



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 501/00, A61K 31/545	A1	(11) International Publication Number: WO 92/17482 (43) International Publication Date: 15 October 1992 (15.10.92)
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(54) Title: NOVEL 2-SPIROCYCLOPROPYL 4-ACYLCEPHEMS AND PROCESSES FOR THE PREPARATION THEREOF (I) (57) Abstract Derivatives of 2-spirocyclopropyl 4-acylcephem sulfones of formula (I) are provided which are useful as potent elastase inhibitors and hence are useful in the prevention, control and treatment of inflammatory conditions, especially arthritis and emphysema.		

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NOVEL 2-SPIROCYCLOPROPYL 4-ACYLCEPHEMS AND PROCESSES
FOR THE PREPARATION THEREOFBACKGROUND OF THE INVENTION:

5 Serine proteases are an important class of enzymes which have a serine residue at the active site. Elastase is one such serine protease which is released from azurophilic granules of human polymorphonuclear leukocytes (PMN) and macrophages by inflammatory stimuli. Human
10 leukocyte elastase (HLE) has been reported to be capable of degrading the connective tissue component elastin in addition to a number of other connective tissue substrates resulting in a variety of clinically important inflammatory diseases e.g. pulmonary emphysema, rheumatoid arthritis,
15 spondylitis, psoriasis, osteoarthritis, chronic bronchitis, cystic fibrosis, and respiratory distress syndrome (RDS). Under normal conditions, the proteolytic activity of elastase in the extracellular environment is limited by the presence of excess of natural inhibitors like α_1 protease
20 inhibitor (α_1 PI) and α_2 macroglobulin. Marked reduction in serum α_1 PI either genetic or due to oxidants, results in protease-antiprotease imbalance and thus leads to uncontrolled proteolysis of connective tissue, primarily of the lung and joints [J. Travis et al. Ann. Rev. Biochem.,
25 52, 655 (1983)]. Pulmonary emphysema is a disease characterized by a progressive loss of lung elasticity and resulting in respiratory difficulty. This loss of lung elasticity is caused by progressive destruction of the structure of lung tissue by elastase released from
30 leukocytes. Use of low molecular weight synthetic human leukocyte elastase (HLE) inhibitors would be an ideal

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therapeutic approach in controlling the various inflammatory conditions.

Cephem sulfones have been described as elastase inhibitors in various patents and publications. See, for example, US patent no. 4, 547,371; EP patent nos. 267,723 and 337,704; AU patent nos. 80624/87 and 32762/89; J. Med. Chem., 33, 2513 (1990); J. Med. Chem., 33, 2522 (1990); J. Med. Chem., 33, 2529 (1990); J. Org. Chem., 54, 3907 (1989), Eur. J. Med. Chem., 24, 599 (1989); Am. Rev. Respir. Dis., 141, 672 (1990); J. Cell. Biochem., 39, 47 (1989); and Nature, 322, 192 (1986).

BRIEF SUMMARY OF THE INVENTION:

We have found that a group of new substituted cephalosporin sulfones are potent elastase inhibitors and hence are useful as anti-inflammatory or anti-degenerative agents. Accordingly, an object of this invention is to provide new elastase inhibitors which are useful for controlling various clinically important inflammatory or degenerative conditions mediated particularly by elastase.

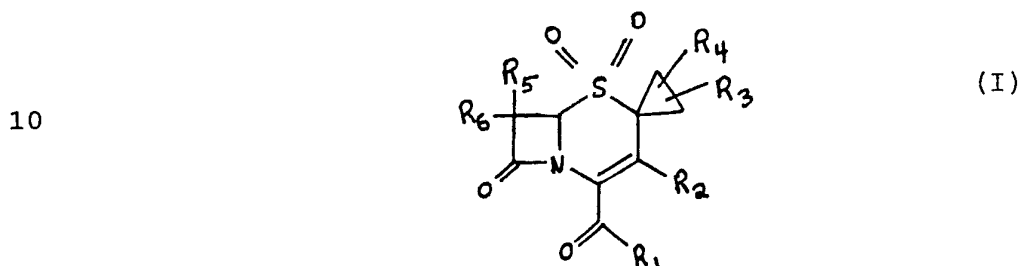
Another object of the present invention is to provide a pharmaceutical or veterinary composition for administering the active substituted cephalosporin sulfones as elastase inhibitors. Another object of the present invention is to provide a method of controlling inflammatory and degenerative diseases by administering a therapeutically effective amount of one or more of the active compounds of the present invention represented by the formula (I) in

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humans or warm-blooded mammals in need of such treatment.

The present invention relates to 2-spirocyclopropyl 4-acylcephem sulfones, their preparation, and to pharmaceutical and veterinary compositions containing them.

