COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952
APPLICATION FOR A STANDARD PATENT

Merck & Co., Inc., of 126 East Lincoln Avenue, Rahway, New Jersey, UNITED STATES OF AMERICA, hereby apply for the grant of a standard patent for an invention entitled:

New Substituted Azetidinones as Anti-Inflammatory and Antidegenerative Agents

which is described in the accompanying complete specification.

Details of basic application(s):

Basic Applic. No: Country: Application Date:
179,688  US  11 April 1988

The address for service is:

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31 Market Street
Sydney New South Wales Australia

DATED this TENTH day of APRIL 1989

Merck & Co., Inc.

By:

Registered Patent Attorney

TO:  THE COMMISSIONER OF PATENTS
OUR REF:  90872
S&F CODE:  58190

5006674  10/04/89

5845/2
COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952-60

DECLARATION IN SUPPORT OF A CONVENTION
APPLICATION FOR A PATENT OR PATENT
OF ADDITION

In support of the Convention Application made for a patent for an invention
entitled

New Substituted Azetidinones as Anti-Inflammatory and Antidegenerative Agents

I, JAMES F. NAUGHTON
of MERCK & CO., Inc., 126 East Lincoln Avenue,
Rahway, New Jersey, United States of America
do solemnly and sincerely declare as follows:

1. I am authorised by MERCK & CO., Inc.,
the applicant for the patent to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was made
in the United States of America on 11 April 1988
by Shrenik K. Shah, Paul E. Finke, James B. Doherty, Peter L. Barker,
William Hagmann, Conrad P. Dorn, Raymond A. Firestone

3. Shrenik K. Shah, Paul E. Finke, James B. Doherty, Peter L. Barker,
William Hagmann, Conrad P. Dorn, and Raymond A. Firestone reside at
25 Denise Court, Metuchen, New Jersey 08840; 34 Inwood Drive,
Milltown, New Jersey 08850; 559 Columbia Street, New Milford,
New Jersey 07646; 518 Hort Street, Westfield, New Jersey 07090;
309 Hyler Avenue, Westfield, New Jersey 07090; 972 Fernwood Avenue,
Plainfield, New Jersey 07062; and 387 Temple Street, New Haven,
Connecticut 06511, United States of America

4. The basic application referred to in paragraph 2 of this Declaration
was the first application made in a Convention country in respect of
the invention the subject of the application.

Declared at Rahway, New Jersey, U.S.A.
this 15th day of March 1989.

MERCK & CO., Inc.

James F. Naughton
Director-Administration
Off. of Sr. V.P. & Gen. Counsel
We have found that a group of new substituted azetidinones are potent elastase inhibitors and therefore are useful anti-inflammatory/antidegenerative agents.

1. A compound of formula (I)

wherein R and R¹ independently are C₁₋₆ alkyl or C₁₋₆ alkoxy-C₁₋₆ alkyl; M is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₁₋₆ alkoxy-C₁₋₆ alkyl; X₅ is hydrogen, C₁₋₆ alkyl, halo-C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, carboxy, carboxy-C₁₋₆ alkyl, carboxy-C₁₋₆ alkenyl, carboxy-C₁₋₆ alkenylamino, carboxy-C₂₋₆ alkyl, hydroxyc-C₁₋₆ alkyl, C₁₋₆ alkenyl, C₁₋₆ alkenylamino, or di-(C₁₋₆ alkyl)-amino-C₁₋₆ alkyl; and X₆ is hydrogen, C₁₋₆ alkyl, halo, carboxy, C₁₋₆ alkoxy, phenyl, C₁₋₆ alkylcarbonyl, di-(C₁₋₆ alkyl)amino, phenoxy, methylenedioxy, 2,3-furanyl, or 2,3-thienyl; or a pharmaceutically acceptable salt thereof.
12. A pharmaceutical composition for the inhibition of human leukocyte elastase which comprises a nontoxic therapeutically effective amount of a compound of any one of Claims 1 to 7 and a pharmaceutically acceptable carrier.
New Substituted Azetidinones as Anti-Inflammatory and Antidegenerative Agents

The following statement is a full description of this invention, including the best method of performing it known to me/us.
TITLE OF THE INVENTION
NEW SUBSTITUTED AZETIDINONES AS ANTI-INFLAMMATORY
AND ANTIDEGENERATIVE AGENTS

ABSTRACT OF THE INVENTION
New substituted azetidinones are found to be potent elastase inhibitors and thereby useful anti-inflammatory/antidegenerative agents.
TITLE OF THE INVENTION
NEW SUBSTITUTED AZETIDINONES AS ANTI-INFLAMMATORY AND ANTIDEGENERATIVE AGENTS

BACKGROUND OF THE INVENTION
We have found that a group of new substituted azetidinones are potent elastase inhibitors and therefore are useful anti-inflammatory/antidegenerative agents.

Proteases from granulocytes and macrophages have been reported to be responsible for the chronic tissue destruction mechanisms associated with inflammation, including rheumatoid arthritis and emphysema. Accordingly, specific and selective inhibitors of these proteases are candidates for potent anti-inflammatory agents useful in the treatment of inflammatory conditions resulting in connective tissue destruction, e.g. rheumatoid arthritis, emphysema, bronchial inflammation.
osteoaarthritis, spondylitis, lupus, psoriasis, atherosclerosis, sepsis, septicemia, shock, periodontitis, cystic fibrosis and acute respiratory distress syndrome.

The role of proteases from granulocytes, leukocytes or macrophages are related to a rapid series of events which occurs during the progression of an inflammatory condition:

(1) There is a rapid production of prostaglandins (PG) and related compounds synthesized from arachidonic acid. This PG synthesis has been shown to be inhibited by aspirin-related nonsteroidal anti-inflammatory agents including indomethacin and phenylbutazone. There is some evidence that protease inhibitors prevent PG production;

(2) There is also a change in vascular permeability which causes a leakage of fluid into the inflamed site and the resulting edema is generally used as a marker for measuring the degree of inflammation. This process has been found to be induced by the proteolytic or peptide cleaving activity of proteases, especially those contained in the granulocyte, and thereby can be inhibited by various synthetic protease inhibitors, for example, N-acyl benzisothiazolones and the respective 1,1-dioxides. Morris Zimmerman et al., J. Biol. Chem., 255, 9848 (1980); and
There is an appearance and/or presence of lymphoid cells, especially macrophages and polymorphonuclear leukocytes (PMN). It has been known that a variety of proteases are released from the macrophages and PMN, further indicating that the proteases do play an important role in inflammation.

In general, proteases are an important family of enzymes within the peptide bond cleaving enzymes whose members are essential to a variety of normal biological activities, such as digestion, formation and dissolution of blood clots, the formation of active forms of hormones, the immune reaction to foreign cells and organisms, etc., and in pathological conditions such as the degradation of structural proteins at the articular cartilage/pannus junction in rheumatoid arthritis etc.

Elastase is one of the proteases. It is an enzyme capable of hydrolyzing the connective tissue component elastin, a property not contained by the bulk of the proteases present in mammals. It acts on a protein's nonterminal bonds which are adjacent to an aliphatic amino acid. Neutrophil elastase is of particular interest because it has the broadest spectrum of activity against natural connective tissue substrates. In particular, the elastase of the granulocyte is important because, as described above, granulocytes participate in acute inflammation and in acute exacerbation of chronic forms of inflammation which characterize many clinically important inflammatory diseases.
Proteases may be inactivated by inhibitors which block the active site of the enzyme by binding tightly thereto. Naturally occurring protease inhibitors form part of the control or defense mechanisms that are crucial to the well-being of an organism. Without these control mechanisms, the proteases would destroy any protein within reach. The naturally occurring enzyme inhibitors have been shown to have appropriate configurations which allow them to bind tightly to the enzyme. This configuration is part of the reason that inhibitors bind to the enzyme so tightly (see Stroud, "A Family of Protein-Cutting Proteins" Sci. Am. July 1974, pp. 74-88). For example, one of the natural inhibitors, \( \alpha_1 \)-Antitrypsin, is a glycoprotein contained in human serum that has a wide inhibitory spectrum covering, among other enzymes, elastase both from the pancreas and the PMN. This inhibitor is hydrolyzed by the proteases to form a stable acyl enzyme in which the active site is no longer available. Marked reduction in serum \( \alpha_1 \)-antitrypsin, either genetic or due to oxidants, has been associated with pulmonary emphysema which is a disease characterized by a progressive loss of lung elasticity and resulting respiratory difficulty. It has been reported that this loss of lung elasticity is caused by the progressive, uncontrolled proteolysis or destruction of the structure of lung tissue by proteases such as elastase released from leukocytes. J. C. Powers, TIBS, 211 (1976).

