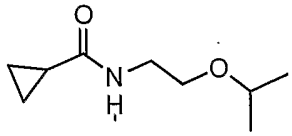
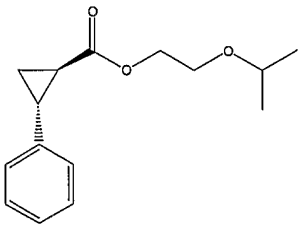
TABLE 1

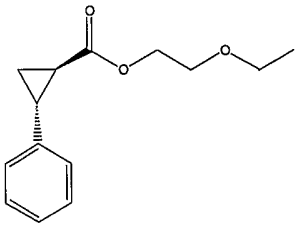
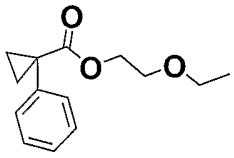
Example	Compound	Molecular Weight	Starting Carbonyl Chloride	Starting R'-YH compound
1 MM054	 Cyclopropanecarboxylic acid 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester	232.28	P*	2-[2-(2-Methoxy-ethoxy)-ethoxy]-ethanol
2 MM055	 (Cyclobutanecarbonyl-amino)-acetic acid	157.17	B**	Methyl ester glycine hydrochloride (Amino Acid)
3 MM056	 Cyclobutanecarboxylic acid 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester	246.31	B	2-[2-(2-Methoxy-ethoxy)-ethoxy]-ethanol
4 MM057	 Cyclopropanecarboxylic acid 2-(2-benzyloxy-ethoxy)-ethyl ester	264.31	P	2-(2-Benzyloxy-ethoxy)-ethanol
5 MM058	 2-(Cyclopropanecarbonyl-amino)-propionic acid	157.17	P	Methyl ester alanine hydrochloride (Amino Acid)

6 MM059	 Cyclobutanecarboxylic acid 2-(2-benzyloxy-ethoxy)-ethyl ester	278.34	B	2-(2-Benzyloxy-ethoxy)-ethanol
7 MM060	 Cyclobutanecarboxylic acid, 2-(2-butoxy-ethoxy)-ethyl ester	244.32	B	2-(2-Butoxy-ethoxy)-ethanol
8 MM061	 Cyclobutanecarboxylic acid, 2-(2-ethoxy-ethoxy)-ethyl ester	216.27	B	2-(2-ethoxy-ethoxy)-ethanol
9 MM062	 Cyclopropanecarboxylic acid 2-(2-dimethylamino-ethoxy)-ethyl ester	201.26	P	2-(2-dimethylamino-ethoxy)-ethanol
10 MM063	 Cyclobutanecarboxylic acid 2-(2-dimethylamino-ethoxy)-ethyl ester	215.29	B	2-(2-dimethylamino-ethoxy)-ethanol

11 MM064	 Cyclopropanecarboxylic acid 2-(2-hexyloxy-ethoxy)-ethyl ester	258.35	P	2-(2-hexyloxy-ethoxy)-ethanol
12 MM065	 Cyclobutanecarboxylic acid 2-(2-hexyloxy-ethoxy)-ethyl ester	272.39	B	2-(2-hexyloxy-ethoxy)-ethanol
13 MM066	 Cyclopropanecarboxylic acid 2-(2-methoxy-ethoxy)-ethyl ester	188.23	P	2-(2-methoxy-ethoxy)-ethanol
14 MM067	 Cyclobutanecarboxylic acid 2-(2-methoxy-ethoxy)-ethyl ester	202.25	B	2-(2-methoxy-ethoxy)-ethanol
15 MM068	 Cyclopropanecarboxylic acid 2-ethoxy-ethyl ester	158.20	P	2-ethoxy-ethanol
16 MM069	 Cyclobutanecarboxylic acid 2-ethoxy-ethyl ester	172.23	B	2-ethoxy-ethanol

17 MM070	 Cyclopropanecarboxylic acid 2-isopropoxy-ethyl ester	172.23	P	2-Isopropoxy-ethanol
18 MM071	 Cyclobutanecarboxylic acid 2-isopropoxy-ethyl ester	186.25	B	2-Isopropoxy-ethanol
19 MM072	 Cyclopropanecarboxylic acid, 2-(2-cyclopropanecarbonyloxy-ethoxy)-ethyl ester	242.27	P	2-(2-Hydroxy-ethoxy)-ethanol
20 MM073	 Cyclobutanecarboxylic acid, 2-(2-cyclobutanecarbonyloxy-ethoxy)-ethyl ester	270.32	B	2-(2-Hydroxy-ethoxy)-ethanol
21 MM074	 Cyclopropanecarboxylic acid,2-[2-(2-cyclopropanecarbonyloxy-ethoxy)-ethoxy}ethyl ester	286.32	P	2-[2-(2-Hydroxy-ethoxy)-ethoxy]-ethanol
22 MM075	 Cyclobutanecarboxylic acid,2-[2-(2-cyclobutanecarbonyloxy-ethoxy)-ethoxy}ethyl ester	314.37	B	2-[2-(2-Hydroxy-ethoxy)-ethoxy]-ethanol

23 MM076	 Cyclopropanecarboxylic acid 2-[{2-[bis(2-cyclopropanecarbonyloxy-ethyl)-amino]-ethyl}-(2-cyclopropanecarbonyloxy-ethyl)-amino] ethyl ester	508.60	P	N,N,N',N'-Tetrakis(2-hydroxyethyl) ethyl-enediamine
24 MM077	 Cyclopropanecarboxylic acid (2-isopropoxy-ethyl)-amide	171.24	P	2-Aminoethyl isopropyl ether
25 MM078	 trans-2-Phenyl-cyclopropanecarboxylic acid 2-isopropoxy-ethyl ester	248.32	trans-2-phenyl-cyclopro-panecar-bonyl chloride	2-Isopropoxy-ethanol

26 MM079	 trans-2-Phenyl-cyclopropanecarboxylic acid 2-ethoxy-ethyl ester	234.29	trans-2-phenyl-cyclopro-panecar-bonyl chloride	2-ethoxy-ethanol
27 MM080	 1-Phenyl-cyclopropanecarboxylic acid 2-ethoxy-ethyl ester	234.29	1-phenyl-cyclo-propane-carbonyl chloride	2-ethoxy-ethanol

a. P* Cyclopropanecarbonyl chloride

b. B** Cyclobutanecarbonyl chloride

EXAMPLE A

Glucose oxidation stimulation in untreated myocardium cells and myocardium cells treated with cyclopropanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester.

Rat hearts were cannulated for isolated working heart 60 min aerobic perfusions as described in *J Pharmacol Exp Ther* . 1993; 264:135 -144, the entire disclosure of which is incorporated herein by reference.

Male Sprague-Dawley rats (0.3-0.35 kg) were anesthetized with pentobarbital sodium (60 mg/kg IP) and hearts were quickly excised, the aorta was cannulated and a

retrograde perfusion at 37°C was initiated at a hydrostatic pressure of 60 mm Hg. Hearts were trimmed of excess tissue, and the pulmonary artery and the opening to the left atrium were then cannulated. After 15 min of Langendorff perfusion, hearts were switched to the working mode by clamping the aortic inflow line from the Langendorff reservoir and opening the left atrial inflow line. The perfusate was delivered from an oxygenator into the left atrium at a constant preload pressure of 11 mm Hg. Perfusate was ejected from spontaneously beating hearts into a compliance chamber (containing 1 ml of air) and into the aortic outflow line. The afterload was set at a hydrostatic pressure of 80 mm Hg. All working hearts were perfused with Krebs'-Henseleit solution containing calcium 2.5 mmol/L, glucose 5.5 mmol/L, 3% bovine serum albumin (fatty acid free, initial fractionation by heat shock, Sigma), and with 1.2 mmol/L palmitate. Palmitate was bound to the albumin as described in *J Bio Chem.* 1992; 267:3825-3831, the entire disclosure of which is incorporated herein by reference.

The perfusate was recirculated, and pH was adjusted to 7.4 by bubbling with a mixture containing 95% O_2 and 5% CO_2.

Spontaneously beating hearts were used in all perfusions. Heart rate and aortic pressure were measured with a Biopac Systems Inc. blood pressure transducer connected to the aortic outflow line. Cardiac output and aortic flow were measured with Transonic T206 ultrasonic flow probes in the preload and afterload lines, respectively. Coronary flow was calculated as the difference between cardiac output and aortic flow. Cardiac work was calculated as the product of systolic pressure and cardiac output.

Measurement of Glucose Oxidation : Glucose oxidation was measured simultaneously by perf using hearts with [U -^{14}C] glucose according to the procedures discussed in Saddik M, et al., *J Bio Chem.* 1992; 267:3825 -3831. The entire disclosure of this reference is incorporated herein by reference. The total myocardial $^{14}CO_2$ production was determined at 10 -min intervals from the 60 -min aerobic period. Glucose oxidation rates were determined by quantitative measurement of $^{14}CO_2$ production as described in Barbour RL, et al.,. *Biochemistry.* 1984; 1923:6503 -6062. The entire disclosure of this referenc e is incorporated herein by reference. $^{14}CO_2$ production for the control group were compared with the $^{14}CO_2$ production for the group treated with cyclopropanecarboxylic acid, 2 -[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester. Results are shown on Figure 1 and TABLE 2.

EXAMPLE B

(1) Glucose oxidation stimulation in myocardium cells treated with cyclobutanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester.

The procedure of Example A for was followed except that cyclobutanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester in 1 µM, 10 µM, 100 µM and 1000 µM amounts was added to the buffer in place of the cyclopropanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester. The results are illustrated in Figure 2 and TABLE 2.

(2) Glucose oxidation stimulation in myocardium cells treated with cyclopropanecarboxylic acid, 2-isopropoxy ethyl ester.

The procedure of Example A was followed except that cyclopropanecarboxylic acid, 2-isopropoxy-ethyl ester in 1 μM, 10 μM, 100 μM and 1000 μM amounts was added to the buffer in place of the cyclopropanecarboxylic acid, 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester. The results are illustrated in Figure 3 and TABLE 2.

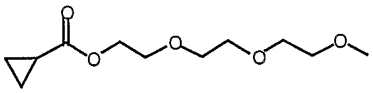
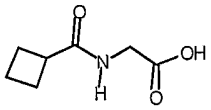
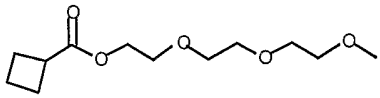
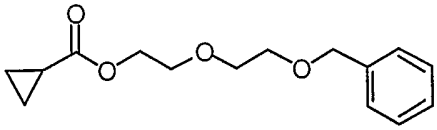
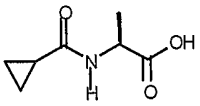
(3) Glucose oxidation stimulation in myocardium cells treated with various cyclopropanecarboxylic acid and cyclobutanecarboxylic acid derivatives.

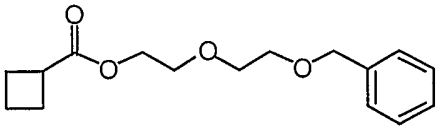
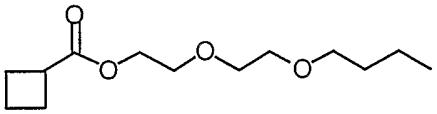
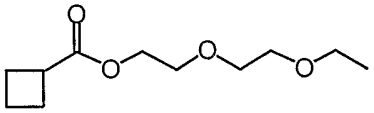
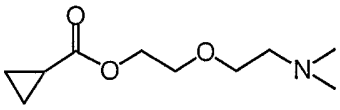
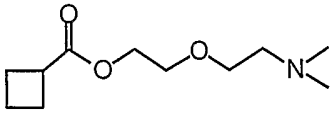
The procedure of Example A was followed except that various cyclobutanecarboxylic acid derivatives, cyclopropanecarboxylic acid derivatives and cyclobutanecarboxylic acid in the amounts of 100 μM or 1000 μM was added to the buffer in place of the cyclopropanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester. The results are illustrated in TABLE 2.

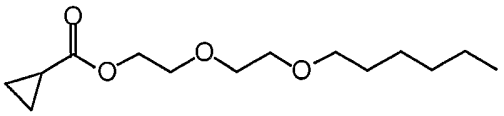
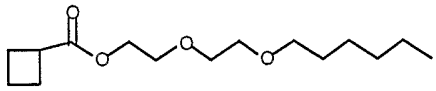
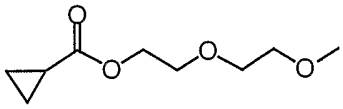
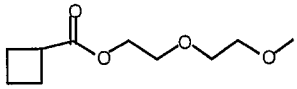
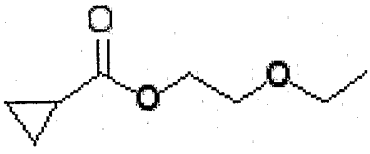
(4) Glucose oxidation stimulation in myocardium cells treated with cyclopropanecarboxylic acid.

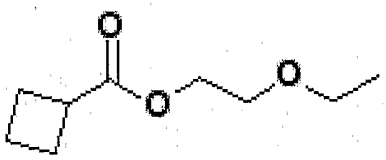
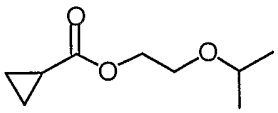
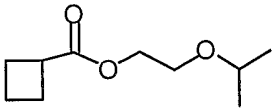
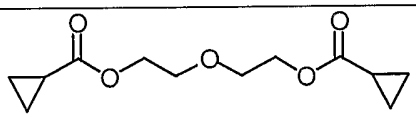
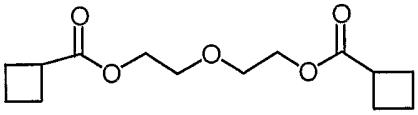
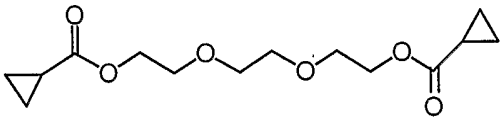
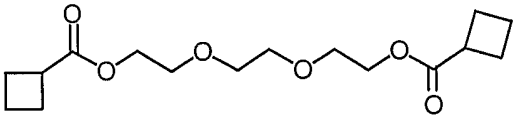
The procedure of Example A was followed except that cyclobutanecarboxylic acid the amounts of 0.001 μM, 0.01 μM, 01 μM, 1 μM, 10 μM, and 100 μM was added to the buffer in place of the cyclopropanecarboxylic acid, 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester. The results are illustrated in Figure 4 and TABLE 2.

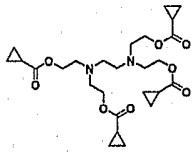
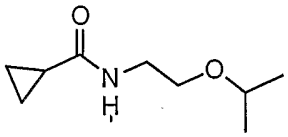
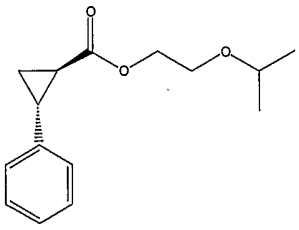
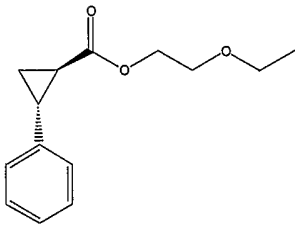
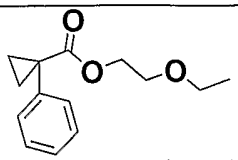
TABLE 2.