Rheumatoid arthritis is characterized by a progressive destruction of articular cartilage both
on the free surface bordering the joint space and at the erosion front built up by synovial tissue toward the cartilage. This destruction process, in turn, is attributed to the protein-cutting enzyme elastase which is a neutral protease present in human granulocytes. This conclusion has been supported by the following observations:

(1) Recent histochemical investigations showed the accumulation of granulocytes at the cartilage/pannus junction in rheumatoid arthritis; and


Accordingly, an object of this invention is to discover new protease inhibitors, especially elastase inhibitors, useful for controlling tissue damage and various inflammatory or degenerative conditions mediated by proteases particularly elastase.

Another object of the present invention is to provide pharmaceutical compositions for
administering the active substituted azetidinones as protease inhibitors especially human leukocyte elastase.

Still a further object of this invention is to provide a method of controlling inflammatory conditions by administering a sufficient amount of one or more of the active, substituted azetidinones in a mammalian species in need of such treatment.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to potent elastase inhibitors of formula (I) which are useful in the prevention, control and treatment of inflammatory/degenerative conditions especially arthritis and emphysema.

A large number of the azetidinone derivatives of formula (I) are known antibiotics which have been described in patents and various publications.

The formula of the substituted azetidinones which are found to exhibit anti-inflammatory and antidegenerative activities by the present invention are represented as follows:

\[
\text{[Diagram of formula (I)]}
\]

wherein R and R\(^1\) independently are C\(_{1-6}\) alkyl or C\(_{1-6}\) alkoxy-C\(_{1-6}\) alkyl, preferably C\(_{1-6}\) alkyl, especially methyl or ethyl; M is hydrogen, C\(_{1-6}\) alkyl, C\(_{2-6}\) alkenyl, or C\(_{1-6}\) alkoxy-C\(_{1-6}\) alkyl, preferably C\(_{1-3}\) alkyl or allyl, especially n-propyl; X\(_5\) is hydrogen, C\(_{1-6}\) alkyl, halo-C\(_{1-6}\) alkyl, C\(_{2-6}\) alkenyl, C\(_{2-6}\) alkynyl, carboxy, carboxy-C\(_{1-6}\) alkyl, carboxy-C\(_{1-6}\) alkylcarbonyl, carboxy-C\(_{1-6}\) alkylcarbonylamino, carboxy-C\(_{2-6}\) alkenyl, hydroxy-C\(_{1-6}\) alkyl, C\(_{1-6}\) alkylcarbonyl, C\(_{1-6}\) alkylcarbonylamino, or di-(C\(_{1-6}\) alkyl)-amino-C\(_{1-6}\) alkylcarbonylamino; and X\(_6\) is hydrogen, C\(_{1-6}\) alkyl, halo, carboxy, C\(_{1-6}\) alkoxy, phenyl, C\(_{1-6}\) alkylcarbonyl, di-(C\(_{1-6}\) alkyl)amino, phenoxy, methylenedioxy, 2,3-furanyl, or 2,3-thienyl, preferably hydrogen, C\(_{1-6}\) alkyl, 3,4-methylenedioxy or phenyl, especially 4-methyl; or a pharmaceutically acceptable salt thereof.

In a further embodiment of this invention there is provided a process for the preparation of compounds of formula (I) which process comprises
reacting a compound of the following formula (B)

\[
\begin{align*}
R & \quad OAc \\
& \quad \text{NH}
\end{align*}
\]

(B)

with a compound of the formula (C)

\[
\begin{align*}
& \quad \text{HO} \\
& \quad \text{X}_5
\end{align*}
\]

(C)

wherein \( X' \) is hydrogen, \( C_{1-6} \) alkyl, halo-\( C_{1-6} \) alkyl, \( C_{2-6} \) alkenyl, \( C_{2-6} \) alkynyl, \( C_{1-6} \) alkoxy carbonyl, \( C_{1-6} \) alkoxy carbonyl-\( C_{1-6} \) alkyl, \( C_{1-6} \) alkoxy carbonyl-\( C_{1-6} \) alkyl carbonyl, \( C_{1-6} \) alkoxy carbonyl-\( C_{1-6} \) alkyl carbonyl, \( C_{1-6} \) hydroxy alkyl, \( C_{1-6} \) alkyl carbonyl, \( C_{1-6} \) alkyl carbonyl amino, or \( \text{di-}(C_{1-6} \text{ alkyl})\text{amino-}C_{1-6} \text{ alkyl} \) under basic conditions to afford a compound of the formula (D)

\[
\begin{align*}
& \quad R \\
& \quad \text{O} \\
& \quad \text{NH} \\
& \quad \text{X}_5
\end{align*}
\]

(D)

and (2) reacting compound (D) with a compound of the formula (E)

\[
\begin{align*}
& \quad \text{O=CN-CH} \\
& \quad \text{H} \\
& \quad \text{X}_6
\end{align*}
\]

(E)

under basic conditions, and optionally converting \( X' \) into \( X \), to yield the compound of formula (I)

\[
\begin{align*}
& \quad R \\
& \quad \text{O} \\
& \quad \text{CONHCH} \\
& \quad \text{X}_5 \\
& \quad \text{X}_6
\end{align*}
\]

(I)
The compounds of the present invention are either known or are prepared among other methods by the following representative schemes.

**PREPARATIVE STEPS:**

1. **Scheme (a)** as illustrated by preparations 16-19.

   

   ![Chemical structure](image1)

   where \( Y \) is \(-\text{NO}_2\), \(-\text{CH}_3\), \(-\text{OCH}_3\), \(-\text{Cl}\), \(-\text{F}\), etc.; \( X \) is halo, e.g., \( \text{Cl}\), \( \text{Br}\) or \( \text{I}\); \( Z \) is \( \text{BCO} \) or \( \text{BSO}_2 \).

2. **Scheme (b)** as illustrated by preparations 1-4.

   

   ![Chemical structure](image2)

   wherein \( X \) is halo; \( Z \) is as previously defined, e.g., \(-\text{SO}_2\)-\( \text{p-NO}_2\)-\( \text{Ph}\), \(-\text{COCH}_3\), \(-\text{CH}_2\text{OTs}\), etc. wherein \( \text{Ph} \) represents phenyl or substituted phenyl.
Scheme (c) as illustrated by preparations 5-15.

\[
\text{HO-C-COOR'} + \text{NH}_2\text{-C-OH} \rightarrow \text{COOR'}
\]

\[
\text{R'CH}_2\text{COCl}
\]

\[
\text{NH}_2\text{-C-COOR'} \xrightarrow{\text{Reduction when } R' = N_3} \text{COOR'}
\]

\[
\text{acylation } R'\text{COX}
\]

\[
\text{Reduction when } R' = N_3
\]

wherein \(R^6\) is H, CF₃, CH₃, etc.; \(R^5\) and \(R^1\) are as previously defined; and CAN is ceric ammonium nitrate.

Scheme (d) as illustrated by preparations 2-3.

\[
\text{R'}\text{COCH}_3 + \text{cISO}_2\text{N=C=O} \rightarrow \text{COCH}_3
\]

Scheme (e) as taught by M. A. Krook and M. J. Miller (J. Org. Chem., 1985, 50, 1126-1128), the following type of compounds can be prepared.

\[
\text{RHN} + \text{OH} \xrightarrow{\text{MsCl}} \text{NHOCCH}_2\text{Ph}
\]

\[
\text{RHN} \xrightarrow{t-\text{BuOK}} \text{NHOCCH}_2\text{Ph}
\]

the following class of compounds can be prepared.

\[
R^2\text{CHO} + \text{LiN(TMS)} \rightarrow R^2\text{CH} = \text{N(TMS)} \\
R^1\text{CHCOOR}^3 \rightarrow R^1\text{C} = \text{C}\text{OR}^5
\]

wherein \(R^5\) is as previously defined; and TMS is trimethylsilyl.