Compound of Example No.	Compound	Screening Concentration (μM)	Glucose Oxidation (% above control)
1 MM054	 Cyclopropanecarboxylic acid 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester	100	102%
2 MM055	 (Cyclobutanecarbonyl-amino)-acetic acid	1000 μM	58%
3 MM056.	 Cyclobutanecarboxylic acid 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester	100 μM	54%
4 MM057	 Cyclopropanecarboxylic acid 2-(2-benzyloxy-ethoxy)-ethyl ester	100 μM	104%
5 MM058	 2-(Cyclopropanecarbonyl-amino)-propionic acid	1000 μM	40%

6 MM059	 Cyclobutanecarboxylic acid 2-(2-benzyloxy-ethoxy)-ethyl ester	100 µM	68%
7 MM060	 Cyclobutanecarboxylic acid, 2-(2-butoxy-ethoxy)-ethyl ester	100 µM	65%
8 MM061	 Cyclobutanecarboxylic acid, 2-(2-ethoxy-ethoxy)-ethyl ester	Not screened	
9 MM062	 Cyclopropanecarboxylic acid 2-(2-dimethylamino-ethoxy)-ethyl ester	100 µM	77%
10 MM063	 Cyclobutanecarboxylic acid 2-(2-dimethylamino-ethoxy)-ethyl ester	100 µM	41%

11 MM064	 Cyclopropanecarboxylic acid 2-(2-hexyloxy-ethoxy)-ethyl ester	100 µM	83%
12 MM065	 Cyclobutanecarboxylic acid 2-(2-hexyloxy-ethoxy)-ethyl ester	100 µM	0%
13 MM066	 Cyclopropanecarboxylic acid 2-(2-methoxy-ethoxy)-ethyl ester	100 µM	20%
14 MM067	 Cyclobutanecarboxylic acid 2-(2-methoxy-ethoxy)-ethyl ester	100 µM	50%
15 MM068	 Cyclopropanecarboxylic acid 2-ethoxy-ethyl ester	100 µM	416%

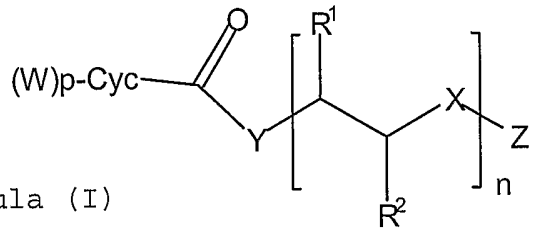
16 MM069	 Cyclobutanecarboxylic acid 2-ethoxy-ethyl ester	100 µM	162%
17 MM070	 Cyclopropanecarboxylic acid 2-isopropoxy-ethyl ester	100 µM	208%
18 MM071	 Cyclobutanecarboxylic acid 2-isopropoxy-ethyl ester	100 µM	97%
19 MM072	 Cyclopropanecarboxylic acid, 2-(2-cyclopropanecarbonyloxy-ethoxy)-ethyl ester	100 µM	97%
20 MM073	 Cyclobutanecarboxylic acid, 2-(2-cyclobutanecarbonyloxy-ethoxy)-ethyl ester	100 µM	243%
21 MM074	 Cyclopropanecarboxylic acid,2-[2-(2-cyclopropanecarbonyloxy-ethoxy)-ethoxy]-ethyl ester	100 µM	228%
22 MM075	 Cyclobutanecarboxylic acid,2-[2-(2--cyclobutanecarbonyloxy-ethoxy)-ethoxy]-ethyl ester	100 µM	184%

23 MM076	 Cyclopropanecarboxylic acid 2-[{2-[bis(2-cyclopropanecarbonyloxy-ethyl)-amino]-ethyl}-(2-cyclopropanecarbonyloxy-ethyl)-amino] ethyl ester	100 µM	274%
24 MM077	 Cyclopropanecarboxylic acid (2-isopropoxy-ethyl)-amide	100 µM	217%
25 MM078	 trans-2-Phenyl-cyclopropanecarboxylic acid 2-isopropoxy-ethyl ester	100 µM	200%
26 MM079	 trans-2-Phenyl-cyclopropanecarboxylic acid 2-ethoxy-ethyl ester	not screened	
27 MM080	 1-Phenyl-cyclopropanecarboxylic acid 2-ethoxy-ethyl ester	not screened	

A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A compound represented by Formula (I):



Formula (I)

wherein

W is C_1-C_6 alkyl, halogen, or aryl;

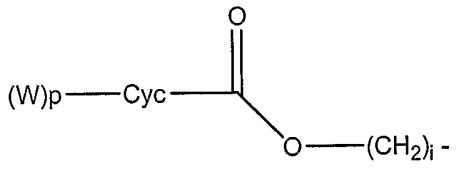
Cyc is C_3 or C_4 cycloalkyl;

p is an integer from 0 to 3 when Cyc is C_4 cycloalkyl, or p is an integer from 0 to 2 when Cyc is C_3 cycloalkyl;

Y is O, S, or NR;

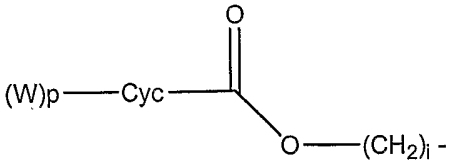
X is O, S, NR, or CR^3R^4;

R is H, alkyl, aryl, or

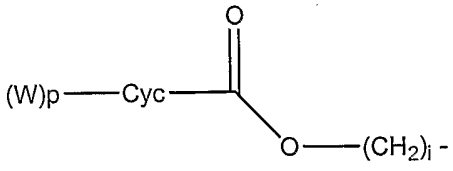


where i is an integer from 2 to 4;

Z is H, alkyl, cycloalkyl, aryl or (cyclo)alkylcarbonyl or



if X is NR and R is



;

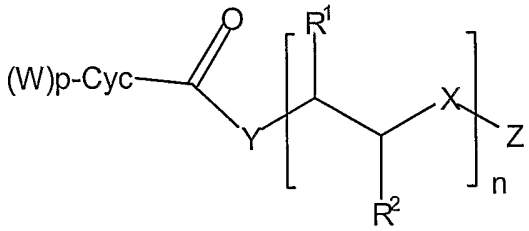
R^1 is H, alkyl, aryl or O;

R^2 is H, alkyl or aryl;

R^3 and R^4 are, independently, H, alkyl or aryl; and

n is an integer from 1 to 10; or a pharmaceutically acceptable salt, ester or prodrug thereof.

2. A compound according to claim 1 represented by Formula (Ia):



Formula (Ia)

wherein

W is C_1-C_6 alkyl, halogen, or aryl;

Cyc is C_3 or C_4 cycloalkyl;

p is an integer from 0 to 3 when Cyc is C_4 cycloalkyl, or p is an integer from 0 to 2 when Cyc is C_3 cycloalkyl;

Y is O, S, or NR;

X is O, S, NR, or CR^3R^4;

R is H, alkyl or aryl;

Z is H, alkyl, cycloalkyl, aryl or (cyclo)alkylcarbonyl;

R^1 is H, alkyl, aryl or O;

R^2 is H, alkyl or aryl;

R^3 and R^4 are, independently, H, alkyl or aryl; and

n is an integer from 1 to 10; or a pharmaceutically acceptable salt, ester or prodrug thereof.