Scheme (g) as taught by P. J. Reider and E. J. J. Grabowski (J. Org. Chem., 23, p. 2293, 1982); the following groups of compounds can be prepared.

\[
\text{CH}_2\text{CHNH}_2\cooh \\
1) \text{PhCH}_2\text{OH/H}^+ \\
2) \text{TMSCl} \\
3) \text{tBuMgCl}
\]

wherein \(R^1\) is as previously defined.

Scheme (h) as illustrated by Examples 1 and 2:
This invention also relates to a method of treating inflammation in patients using a compound of Formula (I), particularly a preferred compound as the active constituent.

It has been found that the compounds of Formula (I) are effective inhibitors of the proteolytic function of human granulocyte elastase as shown below:

Table I

<table>
<thead>
<tr>
<th>R</th>
<th>R¹</th>
<th>R²</th>
<th>B₁</th>
<th>k_{obs}/I</th>
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Table I cont'd

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JLH/1015C
### Table I cont'd

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Me represents CH₃.
Ph represents phenyl
Pr represents propyl
Bu represents butyl

### Table III

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>R²</th>
<th>B¹</th>
<th>k_{obs}/I</th>
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<tbody>
<tr>
<td>O-(4-COOH-Ph)</td>
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<tr>
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### Table IV

![Chemical Structure](image)
### Table IV cont'd

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### Table V

<table>
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Table VI

<table>
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Table VI
(Continued)

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Table VI
(Continued)

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Accordingly, the compounds of Formula (I) can be used to reduce inflammation and relieve pain in diseases such as emphysema, rheumatoid arthritis, osteoarthritis, gout, bronchial inflammation, atherosclerosis, sepsis, septicemia, shock, periodontitis, cystic fibrosis, infectious arthritis, rheumatic fever and the like.

For treatment of inflammation, fever or pain, the compounds of Formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.
The pharmaceutical compositions containing, the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparation. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glycercyl monostearate or glycercyl distearate may be employed. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for
example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadeca-ethyleneoxyctanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The said aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspension may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid
paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oils, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soybean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.
Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of Formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.
For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the anti-inflammatory agents are employed.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 5 mg to 5 gm of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 25 mg to about 500 mg of active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.
**Preparation 1**

1-p-nitrophenylsulfonyl-4-benzyloxy carbonyl azetidin-2-one

Diazabicycloundecane (152 mg, 1 mM) was added to a mixture of 205 mg (1 mM) 4-benzyloxy carbonyl azetidin-2-one and 181 mg (1 mM) p-nitrobenzenesulfonyl chloride in 10 ml methylene chloride at room temperature. After stirring 2-1/2 hours, the orange solution was washed with water, dried over MgSO₄, and concentrated in vacuo. The residue was chromatographed on silica gel in hexane/ethyl acetate to yield 64 mg of 1-p-nitrophenylsulfonyl-4-benzyloxy carbonyl azetidin-2-one.

NMR (CDCl₃): δ 3.3 (2H, doublet-quartet), 4.8 (qt. 1H), 5.2 (s, 2H), 7.1 (s, 5H), 8.2 (mlt. 4H).

**Preparation 2**

1-Acetyl-3,3-dimethyl-4-acetoxy azetidin-2-one

**Step A: Preparation of 2-methyl-prop-1-enylacetate**

A mixture of 72 g (1 M) isobutyraldehyde, 153 g (1.5 M) acetic anhydride and 12 g (0.125 M) potassium acetate was refluxed seven hours. The cooled reaction mixture was washed with water and stirred with 300 ml saturated NaHCO₃ at 0°C for 45 minutes. The organic phase was dried over K₂CO₃ to yield a yellow oil which was distilled at atmospheric pressure to give 35.41 g (31%) of 2-methyl-prop-1-enylacetate, b.p. 122-126°.

NMR (CDCl₃): δ 1.6 (s, 6H), 2.1 (s, 3H), 6.9 (mlt. 1H).
Step B: Preparation of 3,3-dimethyl-4-acetoxy-azetidin-2-one

Chlorosulfonyl isocyanate (16 ml) was added to a solution of 22.8 g (0.2 M) 2-methyl prop-1-enyl acetate in 50 ml methylene chloride at 0° under nitrogen. After stirring at 0° for 20 hours, the reaction mixture was added to a mixture of 20 ml water, 90 g ice, 48 g NaHCO₃ and 16.6 g Na₂SO₃ and stirred at 0° for 30 minutes. This was then extracted with 300 ml CH₂Cl₂ and the organic phase washed with brine, dried over MgSO₄ and concentrated in vacuo to give 27.75 g oil which was chromatographed on silica gel in hexane/ethyl acetate to yield 2.17 g (8.5%) of 3,3-dimethyl-4-acetoxy-azetidin-2-one.

NMR (CDCl₃): δ 1.2 (s, 3H), 1.3 (s, 3H), 2.2 (s, 3H), 5.6 (s, 1H).

Step C: Preparation of 1-acetyl-3,3-dimethyl-4-acetoxyazetidin-2-one

A mixture of 283.3 mg (1.8 mM) 3,3-dimethyl-4-acetoxyazetidin-2-one, 2 ml pyridine and 2 ml acetic anhydride was heated to 100° in a sealed tube for 36 hours. The reaction mixture was concentrated in vacuo and the residue chromatographed on silica gel in hexane/ethyl acetate to yield 295 mg (82%) of 1-acetyl-3,3-dimethyl-4-acetoxyazetidin-2-one.

NMR (CDCl₃): δ 1.2 (s, 3H), 2.2 (s, 3H), 2.5 (s, 3H), 6.1 (s, 1H).
Preparation 3
1-Acetyl-4-acetoxy-3-n-propylazetidin-2-one

Step A: Preparation of Pent-1-enyl acetate

A mixture of 86 g (1M) valeraldehyde, 153 g (1.5 M) acetic anhydride, and 12 g (0.125 M) potassium acetate, was refluxed for 8 hours. The cooled mixture was then stirred with 100 ml saturated aqueous NaHCO₃ for one hour. The organic phase is separated, dried over K₂CO₃, and distilled at 40 mm to yield 46.15 g (45%) of pent-1-enylacetate, b.p. 89°C.

NMR (CDCl₃): δ 1.0 (tr, 3H), 1.2-2.0 (mlt., 4H), 2.1 (s, 3H), 4.7-5.6 (mlt. 1H), 7.0-7.3 (mlt., 1H).

Step B: Preparation of 4-acetoxy-3-n-propylazetidin-2-one

Eight hundred microliters of chlorosulfonyl isocyanate was added to a solution of 1.28 g (10 mM) pent-1-enyl acetate in 5 ml methylene chloride at 0° under nitrogen. After stirring at 0° 5 days, the reaction mixture was added dropwise to a mixture of 5 g ice, 1.15 ml water, 2.82 g NaHCO₃ and 1.0 g Na₂SO₃ and stirred at 0° for 30 minutes. The mixture was extracted with 2 X 25 ml methylene chloride and the combined organic phases washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was chromatographed on silica gel in hexane/ethyl acetate to yield 60 mg trans 4-acetoxy-3-n-propylazetidin-2-one (3.4%).

NMR (CDCl₃): δ 1.0 (mlt., 3H), 1.7 (mlt., 4H), 2.2 (s, 3H), 3.2 (tr, 1H), 5.6 (s, 1H), 6.7 (1rs, 1H).
Step C: Preparation of 1-acetyl-4-acetoxy-3-n-propyl-azetidin-2-one

A mixture of 56 mg (0.33 mM) 4-acetoxy-3-propylazetidin-2-one, 1 ml acetic anhydride and 1 ml pyridine was stirred at 100° in a sealed tube for 24 hours. After concentrating in vacuo the residue was chromatographed on silica gel in hexane/ethyl acetate, to yield 16 mg (23%) 1-acetyl-4-acetoxy-3-n-propylazetidine-2-one.

NMR (CDCl₃): δ 1.0 (br tr, 3H), 1.7 (m, 4H), 2.2 (s, 3H), 2.4 (s, 3H), 3.2 (tr, 1H), 6.1 (d, 1H).

Preparation 4

1-Acetyl-4-methylsulfonylazetidin-2-one

Step A: Preparation of 1-acetyl-4-methylthioazetidin-2-one

A mixture of 300 mg (2.6 mM) 4-methylthioazetidin-2-one, 10 ml acetic anhydride and 10 ml pyridine was stirred at 100° in a sealed tube 24 hours. After concentrating in vacuo, the residue was chromatographed on silica gel in hexane/ethyl acetate to yield 324 mg (78%) of 1-acetyl-4-methylthioazetidine-2-one.

NMR (CDCl₃): δ 2.4 (s, 3H), 2.41 (s, 3H), 3.2 (doublet-quartet, 2H), 5.1 (doublet-doublet, 1H).

Step B: Preparation of N-acetyl-4-methylsulfinylazetidin-2-one

A mixture of 130 mg (0.82 mM) N-acetyl-4-methylthioazetidinone and 200 mg (0.93 mM) 80% m-chloroperbenzoic acid in 5 ml methylene chloride was stirred at room temperature 5 minutes. After
removing the solvent in vacuo. The residue was chromatographed on 2-2000 μ silica gel plates in hexane/ethyl acetate to yield 57 mg (40%) of 1-acetyl-4-methylsulfinylazetidine-2-one.

NMR (CDCl₃): δ 2.4 (s, 3H), 2.6 (s, 3H), 3.5 (mlt., 2H), 4.9 (mlt., 1H).

**Preparation 5**

3-Azido-4-carboethoxy-1-(p-methoxyphenyl)azetidin-2-one

To a solution of 3.06 g of azidoacetyl chloride in 50 ml of CH₂Cl₂ was added dropwise a solution of 3.57 ml of triethylamine and 5.3 g of the imine formed from ethylglyoxalate and p-anisidine in 50 ml CH₂Cl₂, with cooling at such a rate that the reaction temperature remained below 5°C. The reaction was then stirred at room temperature for three hours and then washed sequentially with 1N HCl, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. The organic phase was dried over magnesium sulfate, filtered, and evaporated, and the crude residue was recrystallized from carbon tetrachloride/hexane to afford 3.7 g. of 3-azido-4-carboethoxy-1-(p-methoxyphenyl)azetidine-2-one; m.p. 80-85°C.

NMR (CDCl₃): δ 7.2 (d, J=9, 2H), 6.75 (d, J=9, 2H), 4.9 (d, J=6, 1H), 4.6 (d, J=6, 1H), 4.25 (q, J=8, 2H), 3.7 (s, 3H), 1.25 (t, J=8, 3H).

**Preparation 6**

4-Carboethoxy-3-chloro-1-(p-methoxyphenyl)azetidine-2-one

4-carboethoxy-3-chloro-1-(p-methoxyphenyl)azetidine-2-one was prepared by following the same
procedure as described in Example 5 but using chloroacetyl chloride and the imine formed from ethylglyoxalate and p-anisidine as the starting material. The crude product was recrystallized from ether (hexane) to give 3.1 g of 4-carboethoxy-3-chloro-1-(p-methoxyphenyl)azetidine-2-one, m.p. 99-100°.

NMR (CDCl₃): 6 7.2 (d, J=9, 2H), 6.8 (d, J=9, 2H), 5.1 (d, J=6, 1H), 4.7 (d, J=6, 1H), 4.25 (q, J=7, 2H), 3.7 (s, 3H), 1.25 (t, J=7, 3H).

Preparation 7

4-Carboethoxy-3-methoxy-1-(p-methoxyphenyl)azetidine-2-one

4-Carboethoxy-3-methoxy-1-(p-methoxyphenyl)azetidine-2-one was prepared by following the same procedure as described in Example 5 but using methoxyacetyl chloride as the starting material. After chromatography the compound crystallized as a white solid; m.p. 116-118°.

NMR (CDCl₃): 6 7.2 (d, J=9, 2H), 6.75 (d, J=9, 2H), 4.7 (d, J=5, 1H), 4.6 (d, J=5, 1H), 4.2 (q, J=5, 2H), 3.7 (s, 3H), 3.5 (s, 3H), 1.2 (t, J=5, 3H).

Preparation 8

4-Carboethoxy-1-(p-methoxyphenyl)-3-phenylazetidine-2-one

To a solution of 17 ml of triethylamine and 5.0 g of the imine formed from ethyl glyoxalate and p-anisidine in 100 ml of refluxing 1,2-dichloroethane was added dropwise over 2 hours a solution of 16 ml of freshly distilled phenylacetyl chloride in 50 ml
After refluxing for three hours, the reaction was worked-up as per the 3-azidoazetidinone. The crude residue was chromatographed to yield the cis and trans isomers of 4-carboethoxy-1-(p-methoxyphenyl)-3-phenylazetidin-2-one as oils; 

cis: NMR (CDCl₃): 6 7.2 (m, 7H), 6.7 (d, J=9, 2H), 4.7 (s, 2H), 3.6 (s, 3H), 3.6 (q, J=7, 2H), 0.7 (t, J=7, 3H); trans: NMR (CDCl₃): 6 7.3 (m, 7H), 6.8 (d, J=9, 2H), 4.5 (d, J=2, 1H), 4.45 (d, J=2, 1H), 4.1 (q, J=7, 2H), 3.6 (s, 3H), 1.2 (t, J=7, 3H).

Preparation 9

4-Carboethoxy-1-(p-methoxyphenyl)-3-vinylazetidin-2-one was prepared by following the same procedure as described in Example 8 but using crotonyl chloride as the reagent. After chromatography the cis and trans isomers of the compound were obtained; cis (m.p. 70-72°), NMR (CDCl₃): 6 7.2 (d, J=9, 2H), 6.8 (d, J=9, 2H), 5.2-5.8 (m, 3H), 4.6 (d, J=6, 1H), 4.2 (m, 3H), 3.7 (s, 3H), 1.2 (t, J=7, 3H); trans (oil), NMR (CDCl₃): 6 7.25 (d, J=9, 2H), 6.8 (d, J=9, 2H), 5.7-6.2 (m, 1H), 5.2-5.5 (m, 2H), 4.25 (br.s., 1H), 4.2 (q, J=7, 2H), 3.9 (dd, J=1, Jz=6, 1H), 3.75 (s, 1H), 1.25 (t, J=7, 3H).

Preparation 10

4-Carboethoxy-3-ethyl-1-(p-methoxyphenyl)azetidin-2-one

The cis and trans isomers of 4-carboethoxy-3-vinyl-1-(p-methoxyphenyl)azetidine-2-one are each
hydrogenated with palladium on carbon in ethanol to yield the corresponding cis and trans isomers of 4-carboethoxy-3-ethyl-1-(p-methoxy-phenyl)azetidine-2-one.

5

Preparation 11

4-Carboethoxy-1-(p-methoxyphenyl)-3-(N-methyl-trifluoroacetamido)azetidin-2-one

A solution of 2.16 g of 3-azido-4-carboethoxy-1-(p-methoxyphenyl)-azetidine-2-one in ethanol was hydrogenated with palladium to yield 4-carboethoxy-1-(p-methoxyphenyl)-3-aminoazetidin-2-one. This amine was acylated with 1.1 ml of trifluoroacetic anhydride in 10 ml CH₂Cl₂ containing 1.5 ml pyridine, followed by methylation using 1 ml dimethyl sulfate in 30 ml acetone containing 3 g potassium carbonate. After isolation, the crude product was crystallized to give 2.2 g of 4-carboethoxy-1-(p-methoxyphenyl)-3-(N-methyltrifluoroacetamido)azetidin-2-one, m.p. 102-104°.

NMR (CDCl₃): 6 7.2 (d, J=9, 2H), 6.75 (d, J=9, 2H), 5.5 (d, J=6, 1H), 4.7 (d, J=6, 1H), 4.2 (q, J=7, 2H), 3.7 (s, 3H), 3.2 (br.s., 3H), 1.2 (t, J=7, 3H).