3. The compound according to claim 1, wherein p is 0.

4. The compound according to claim 3, wherein Y is O;

X is NR or O;

R^1, R^2, R^3 and R^4 are H;

n is 1 to 4; and

Z is lower alkyl, cycloalkyl or phenyl.

5. The compound according to claim 3, wherein Y is NR;

X is O;

R^1, R^2, R^3 and R^4 are H;

n is 1 or 2; and

Z is H.

6. The compound according to claim 3, wherein said compound is selected from

cyclopropanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester;

cyclobutanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester;

(cyclobutanecarbonyl-amino)-acetic acid;

cyclopropanecarboxylic acid 2-(2-benzyloxy-ethoxy)-ethyl ester;

2-(cyclopropanecarbonyl-amino)-propionic acid;

cyclobutanecarboxylic acid 2-(2-benzyloxy-ethoxy)-ethyl ester;

cyclobutanecarboxylic acid, 2-(2-butoxy-ethoxy)-ethyl ester;

cyclobutanecarboxylic acid, 2-(2-ethoxy-ethoxy)-ethyl ester;

cyclopropanecarboxylic acid 2-(2-dimethylamino-ethoxy)-ethyl ester;

cyclobutanecarboxylic acid 2-(2-dimethylamino-ethoxy)-ethyl ester;

cyclopropanecarboxylic acid 2-(2-hexyloxy-ethoxy)-ethyl ester;

cyclobutanecarboxylic acid 2-(2-hexyloxy-ethoxy)-ethyl ester;

cyclopropanecarboxylic acid 2-(2-methoxy-ethoxy)-ethyl ester;

cyclobutanecarboxylic acid 2-(2-methoxy-ethoxy)-ethyl ester;

cyclopropanecarboxylic acid 2-ethoxy-ethyl ester;

cyclobutanecarboxylic acid 2-ethoxy-ethyl ester;

cyclopropanecarboxylic acid 2-isopropoxy-ethyl ester;

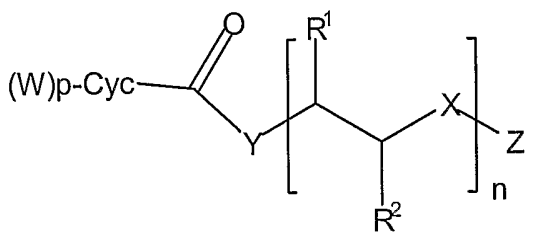
cyclobutanecarboxylic acid 2-isopropoxy-ethyl ester;

cyclopropanecarboxylic acid, 2-(2-cyclopropanecarbonyloxy-ethoxy)-ethyl ester;

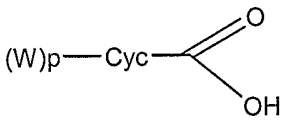
cyclopropanecarboxylic acid, 2-[2-(2-cyclopropanecarbonyloxy-ethoxy)-ethoxy]-ethyl ester; and

cyclobutanecarboxylic acid, 2-[2-(2-cyclobutanecarbonyloxy-ethoxy)-ethoxy]-ethyl ester.

7. A pharmaceutical composition comprising at least one compound represented by Formula (I), or Formula (II):



Formula (I)



Formula (II)

wherein

W is C_1-C_6 alkyl, halogen, or aryl;

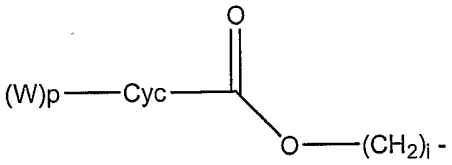
Cyc is C_3 or C_4 cycloalkyl;

p is an integer from 0 to 3 when Cyc is C_4 cycloalkyl, or p is 0 to 2 when Cyc is C_3 cycloalkyl;

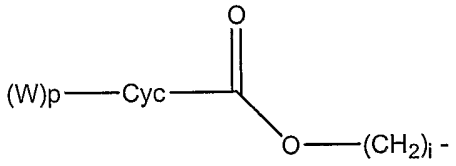
Y is O, S, or NR;

X is O, S, NR, or CR^3R^4;

Z is H, alkyl, cycloalkyl, aryl or (cyclo)alkylcarbonyl or

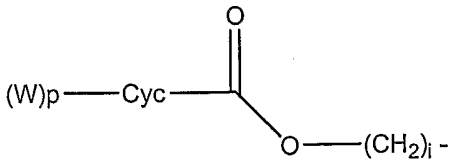


if X is NR and R is



;

R is H, alkyl, aryl, or



where i is an integer from 2 to 4;

R^1 is H, alkyl, aryl or O;

R^2 is H, alkyl or aryl;

R^3 and R^4 are, independently, H, alkyl or aryl; and

n is an integer from 1 to 10; or a pharmaceutically acceptable salt, ester or prodrug thereof; and

a pharmaceutically acceptable carrier, diluent, excipient or mixtures thereof.

8. A pharmaceutical composition according to claim 7, wherein said compound is represented by Formula (I), and wherein

p is 0;

Y is O;

X is NR or O;

R^1, R^2, R^3 and R^4 are H;

n is 1 to 4; and

Z is lower alkyl, cycloalkyl or phenyl.

9. A pharmaceutical composition according to claim 7, wherein said compound is represented by the Formula (I), and wherein

p is 0;

Y is NR;

X is O;

R^1, R^2, R^3 and R^4 are H;

n is 1 or 2; and

Z is H.

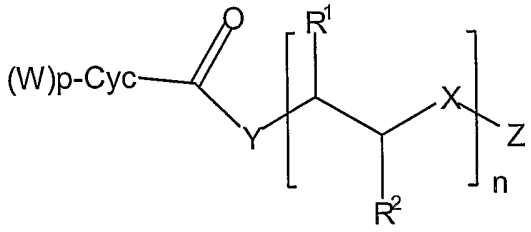
10. A pharmaceutical composition according to claim 7, wherein said compound is represented by the Formula (II), wherein p is 0.

11. A pharmaceutical composition according to claim 7, wherein said composition is in the form of tablets, pills, capsules, aqueous solutions, or sterile suspensions or solutions.

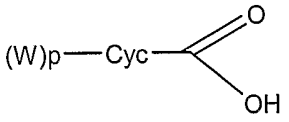
12. A pharmaceutical composition according to claim 7, wherein said at least one compound is selected from the group consisting of cyclopropanecarboxylic acid; cyclobutanecarboxylic acid; cyclopropanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester; cyclobutanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester; (cyclobutanecarbonyl-amino)-acetic acid; cyclopropanecarboxylic acid, 2-(2-benzyloxy-ethoxy)-ethyl ester; 2-(cyclopropanecarbonyl-amino)-propionic acid; cyclobutanecarboxylic acid 2-(2-benzyloxy-ethoxy)-ethyl ester; cyclobutanecarboxylic acid 2-(2-butoxy-ethoxy)-ethyl ester; cyclobutanecarboxylic acid 2-(2-ethoxy-ethoxy)-ethyl ester; cyclopropanecarboxylic acid 2-(2-dimethylamino-ethoxy)-ethyl ester; cyclobutanecarboxylic acid 2-(2-dimethylamino-ethoxy)-ethyl ester; cyclopropanecarboxylic acid 2-(2-hexyloxy-ethoxy)-ethyl ester; cyclobutanecarboxylic acid 2-(2-hexyloxy-ethoxy)-ethyl ester; cyclopropanecarboxylic acid 2-(2-methoxy-ethoxy)-ethyl ester; cyclobutanecarboxylic acid 2-(2-methoxy-ethoxy)-ethyl ester; cyclopropanecarboxylic acid 2-ethoxy-ethyl ester; cyclobutanecarboxylic acid 2-ethoxy-ethyl ester; cyclopropanecarboxylic acid 2-isopropoxy-ethyl ester; cyclobutanecarboxylic acid 2-isopropoxy-ethyl ester; cyclopropanecarboxylic acid, 2-(2-cyclopropanecarbonyloxy-ethoxy)-ethyl ester; cyclopropanecarboxylic acid, 2-[2-(2-

cyclopropanecarbonyloxy-ethoxy)-ethoxy]-ethyl ester; and cyclobutanecarboxylic acid, 2-[2-(2-cyclobutanecarbonyloxy-ethoxy)-ethoxy]-ethyl ester.