Preparation 12

4-Carboethoxy-3-methoxyazetidin-2-one

To a solution of 1.4 g of 4-carboethoxy-3-methoxy-1-(p-methoxyphenyl)azetidine-2-one in 50 ml acetonitrile at 0° was added a solution of 8.23 g of ceric ammonium nitrate in 50 ml H₂O over 3 minutes. After stirring at 0° for 1 hour the solution was poured into 200 ml of 10% sodium sulfite and extracted
with 3 X 75 ml of ethyl acetate. The combined organic
extracts were washed with 10% sodium sulfite and
saturated sodium chloride solutions and dried over
sodium sulfate. Filtration and evaporation gave an
amber oil which was recrystallized from methylene
chloride/hexane to give 700 mg of 4-carboethoxy-3-
methoxyazetidine-2-one; m.p. 91-92°.
NMR (CDCl₃): δ 7.1 (br.s, 1H), 4.7 (dd, J₁=2,
J₂=5, 1H), 4.3 (d, J=5, 1H), 4.15 (q, J=7, 2H), 3.4
(s, 3H), 1.25 (t, J=7, 3H).
Following substantially the same procedure
as described in Example 12 but using an appropriate
3-substituted azetidinone compounds (a) - (f) were
prepared:
(a) 4-Carboethoxy-3-chloroazetidin-2-one
NMR (CDCl₃): δ 7.3 (br.s., 1H), 5.0
(dd, J₄=2, J₂=6, 1H), 4.4 (d, J=6, 1H), 4.2
(q, J=7, 2H), 1.3 (t, J=7, 3H).
(b) 4-Carboethoxy-3-phenylazetidin-2-one-2-(cis and
trans)
NMR (CDCl₃): cis: δ 7.2 (s, 5H), 6.4
(br.s., 1H), 4.7 (d, J=6, 1H), 4.4 (d, J=6, 1H), 3.7
(q, J=7, 2H), 0.75 (t, J=7, 3H); trans: δ 7.2 (s,
5H), 6.9 (br.s., 1H), 4.3 (br.d, J=2, 1H), 4.1 (q,
J=7, 2H), 4.0 (d, J=2, 1H), 1.2 (t, J=7, 3H).
(c) 4-Carboethoxy-3-(N-methyltrifluoroacetamido)
azetidin-2-one
NMR (CDCl₃): δ 7.2 (br.s., 1H), 5.4 (d,
J=6, 1H), 4.5 (d, J=6, 1H), 4.15 (q, J=7, 2H), 3.2
(s, 3H), 1.2 (t, J=7, 3H).
(d) 4-Carboethoxy-3-vinylazetidin-2-one (cis and trans)

NMR (CDCl₃) cis: δ 7.1 (br.s., 1H), 5.2-5.8 (m, 3H), 4.0-4.4 (m, 4H), 1.25 (t, J=7, 3H);
trans: δ=7.25 (br.s., 1H), 5.0-6.2 (m, 3H), 4.1 (q, J=7, 2H), 3.9 (d, J=2, 1H), 3.7 (dd, J₁=2, J₂=7, 1H), 1.2 (t, J=7, 3H).

(e) 4-Carboethoxy-3-ethylazetidin-2-one

Cis: NMR(CDCl₃): δ 6.9 (br. s., 1H); 4.2 (m, 3H); 3.4 (dd, J₁=6, J₂=8, 1H); 1.51 (q, J=8, 2H); 1.2 (t, J=7, 3H); 1.0 (t, J=8, 3H).
Trans: NMR(CDCl₃): δ 6.8 (br. s., 1H); 4.2 (q, J=7, 2H); 3.8 (d, J=2, 1H); 3.2 (dd, J₁=2, J₂=7, 1H); 1.8 ((dq, J₁=2, J₂=8, 2H); 1.2 (t, J=7, 3H); 1.0 (t, J=8, 3H).

(f) 3-Azido-4-carboethoxazetidin-2-one

Preparation 13

4-Carboethoxy-3-(N-methyltrifluoroacetamido)azetidine-2-one-1-sulfonic acid tetrabutylammonium salt

To a solution of 140 mg of 4-carboethoxy-3-(N-methyltrifluoroacetamido)azetidine-2-one in 5 ml of pyridine at 80° was added 250 mg of sulfur trioxide pyridine complex, and the resulting mixture was stirred for 30 minutes at 80°. The solution was poured into 100 ml of 0.5 N KH₂PO₄ and extracted with 2 X 25 ml of methylene chloride. The combined organic washes were back-extracted with 25 ml of KH₂PO₄ solution. The combined aqueous phases were then treated with 680 mg of tetrabutylammonium
hydrogen sulfate and extracted with 3 X 50 ml of methylene chloride. After drying (sodium sulfate) and evaporation of the organic phase the crude 4-carboethoxy-3-(N-methyltrifluoroacetamido)azetidine-2-one-l-sulfonic acid tetrabutylammonium salt was chromatographed to yield an oil.

NMR (CDCl₃): δ 5.3 (d, J=6, 1H), 4.7 (d, J=6, 1H), 4.15 (q, J=7, 2H), 3.2 (m, 11H), 0.8-1.8 (m, 31H).

Applying the same procedure as described above, the following tetrabutylammonium salts of other azetidine derivatives were prepared:

(a) 4-Carboethoxy-3-methoxyazetidin-2-one-l-sulfonic acid tetrabutylammonium salt

NMR (CDCl₃): δ 4.55 (d, J=6, 1H), 4.5 (d, J=6, 1H), 4.1 (q, J=7, 2H), 3.4 (s, 3H), 3.2 (m, 8H), 0.8-1.8 (m, 31H).

(b) 4-Carboethoxy-3-vinylazetidin-2-one-l-sulfonic acid tetrabutylammonium salt

Preparation 14

4-Carboethoxy-1-(p-nitrobenzenesulfonyl)-3-phenylazetidin-2-one

To a solution of 720 mg of 4-carboethoxy-3-trans-phenylazetidin-2-one in 20 ml methylene chloride at 0° were added sequentially 595 mg of p-nitrobenzenesulfonyl chloride and 0.48 ml of DBU. The solution was stirred for several hours, diluted with 50 ml of methylene chloride, washed once with water and dried over sodium sulfate. Filtration and
evaporation gave a crude residue which was chromatographed to yield pure 4-carboethoxy-1-(p-nitrobenzenesulfonyl)-3-phenyl-azetidin-2-one. NMR (CDCl₃): δ 8.3 (d, J=9, 2H), 8.2 (d, J=9, 2H), 7.2 (br.s., 5H), 4.0 (q, J=7, 2H), 3.7 (m, 2H), 1.2 (t, J=7, 3H). Similarly prepared was the corresponding cis-3-phenyl compound. NMR (CDCl₃): δ 8.4 (d, J=9, 2H), 8.25 (d, J=9, 2H), 7.2 (s, 5H), 5.0 (s, 1H), 3.7 (m, 3H), 0.85 (t, 5=7, 3H).

Following the same procedure as described above but using appropriate reagents, the following compounds were prepared:

(a) 4-Carboethoxy-1-(p-nitrobenzensulfonyl)-3-vinyl-azetidin-2-one

NMR (CDCl₃): cis: δ 8.3 (d, J=9, 2H), 8.2 (d, J=9, 2H), 5.2-6.0 (m, 3H), 4.0-4.6 (m, 4H), 1.2 (t, J=7, 3H); trans: δ 8.2 (d, J=9, 2H), 8.15 (d, J=9, 2H), 5.2-6.0 (m, 3H), 3.9-4.4 (m, 4H), 1.25 (t, J=7, 3H).

(b) 4-Carboethoxy-3-ethyl-1-(p-nitrobenzensulfonyl)-azetidin-2-one

(c) 3-Azido-4-carboethoxy-1-(p-nitrobenzensulfonyl) azetidin-2-one

(d) 4-Carboethoxy-3-chloro-1-(p-nitrobenzensulfonyl)-azetidin-2-one
Preparation 15

4-Carboethoxy-3-phenyl-1-trifluoromethanesulfenylazetidin-2-one

To a mixture of 1.2 g of 4-carboethoxy-3-phenylazetidin-2-one and 1.2 ml of triethylamine in 25 ml of methylene chloride at 0°C was added dropwise over 10 minutes 11.25 ml of a 10% solution of trifluoromethanesulfenyl chloride in ether. After stirring for several hours the solution was washed with water, dried over sodium sulfate, filtered and evaporated. The crude residue was chromatographed to yield pure 4-carboethoxy-3-phenyl-1-trifluoromethanesulfenylazetidin-2-one as an oil.

NMR (CDCl₃): 6 7.2 (s, 5H), 4.6 (d, J=3, 1H), 4.3 (m, 3H), 1.3 (t, J=7, 3H).

Preparation 16

1-Tosyloxyethyl-3-n-Propyl-4-p-nitrophenylthioazetidin-2-one

Step A: Preparation of 3-Propyl-4-p-nitrophenylthioazetidin-2-one

3-Propyl-4-acetoxy azetidinone, 171 mg, is refluxed with 200 mg p-nitrophenyl thiol in 10 ml benzene for 6 hours. The solution is washed 3x with aqueous Na₂CO₃, dried with MgSO₄, filtered and evaporated. The residue is chromatographed on silica gel, eluting with 10:1 CHCl₃-EtOAc, affording 3-propyl-4-p-nitrophenylthioazetidin-2-one.
Step B: Preparation of 1-Tosyloxymethyl-3-n-propyl-4-p-nitrophenylthio azetidin-2-one

3-Propyl-4-p-nitrophenylthioazetidin-2-one, 266 mg, is stirred overnight at room temperature with 0.25 ml aqueous formalin (37%) and 17 mg K₂CO₃. Water and formaldehyde are removed in vacuo, and flushed with 2 ml pyridine. The residue is taken up in 4 ml pyridine and treated for 1 hour at room temperature with 200 mg p-toluenesulfonyl chloride.

The pyridine is evaporated and replaced with 5 ml benzene. The solution is washed with aqueous H₃PO₄ and then aqueous K₂HPO₄, dried with MgSO₄, filtered and evaporated. The residue is chromatographed on silica gel, eluting with 25:1 CHCl₃-EtOAc, providing 1-tosyloxymethyl-3-n-propyl-4-p-nitrophenylthio-azetidin-2-one.

Preparation 17

1-Tosyloxymethyl-3-n-propyl-4-p-nitrophenylsulfinyl azetidin-2-one

1-Tosyloxymethyl-3-n-propyl-4-p-nitrophenylsulfinylazetidin-2-one, 450 mg, is treated for 1/2 hour in 10 ml CH₂Cl₂ with 172 mg m-chloroperbenzoic acid. The solution is washed with aqueous K₂HPO₄, dried with MgSO₄, filtered and evaporated, leaving pure 1-tosyloxymethyl-3-n-propyl-4-p-nitrophenylsulfinyl azetidine-2-one.
Preparation 18

1-Acetoxymethyl-4-p-nitrophenylsulfinyl-3-n-propyl-azetidin-2-one

Step A: Preparation of 3-n-propyl-4-p-nitrophenylthioazetidin-2-one

3-n-Propyl-4-acetoxyazetidinone (1.164 g, 6.58 mmole) and 1.02 g (6.58 mmole) p-nitrothiophenol were heated in a tube in the steam bath for 3.5 hours. The reaction mixture was cooled, diluted with 100 ml ethyl acetate, and the organic phase was washed with 100 ml water, 70 ml 1M H₂PO₄ and 3x100 ml saturated K₂CO₃. The organic phase was dried over magnesium sulfate, filtered, and solvent removed in vacuo to yield 1.53 g of yellow crystals which were chromatographed on a silica gel column in chloroform-ethyl acetate (4:1) to give 359 mg (19%) of 3-n-propyl-4-p-nitrophenylthioazetidin-2-one.

NMR (CDCl₃): 6 0.92 (tr, 3H), 1.2-1.6 (br m, 4H), 3.10 (tr, 1H), 4.91 (d, 1H), 7.0 (br s, 1H), 7.50 (d, 2H), 8.20 (d, 2H).

Step B: Preparation of 1-Acetoxymethyl-4-p-nitrophenylthio-3-n-propylazetidin-2-one

A mixture of 273 mg (0.94 mmole) azetidinone from Step A, 26.3 mg paraformaldehyde and 178 mg (0.56 mmole) cesium carbonate was stirred in 20 ml dry tetrahydrofuran at ambient temperature 16.5 hours under nitrogen. A mixture of 430 µl pyridine and 2.56 ml acetic anhydride was added to the reaction mixture and the stirring continued 5 more hours. The solvents were removed in vacuo to give 604 mg crude product which was chromatographed on a silica gel.
flash column in hexane-ethyl acetate 3:1. This gave 102 mg (30%) of 1-acetoxymethyl-4-p-nitrophenylthio-3-n-propylazetidin-2-one.

NMR (CDCl₃): 6 1.0 (tr, 3H), 1.2-1.85 (br m, 4H), 2.1 (s, 3H), 3.22 (tr, 1H), 4.95 (d, 1H), 5.18 (ABBA pattern, J₁=30H, J₂=5H, 2H), 7.65 (d, 2H), 8.22 (d, 2H).

**Step C: Preparation of 1-Acetoxymethyl-4-p-nitrophenylsulfinyl-3-n-propylazetidin-2-one**

To a solution of 46 mg (0.127 mmole) azetidinone from Step B in 4 ml CH₂Cl₂ and 4 ml saturated aqueous NaHCO₃ was added 27 mg (0.127 mM) m-chloroperbenzoic acid and the reaction mixture stirred vigorously 15 minutes. The phases were separated and the organic phase was dried over MgSO₄, filtered and stripped to yield 57 mg crude product which was chromatographed on a 1000 μ silica gel prep TLC plate in chloroform-ethyl acetate 4:1 to yield 15 mg (31%) of 1-acetoxymethyl-4-p-nitrophenylsulfinyl-3-n-propylazetidin-2-one.

NMR (CDCl₃): 6 0.93 (tr, 3H), 1.2-1.8 (br m, 4H), 2.1 (s, 3H), 3.55 (tr, 1H), 4.66 (d, 1H), 5.04 (ABBA pattern, J₁=34H, J₂=6H, 2H), 8.2 (d, 2H), 8.52 (d, 2H).

**Preparation 19**

4-Acetoxy-3-n-propylazetidin-2-one-1-sulfonic acid tetrabutylammonium salt

A solution of 82 mg (0.463 mmole) 3-propyl-4-acetoxy azetidin-2-one in 5 ml pyridine was heated to 80°. 221 Mg (1.39 mmole) sulfur trioxide-pyridine
complex was added and the reaction mixture stirred at 80° one hour. It was then poured into 100 ml 0.5M KH₂PO₄ (aqueous) and washed with 2×25 ml CH₂Cl₂. The combined organic washes were backwashed with 25 ml 0.5M KH₂PO₄. 157 Mg (0.463 mmole) Bu₄NHSO₄ was added to the combined aqueous phases. This was extracted with 2×25 ml CH₂Cl₂ and the combined extracts were dried over MgSO₄, filtered, and stripped in vacuo to yield 12.4 mg of an oily residue which was chromatographed on a small silica gel column, eluted first with 75 ml hexane/ethyl acetate (3:1) to remove starting material, then with 100 ml ethyl acetate/methanol (4:1) to yield 13 mg (5.7%) 4-acetoxyl-3-n-propylazetidin-2-one-1-sulfonic acid tetrabutylammonium salt.

NMR (CDCl₃): δ 1.0 (m, 16H), 1.75 (br m, 20H), 2.16 (s, 3H), 2.90 (br s, H), 3.1 (tr, 1H), 3.3 (tr, 8H), 4.08 (br tr, 1H), 6.18 (s, 1H).