13. A method for increasing glucose utilization in a cell, tissue or organ of a warm blooded animal comprising treating said cell, tissue or organ with glucose utilization effective amount of at least one compound represented by Formula (I) or Formula (II)



Formula (I)



Formula (II)

wherein

W is C_1-C_6 alkyl, halogen, or aryl;

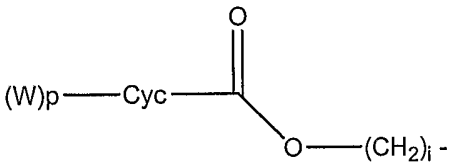
Cyc is C_3 or C_4 cycloalkyl;

p is an integer from 0 to 3 when Cyc is C_4 cycloalkyl, or p is an integer from 0 to 2 when Cyc is C_3 cycloalkyl;

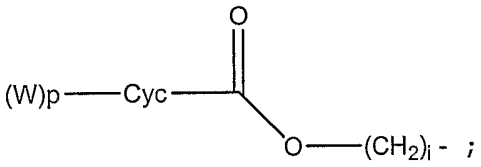
Y is O, S, or NR;

X is O, S, NR, or CR^3R^4;

Z is H, alkyl, cycloalkyl, aryl or (cyclo)alkylcarbonyl or

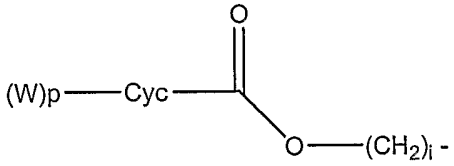


if X is NR and R is



;

R is H, alkyl, aryl or



where i is an integer from 2 to 4;

R^1 is H, alkyl, aryl or O;

R^2 is H, alkyl or aryl;

R^3 and R^4 are, independently, H, alkyl or aryl; and

n is an integer from 1 to 10; or a pharmaceutically acceptable salt, ester or prodrug thereof.

14. A method according to claim 13, wherein said compound is represented by Formula (I), and wherein p=0;

Y is O;

X is NR or O;

R^1, R^2, R^3 and R^4 are H;

n is 1-4; and

Z is lower alkyl, cycloalkyl or phenyl.

15. The method as claimed in claim 13, wherein said compound is represented by Formula (I), and wherein p=0;

Y is NR;

X is O;

R^1, R^2, R^3 and R^4 are H;

n is 1 or 2; and

Z is H.

16. A method according to claim 13, wherein said compound is represented by Formula (II), wherein p is 0.

17. A method according to claim 13, wherein said organ is heart.

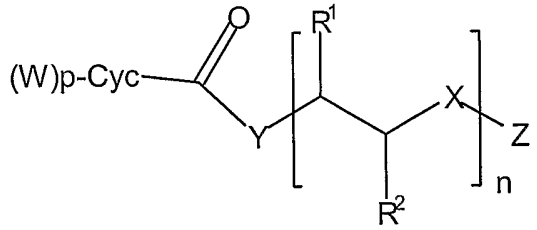
18. A method according to claim 13, wherein said cell is a myocardial cells.

19. The method according to claim 13, wherein said at least one compound is selected from the group consisting of cyclopropanecarboxylic acid; cyclobutanecarboxylic acid; cyclopropanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester; cyclobutanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester; (cyclobutanecarbonyl-amino)-acetic acid; cyclopropanecarboxylic acid, 2-(2-benzyloxy-ethoxy)-ethyl ester; 2-(cyclopropanecarbonyl-amino)-propionic acid; cyclobutanecarboxylic acid 2-(2-benzyloxy-ethoxy)-ethyl ester; cyclobutanecarboxylic acid 2-(2-butoxy-ethoxy)-ethyl ester; cyclobutanecarboxylic acid 2-(2-ethoxy-ethoxy)-ethyl ester; cyclopropanecarboxylic acid 2-(2-dimethylamino-ethoxy)-ethyl ester; cyclobutanecarboxylic acid 2-(2-dimethylamino-ethoxy)-ethyl ester; cyclopropanecarboxylic acid 2-(2-hexyloxy-ethoxy)-ethyl ester; cyclobutanecarboxylic acid 2-(2-

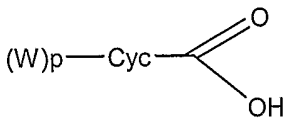
hexyloxy-ethoxy)-ethyl ester; cyclopropanecarboxylic acid 2-(2-methoxy-ethoxy)-ethyl ester; cyclobutanecarboxylic acid (2-methoxy-ethoxy)-ethyl ester; cyclopropanecarboxylic acid 2-ethoxy-ethyl ester; cyclobutanecarboxylic acid 2-ethoxy-ethyl ester; cyclopropanecarboxylic acid 2-isopropoxy-ethyl ester; cyclobutanecarboxylic acid 2-isopropoxy-ethyl ester; cyclopropanecarboxylic acid, 2-(2-cyclopropanecarbonyloxy-ethoxy)-ethyl ester; cyclopropanecarboxylic acid, 2-[2-(2-cyclopropanecarbonyloxy-ethoxy)-ethoxy]-ethyl ester; and cyclobutanecarboxylic acid, 2-[2-(2-cyclobutanecarbonyloxy-ethoxy)-ethoxy]-ethyl ester.

20. A method for treatment of physiological conditions or disorders treatable by increasing glucose utilization comprising:

administering to a patient in need of such treatment, effective amount to increase glucose utilization of a pharmaceutical composition comprising at least one compound represented by Formula (I) or Formula (II)



Formula (I)



Formula (II)

wherein

W is C_1-C_6 alkyl, halogen, or aryl;

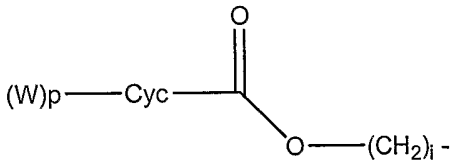
Cyc is C_3 or C_4 cycloalkyl;

p is an integer from 0 to 3 when Cyc is C_4 cycloalkyl, or p is an integer from 0 to 2 when Cyc is C_3 cycloalkyl;

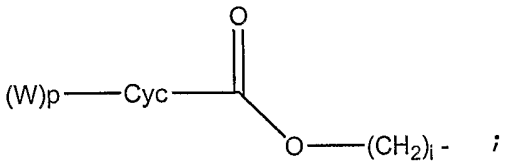
Y is O, S, or NR;

X is O, S, NR, or CR^3R^4;

Z is H, alkyl, cycloalkyl, aryl or (cyclo)alkylcarbonyl or

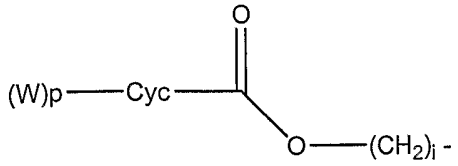


if X is NR and R is



;

R is H, alkyl, aryl or



where i is an integer from 2 to 4;

R^1 is H, alkyl, aryl or O;

R^2 is H, alkyl or aryl;

R^3 and R^4 are, independently, H, alkyl or aryl; and

n is an integer from 1 to 10; or a pharmaceutically acceptable salt, ester or prodrug thereof.