EXAMPLE 1
(3R,4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carboxyphenoxy)azetidin-2-one

Step A: Preparation of (3R,4S)-1-t-butyldimethylsilyl-3-methylazetidin-2-one-4-carboxylic acid

To a solution of 27.5 ml of diisopropylamine in 150 ml of THF at -20°C was added 73.5 ml of 2.4N n-butyl lithium in hexane. After 15 minutes, the solution was cooled to -70°C and a solution of 20 gm of (4S)-1-t-butyldimethylsilylazetidin-2-one-4-carboxylic acid in 75 ml of THF was added. The solution was warmed to -20°C for 15 minutes before a
solution of 13.5 mL of methyl iodide in 20 mL of THF was added. After 30 minutes at -20 to 0°C, the reaction was diluted with 300 mL of ether and then poured into a mixture of ice and 400 mL of 1N HCl. The layers were separated and the aqueous layer extracted with ether. The ether layers were washed with brine, dried over sodium sulfate and evaporated. The residue was crystallized from hexane to give 12-15 gms of (3R,4S)-1-t-butyldimethylsilyl-3-methylazetidin-2-one-4-carboxylic acid.

NMR (CDCl₃): δ .14 (2, 3H), .32 (s, 3H), .91 (d, 3H), .98 (s, 9H), 3.34 (dq, 1H), 3.71 (d, 1H)

Step B: Preparation of (3R,4S)-1-t-butyldimethylsilyl-3-ethyl-3-methylazetidin-2-one-4-carboxylic acid

To a solution of 13 mL of diisopropylamine in 75 mL of THF at -20°C was added 35 mL of 2.4 M n-butyl lithium in hexane. After 15 minutes the solution was cooled to -70°C and a solution of 10 gms of (3R,4S)-1-t-butyldimethylsilyl-3-methylazetidin-2-one-4-carboxylic acid in 50 mL of THF was added. The solution was warmed to -20°C for 15 minutes and a solution of 6.7 mL of ethyl iodide in 10 mL of THF was added. After 30 minutes at -20° to 0°C the reaction was diluted with ether and poured into a mixture of ice and 1 N HCl. The layers were separated and the aqueous layer extracted with ether. The ether layers were each washed with brine, dried over sodium sulfate and evaporated. The residue was crystallized from a minimum amount of hexane to give 8.8 gms of (3R,4S)-1-t-butyldimethylsilyl-3-ethyl-3-methylazetidin-2-one-4-carboxylic acid.
Step C: Preparation of (3R, 4S)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one

To a solution of 13.0 gms of (3R, 4S)-1-t-butylidimethylsilyl-3-ethyl-3-methylazetidin-2-one-4-carboxylic acid in 75 mL of DMF and 15 mL of acetic acid under N₂ was added 23 gms of lead teta-acetate. The reaction was heated at 45-50°C for 18 hours and then poured into ice water and extracted into 2 portions of ether. The ether layers were washed with water, dilute sodium bicarbonate solution and brine, dried over sodium sulfate and evaporated to give 13 gm of crude oil containing a mixture of (3R, 4S) and (3R, 4R)-4-acetoxy-3-ethyl-3-methylazetidin-2-one. To this mixture in 50 mL of acetone was slowly added a solution of 14 gms of t-butyl 4-hydroxybenzoate in 50 mL of acetone, 5 mL of water and 29 mL of 2N sodium hydroxide. The reaction was stirred at room temperature for 64 hours and then diluted with water and extracted with 2 portions of ether. The ether layers were washed with water, diluted sodium bicarbonate solution and brine, dried over sodium sulfate and evaporated. The residue was prep LC'ed with 15-25% ethylacetate/hexanes to give 6.3 gm of the higher R₆ (4R) ether and 1.5 gm of the desired (3R, 4S)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one.

NMR (CDCl₃): δ 1.0 (t, 3H), 1.38 (s, 3H), 1.54 (s, 9H), 1.6-2.0 (m, 2H), 5.30 (s, 1H) 6.7 (brs, 1H), 6.78 (d, 2H), 7.90 (d, 2H).
Step D: Preparation of (3R, 4S)-1-(benzylamino-carbonyl)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one

To a solution of 1.5 gm of (3R, 4S)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one in 25 mL of methylene chloride was added 1.2 mL of benzyl isocyanate, 1.4 mL of triethylamine and 10 mg of 4-dimethylaminopyridine. The reaction was stirred at room temperature for 16 hours and then evaporated. The residue was flash chromatographed eluting with 10 to 25% EtoAc/Hexane to give 2.3 gm of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxy azetidin-2-one.

NMR (CDCl₃): 6.98 (t, 3H), 1.36 (s, 3H) 1.50 (s, 9H), 1.62 (m, 1H), 1.84 (m, 1H), 4.42 (d, 2H), 5.64 (s, 1H), 6.80 (brt, 1H), 7.06 (d, 2H), 7.24 (brs, 5H), 7.90 (d, 2H).

Step E: Preparation of (3R, 4S)-1-(benzylamino-carbonyl)-3-ethyl-3-methyl-4-(4-carboxy)-phenoxyazetidin-2-one

To 2.3 gms of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one in an ice bath under N₂ was added 5 mL of anisole and then 25 mL of precooled trifluoroacetic acid. After 1.5 hours at 0°C, the volatiles were removed in vacuo without heating and the residue flash chromatographed using hexane, then 15% EtoAc/Hexane, then 1% HoAc in 15% EtoAc/hexanes to give after ether trituration 1.8 gms of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carboxy)phenoxyazetidin-2-one.
EXAMPLE 2

Starting with 3,3-diethyl-4-acetoxyazetidin-2-one as prepared in Scheme (d) followed by displacement of the acetate with the appropriate phenol and acylation of the nitrogen with the corresponding chiral isocyanate as shown in Scheme (h) and example 7, steps C-E, the following compounds were prepared. The diastereomers obtained on acylation were separated by silica gel chromatography using 10-30% ethylacetate/hexane solvent mixtures.

(4S)-3,3-diethyl-1-((R)-α-ethylbenzylaminocarbonyl)-4-(4-carboxyethyl)phenoxyazetidin-2-one.

NMR (CDCl₃): 6 0.91 (t, 3H, J=7Hz), 0.91 (t, 3H, J=7Hz), 1.07 (t, 3H, J=7Hz), 1.34 (m, 6H), 1.65 - 2.05 (m, 6H), 3.57 (s, 2H), 4.88 (q, 1H, J=8Hz), 5.58 (s, 1H), 7.0 (d, 1H, J=8Hz), 7.1 - 7.45 (m, 9H)

(4S)-3,3-diethyl-1-((R)-α-n-propylbenzylaminocarbonyl)-4-(4-carboxyethyl)phenoxyazetidin-2-one.

NMR (CDCl₃): 6 0.91 (t, 3H, J=7Hz), 0.91 (t, 3H, J=7Hz), 1.07 (t, 3H, J=7Hz), 1.34 (m, 6H), 1.65 - 2.05 (m, 6H), 3.57 (s, 2H), 4.88 (q, 1H, J=7Hz), 5.58 (s, 1H), 7.0 (d, 1H, J=7Hz), 7.1 - 7.45 (m, 9H)
(4S)-3,3-diethyl-1-((R)-α-allyl-(4-methyl)benzylamino)-carbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one.

NMR (CDCl$_3$): δ 0.96 (t, 3H, J=7Hz), 1.07 (t, 3H, J=7Hz), 1.7 - 2.1 (m, 4H), 2.32 (s, 3H), 2.57 (t, 2H, J=7Hz), 3.58 (s, 2H), 4.95 (q, 1H, J=7Hz), 5.14 (m, 2H), 5.58 (s, 1H), 5.66 (m, 1H), 7.03 (d, 1H, J=7Hz), 7.16 (s, 4H), 7.19 (s, 4H).

(4S)-3,3-diethyl-1-((R)-α-allyl(3,4-methylenedioxy)-benzylaminocarbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one.

NMR (CDCl$_3$): δ 0.96 (t, 3H, J=7Hz), 1.05 (t, 3H, J=7Hz), 1.65 - 2.05 (m, 4H), 2.54 (t, 2H, J=6Hz) 4.87 (q, 1H, J=7Hz), 5.05 - 5.2 (m, 2H), 5.58 (s, 1H), 5.66 (m, 1H), 5.94 (s, 2H), 6.76 (s, 3H), 6.98 (d, 1H, J=7Hz), 7.2 (m, 4H).