21. A method according to claim 20, wherein said disorder or condition is ischemic/reperfusion injury, post myocardial infarction, angina, heart failure, a cardiomyopathy, peripheral vascular disease, diabetes, and lactic acidosis, or symptoms or side effects associated with open heart surgery, bypass surgery, or heart transplant.

22. A method according to claim 21, wherein said disorder or condition is ischemic/reperfusion injury.

23. A method according to claim 20, wherein said compound is represented by the Formula (I), and wherein p is 0;

Y is O;

X is NR or O;

R^1, R^2, R^3 and R^4 are H;

n is 1 to 4; and

Z is lower alkyl, cycloalkyl or phenyl.

24. The method according to claim 20, wherein said compound is represented by the Formula (I), and wherein p=0;

Y is NR;

X is O;

R^1, R^2, R^3 and R^4 are H;

n is 1 or 2; and

Z is H.

25. A method according to claim 20, wherein said compound is represented by the Formula (II), wherein p is 0.

26. The method according to claim 20, wherein said at least one compound is selected from the group consisting of cyclopropanecarboxylic acid; cyclobutanecarboxylic acid; cyclopropanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester; cyclobutanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester; (cyclobutanecarbonyl-amino)-acetic acid; cyclopropanecarboxylic acid, 2-(2-benzyloxy-ethoxy)-ethyl ester; 2-(cyclopropanecarbonyl-amino)-propionic acid; cyclobutanecarboxylic acid 2-(2-benzyloxy-ethoxy)-ethyl ester; cyclobutanecarboxylic acid 2-(2-butoxy-ethoxy)-ethyl ester; cyclobutanecarboxylic acid 2-(2-ethoxy-ethoxy)-ethyl ester; cyclopropanecarboxylic acid 2-(2-dimethylamino-ethoxy)-ethyl ester; cyclobutanecarboxylic acid 2-(2-dimethylamino-ethoxy)-ethyl ester; cyclopropanecarboxylic acid 2-(2-hexyloxy-ethoxy)-ethyl ester; cyclobutanecarboxylic acid 2-(2-hexyloxy-ethoxy)-ethyl ester; cyclopropanecarboxylic acid 2-(2-methoxy-ethoxy)-ethyl ester; cyclobutanecarboxylic acid 2-(2-methoxy-ethoxy)-ethyl ester; cyclopropanecarboxylic acid 2-ethoxy-ethyl ester; cyclobutanecarboxylic acid 2-ethoxy-ethyl ester; cyclopropanecarboxylic acid 2-isopropoxy-ethyl ester; cyclobutanecarboxylic acid 2-isopropoxy-ethyl ester; cyclopropanecarboxylic acid, 2-(2-cyclopropanecarbonyloxy-ethoxy)-ethyl ester; cyclopropanecarboxylic acid, 2-[2-(2-cyclopropanecarbonyloxy-ethoxy)-ethoxy]-ethyl ester; and cyclobutanecarboxylic acid, 2-[2-(2-cyclobutanecarbonyloxy-ethoxy)-ethoxy]-ethyl ester.

27. A kit containing a pharmaceutical composition according to claim 7.

28. A kit according to claim 27, wherein said kit comprises a label or packaging insert containing instructions for use, in vitro, in vivo, or ex vivo, of components of said kit.

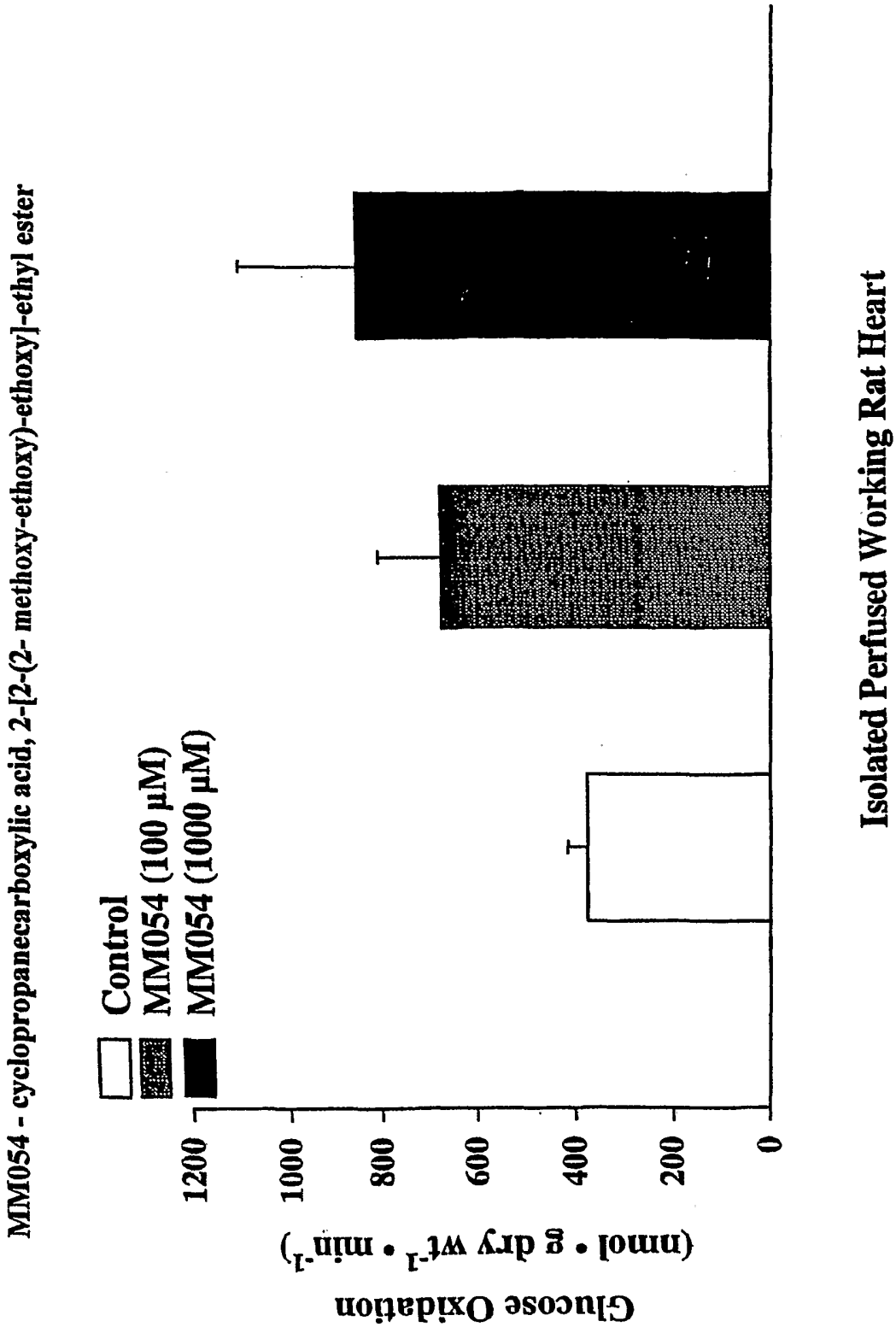

MM054 - cyclopropanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester
Control
MM054 (100 µM)
MM054 (1000 µM)
Glucose Oxidation
(nmol • g dry wt-1 • min-1)
0
200
400
600
800
1000
1200
Isolated Perfused Working Rat Heart

FIG. 1

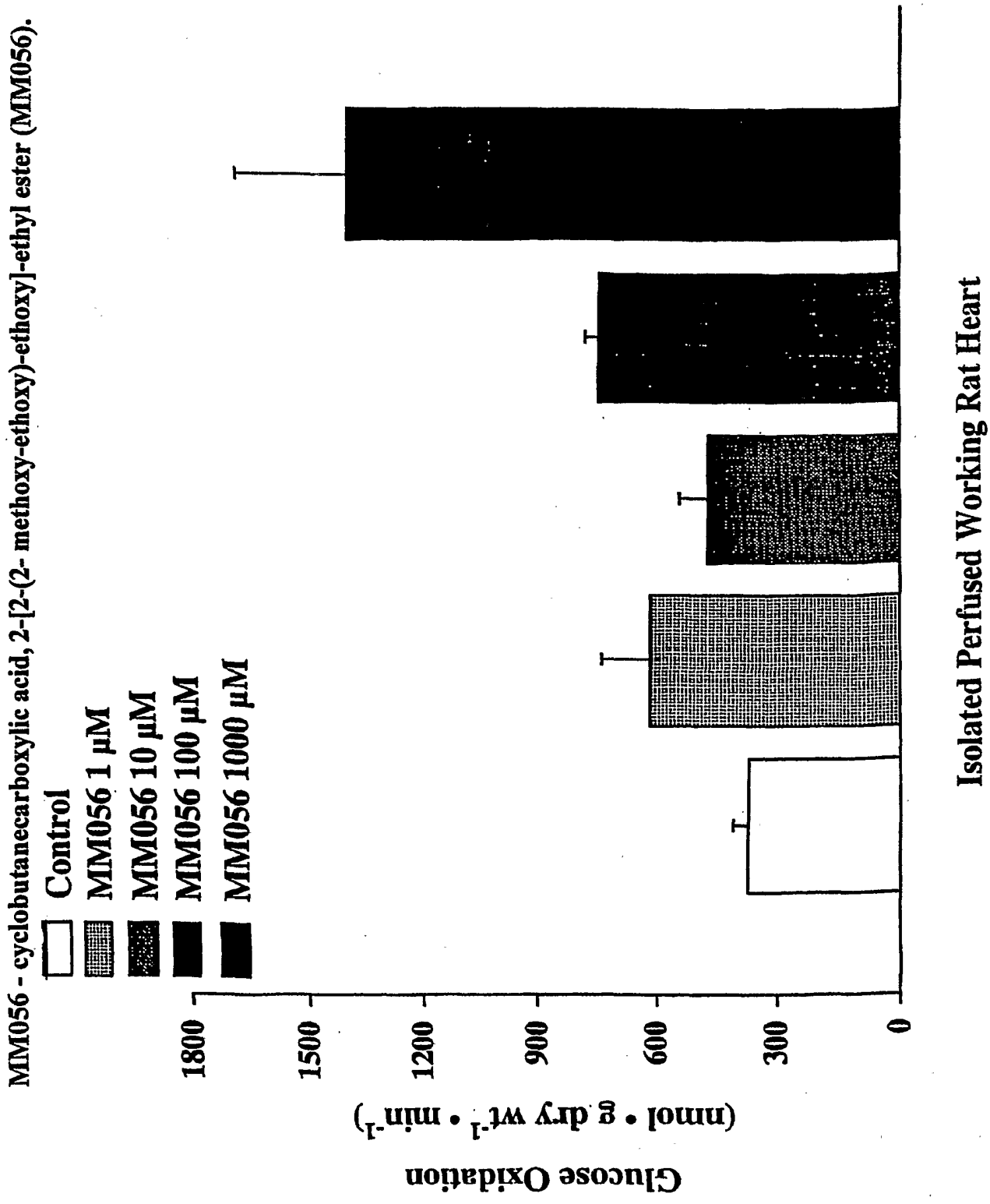

MM056 - cyclobutanecarboxylic acid, 2-[2-(2- methoxy-ethoxy)-ethoxy]-ethyl ester (MM056).
Control
MM056 1 µM
MM056 10 µM
MM056 100 µM
MM056 1000 µM
Glucose Oxidation
(nmol • g dry wt-1 • min-1)
1800
1500
1200
900
600
300
0
Isolated Perfused Working Rat Heart

FIG. 2

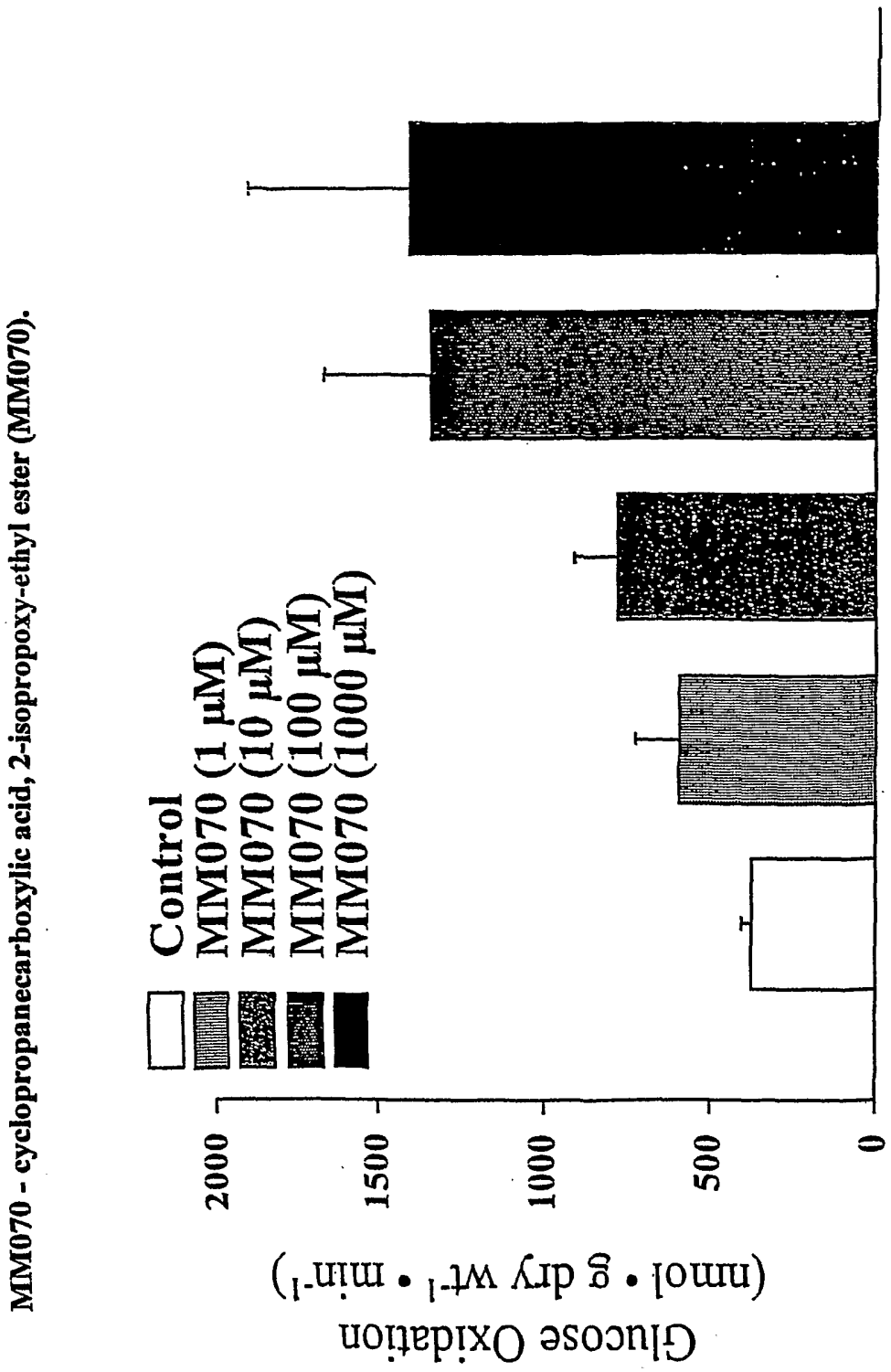

MM070 - cyclopropanecarboxylic acid, 2-isopropoxy-ethyl ester (MM070).
Glucose Oxidation
(nmol • g dry wt-1 • min-1)
2000
1500
1000
500
0
Control
MM070 (1 µM)
MM070 (10 µM)
MM070 (100 µM)
MM070 (1000 µM)