(4S)-3,3-diethyl-1-((R)-α-n-propyl(3,4-methylenedioxy)-benzylaminocarbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one.

NMR (CDCl$_3$): δ 0.9 (t, 3H, J=7Hz), 0.94 (t, 3H, J=7Hz), 1.06 (t, 3H, J=7Hz), 1.3 (m, 2H), 1.65 - 2.1 (m, 6H), 3.58 (s, 2H), 4.76 (q, 1H, J=7Hz), 5.58 (s, 1H), 5.92 (s, 2H), 6.15 (s, 3H) 6.88 (d, 1H, J=7Hz), 7.2 (m, 4H).

(4S)-3,3-diethyl-1-((R)-α-n-propyl(4-methyl)-benzylaminocarbonyl)-4-(4-carboxy)phenoxyazetidin-2-one.

NMR (CDCl$_3$): δ 0.91 (t, 3H, J=7Hz), 0.98 (t, 3H, J=7Hz), 1.07 (t, 3H, J=7Hz) 1.32 (m, 2H), 1.65 - 2.1 (m, 6H), 2.33 (s, 3H), 4.83 (q, 1H, J=7Hz),
5.71 (s, 1H), 6.93 (d, 1H, J=7Hz), 7.16 (s, 4H), 7.25 (d, 2H, J=8Hz), 8.04 (d, 2H, J=8Hz).

(4S)-3,3-diethyl-1-((R)-α-n-propyl(4-methyl)-benzylaminocarbonyl)-4-(4-carboxymethyl)phenoxy-azetidin-2-one.

NMR (CDCl₃): 0.9 (t, 3H, J=7Hz), 0.93 (t, 3H, J=7Hz), 1.07 (t, 3H, J=7Hz) 1.28 (m, 2H), 1.7 - 2.1 (m, 6H), 2.33 (s, 2H), 3.6 (s, 2H), 4.81 (q, 1H, J=7Hz), 5.56 (s, 1H), 6.93 (d, 1H, J=7Hz), 7.15 (s, 4H), 7.2 (s, 4H).
CLAIMS
The claims defining the invention are as follows:

1. A compound of formula (I)

\[ R^1 \]

\[ \text{O} \]

\[ \text{CONHCH}_2 \]

\[ \text{I} \]

\[ X_5 \]

\[ X_6 \]

wherein \( R \) and \( R^1 \) independently are \( C_{1-6} \) alkyl or \( C_{1-6} \) alkoxy-\( C_{1-6} \) alkyl; \( M \) is hydrogen, \( C_{1-6} \) alkyl, \( C_{2-6} \) alkenyl, or \( C_{1-6} \) alkoxy-\( C_{1-6} \) alkyl; \( X_5 \) is hydrogen, \( C_{1-6} \) alkyl, halo-\( C_{1-6} \) alkyl, \( C_{2-6} \) alkenyl, \( C_{2-6} \) alkylnyl, carboxy, carboxy-\( C_{1-6} \) alkyl, carboxy-\( C_{1-6} \) alkyllcarbonyl, carboxy-\( C_{1-6} \) alkyllcarbonylamino, carboxy-\( C_{2-6} \) alkenyl, hydroxy-\( C_{1-6} \) alkyl, \( C_{1-6} \) alkyllcarbonyl, \( C_{1-6} \) alkyllcarbonylamino, or di-(\( C_{1-6} \) alkyl)-amino-\( C_{1-6} \) alkyl; and \( X_6 \) is hydrogen, \( C_{1-6} \) alkyl, halo, carboxy, \( C_{1-6} \) alkoxyl, phenyl, \( C_{1-6} \) alkyllcarbonyl, di-(\( C_{1-6} \) alkyl)amino, phenoxy, methylenedioxy, 2,3-furanyl, or 2,3-thienyl; or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein \( R \) and \( R^1 \) independently are \( C_{1-6} \) alkyl; and \( X_5 \) is carboxy or carboxy-\( C_{1-6} \) alkyl.

3. A compound of Claim 1 or Claim 2 wherein \( M \) is \( C_{1-3} \) alkyl or allyl; and \( X_6 \) is hydrogen, \( C_{1-6} \) alkyl, 3,4-methylenedioxy or phenyl.

4. A compound of Claim 2 or Claim 3 wherein \( R \) is ethyl; and \( R^1 \) is methyl or ethyl.

5. A compound of Claim 4 wherein \( M \) is \( C_{1-3} \) alkyl or allyl; \( X_5 \) is carboxy or carboxy-\( C_{1-6} \) alkyl; and \( X_6 \) is hydrogen, \( C_{1-6} \) alkyl, 3,4-methylenedioxy or phenyl.

6. A compound of Claim 5 wherein \( R \) and \( R^1 \) are ethyl; \( M \) is \( n \)-propyl; \( X_5 \) is 4-carboxymethyl; and \( X_6 \) is 4-methyl.

7. N-benzylalkylaminocarbonyl-4-phenoxy-azetidin-2-one derivatives, substantially as hereinbefore described with reference to Examples 1 and 2.

8. A process for the preparation of the compounds of any one of Claims 1 to 7, which process comprises:

reacting a compound of the following formula (B)
with a compound of the formula (C)

\[
\begin{array}{c}
\text{HO} \\
\text{C} \quad \text{X}_5 \\
\end{array}
\]

\[\text{(C)}\]

wherein \(X_5'\) is hydrogen, \(C_{1-6}\) alkyl, halo-\(C_{1-6}\) alkyl, \(C_{2-6}\) alkenyl, \(C_{2-6}\) alkynyl, \(C_{1-6}\) alkoxy carbonyl, \(C_{1-6}\) alkoxycarbonyl-\(C_{1-6}\) alkyl, \(C_{1-6}\) alkoxy carbonyl-\(C_{1-6}\) alkyl carbonyl, \(C_{1-6}\) alkoxy carbonyl-\(C_{1-6}\) alkyl carbonyl amino, \(C_{1-6}\) alkoxy carbonyl-\(C_{2-6}\) alkenyl, hydroxyalkyl, \(C_{1-6}\) alkyl carbonyl, \(C_{1-6}\) alkyl carbonyl amino, or di-\((C_{1-6}\) alkyl)amino-\(C_{1-6}\) alkyl under basic conditions to afford a compound of the formula (D)

\[
\begin{array}{c}
\text{R} \\
\text{O} \\
\text{NH} \\
\text{X}_5 \\
\end{array}
\]

\[\text{(D)}\]

and (2) reacting compound (D) with a compound of the formula (E)

\[
\begin{array}{c}
\text{O=C=N-CH} \\
\text{M} \\
\text{X}_6 \\
\end{array}
\]

\[\text{(E)}\]

under basic conditions, and optionally converting \(X_5'\) into \(X_5\), to yield the compound of formula (I)

\[
\begin{array}{c}
\text{R} \\
\text{O} \\
\text{CONHCH} \\
\text{X}_5 \\
\end{array}
\]

\[\text{(I)}\]

9. A process of Claim 8 wherein step (1) is in the presence of an alkali metal hydroxide, step (2) is in the presence of a tri-(\(C_{1-6}\) alkyl)amine; and the conversion of \(X_5'\) into \(X_5\) is accomplished in the presence of a strong acid.

10. A process of preparing N-benzylalkylaminocarbonyl-4-phenoxy-
azetidin-2-one azetidinones which process is substantially as hereinbefore described with reference to Examples 1 or 2.

11. The product of the process of any one of Claims 8 to 10.

12. A pharmaceutical composition for the inhibition of human leukocyte elastase which comprises a nontoxic therapeutically effective amount of a compound of any one of Claims 1 to 7 and a pharmaceutically acceptable carrier.

13. A method for the treatment or prophylaxis of inflammation, fever or pain in a patient requiring said treatment or prophylaxis, which method comprises administering to said patient an effective amount of at least one compound according to any one of Claims 1 to 7, or of a composition according to Claim 12.

DATED this SIXTH day of APRIL 1989
Merck & Co., Inc.

Patent Attorneys for the Applicant
SPRUSON & FERGUSON
END