FIG. 3

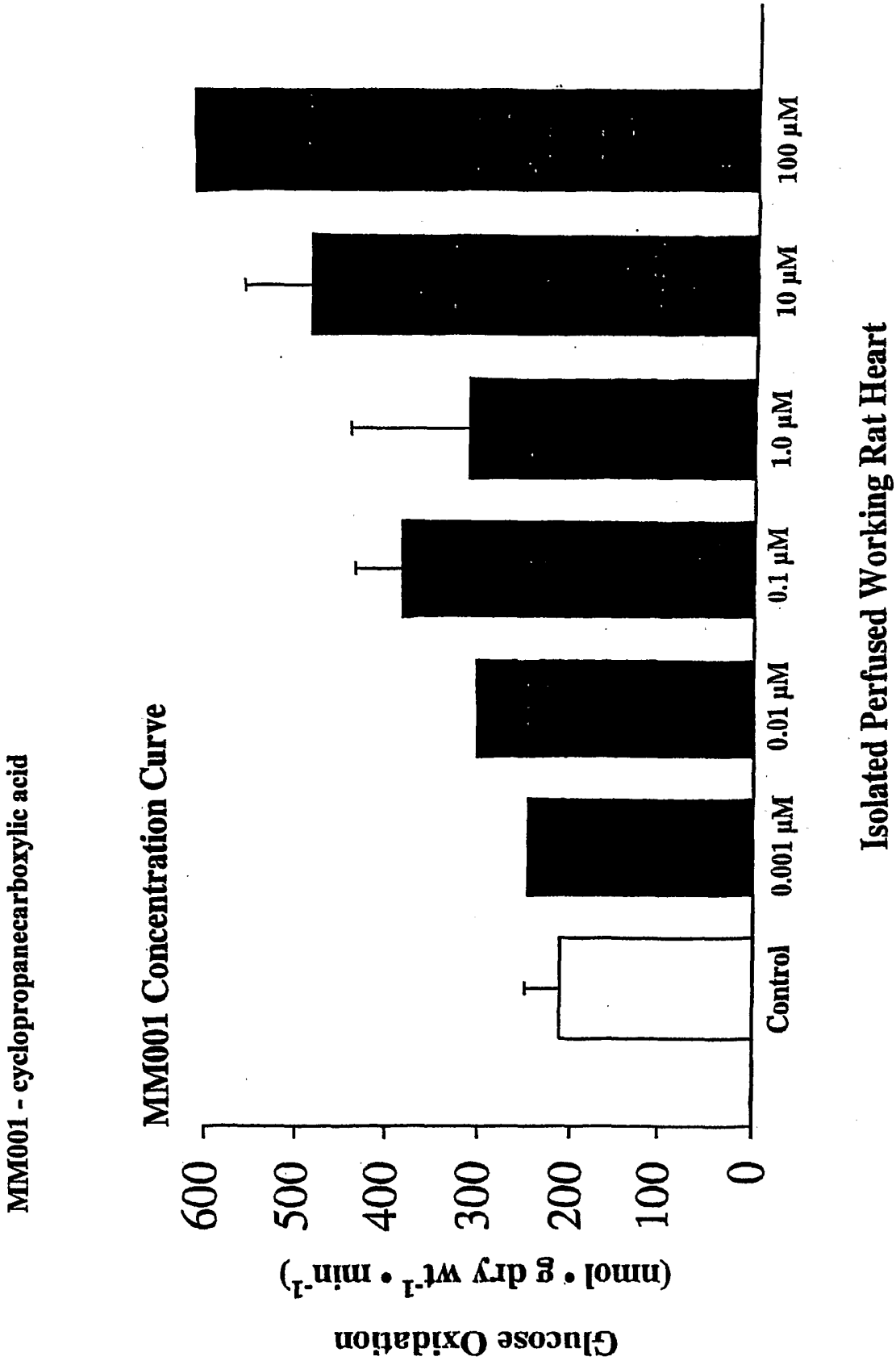

MM001 - cyclopropanecarboxylic acid
MM001 Concentration Curve
Isolated Perfused Working Rat Heart
Glucose Oxidation
(nmol • g dry wt-1 • min-1)
0
100
200
300
400
500
600
Control
0.001 µM
0.01 µM
0.1 µM
1.0 µM
10 µM
100 µM

FIG. 4

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/IB 03/01761

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C69/757 C07C233/63 C07C217/08 A61K31/215 A61K31/164
A61K31/13 A61P3/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 000 315 A (HENRICK CLIVE A ET AL) 28 December 1976 (1976-12-28) example 4 claims 1-12	1-6
X	US 3 957 849 A (HENRICK CLIVE A ET AL) 18 May 1976 (1976-05-18) example 4 claims 1-21	1-6
P,X	WO 02 085294 A (QI MING ;SENOMYX INC (US); ROGERS DAN (US); WARREN CRAIG (US)) 31 October 2002 (2002-10-31) claim 85	1-5

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 July 2003	08/08/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Goetz, G

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 2576757 XP002248454 abstract & J. MED. CHEM., vol. 6, 1963, pages 221-227, ---	1-4
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 2040782 XP002248455 abstract & J. MED. CHEM., vol. 39, no. 22, 1996, pages 4354-4357, ---	1-4
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 7079339 XP002248456 abstract & J. MED. CHEM., vol. 37, no. 15, 1994, pages 2285-2291, ---	1-5
X	US 3 306 727 A (NEIGHBORS) 28 February 1967 (1967-02-28) example 24 ---	1-5
A	BERSIN R M ET AL: "DICHLOROACETATE AS METABOLIC THERAPY FOR MYOCARDIAL ISCHEMIA AND FAILURE" AMERICAN HEART JOURNAL, MOSBY- YEAR BOOK INC., ST. LOUIS, MO, US, vol. 134, no. 5, PART 1, November 1997 (1997-11), pages 841-855, XP001032583 ISSN: 0002-8703 cited in the application the whole document --- -/--	1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HENRICK, CLIVE A. ET AL: "Ovicidal activity and its relation to chemical structure for the two-spotted spider mite (Tetranychus urticae Koch) in a new class of miticides containing the cyclopropyl group" retrieved from STN Database accession no. 85:105335 CA XP002249230 s. RN 60128-48-5, RN 60128-46-3 abstract & JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY (1976), 24(5), 1023-9 , -----	1-5

INTERNATIONAL SEARCH REPORT

Int onal application No.
PCT/IB 03/01761

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 13 to 26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1 to 5
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1 to 5

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to the compounds mentioned in the examples and in claim 6 , to pharmaceutical compositions according to claims 7 to 12 and to the alleged use of the compounds according to claims 13 to 28

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Interna Application No
PCT/IB 03/01761

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4000315 A	28-12-1976	US 3957849 A	18-05-1976
US 3957849 A	18-05-1976	US 4000315 A	28-12-1976
WO 02085294 A	31-10-2002	WO 02085294 A2 US 2003089885 A1	31-10-2002 15-05-2003
US 3306727 A	28-02-1967	US 3277107 A	04-10-1966