In one aspect, the present invention relates to a 2-spirocyclopropyl 4-acylcephem sulfone of the formula



wherein

R_1 is hydrogen; or C_{1-12} straight or branched alkyl; or C_{2-10} alkenyl; or C_{2-10} alkynyl; or C_{3-8} cycloalkyl; or C_{5-8} cyclo-alkenyl; or C_{6-10} aryl; or aralkyl; or aralkenyl; or aralkynyl; or (cycloalkyl)alkyl; or a monocyclic or polycyclic, saturated or unsaturated heterocyclic group containing from 1 to 4 of any one or more of the heteroatoms N, S, or O in each heterocyclic ring; or a fused polycyclic saturated or unsaturated heterocyclic group containing from 1 to 4 of any one or more of the heteroatoms N, S, or O in each heterocyclic ring; or heterocyclalkenyl; or heterocyclalkynyl; wherein the heterocycl, alkyl, alkenyl, and alkynyl groups are as defined above; wherein each of the above organic radicals is unsubstituted or substituted by one or more atoms or groups selected from chloro, bromo, fluoro, cyano, azido, nitro, formyl, C_{1-4} alkyl, trifluoromethyl, C_{2-4} alkenyl, alkynyl, C_{3-6} cycloalkyl,

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hydroxy, alkoxy, carboxy, $-(CH_2)_mCOOH$, $-(CH_2)_mCOOR_{10}$, $-COR_{10}$,
 $-COCF_3$, $-CONH_2$, $-CONHR_{10}$, $-NH_2$, $-NHR_{10}$, $-NR_{10}R_{11}$, $-NHSO_2R_{10}$,
 $-NHCOR_{10}$, $-NHC(=NH)NH_2$, $-OCOR_{10}$, $-OC(O)NH_2$, $-SH$, $-SR_{10}$,
 $-S(O)R_{10}$, $-S(O)_2R_{10}$, and

5 $-SO_3H$;

R_2 is selected from hydrogen; or chloro, bromo, or
fluoro; or $-C_{1-6}$ alkyl; or -trifluoromethyl; or $-C_{2-6}$ alkenyl
(substituted or unsubstituted); or $-C_{2-6}$ alkynyl
(substituted or unsubstituted); or $-C_{3-8}$ cycloalkyl, or
10 $-OR_7$; or $-S(O)_nR_7$; or $-CHO$; or $-COOH$; or $-CH_2O-R_7$; or $-CH_2S(O)_nR_7$; or $-C(O)R_7$; or $-C(O)OR_7$; or $-CH_2OC(O)R_7$; or
 $-CH_2SC(O)R_7$; or $-CH_2C_1$; or $-CH_2Br$; or $-CH_2OC(O)NH_2$; or
 $-CH_2NR_7R_8$; or $-CH_2NH(C_{1-4} \text{ alkyl})$, wherein the alkyl is
either unsubstituted or substituted; or $-CH_2NHC(O)R_7$; or
15 $-CH_2-NR_7R_8R_9$; or $-CH_2-S(O)_nHet$;

R_3 and R_4 are the same or different and may be
hydrogen; or C_{1-6} straight or branched alkyl group; or C_{6-10}
aryl group; or C_{3-8} cycloalkyl group; or aralkyl group; or
saturated or unsaturated monocyclic or fused polycyclic 3-8
20 membered heterocyclic group containing at least one
heteroatom chosen from O, S, and N; or a halogenated C_{1-6}
alkyl; or a hydroxy C_{1-6} alkyl; or $-CH_2COOH$; or $-COOH$; or
 $-COOC_{1-6}$ alkyl group; or $-CH_2COOC_{1-6}$ alkyl;

R_5 is R_1 ; or $-O-R_1$; or $-S(O)_nR_1$; $-OC(O)R_1$; $-OSO_2R_1$; or
25 $-NHC(O)R_1$; or $-NH-Z$; or halogen;

R_6 is hydrogen; or C_{1-4} alkyl; or C_{1-4} alkoxy; or
halogen;

R_7 , R_8 and R_9 are the same or different, and may be
hydrogen; or C_{1-6} lower straight or branched alkyl; or C_{2-6}

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alkenyl; or C₂₋₆ alkynyl; or C₃₋₈ cycloalkyl; or C₆₋₁₀ aryl;
 or aralkyl; or saturated or unsaturated monocyclic or fused
 polycyclic 3 to 8 membered heterocyclic ring containing at
 least one heteroatom chosen from O, S, and N; or, at least
 5 two of them, taken together with the nitrogen atom to which
 they are attached, form a heterocyclic ring;

R₁₀ and R₁₁ may be the same or different and represent
 C₁₋₆ straight or branched alkyl, phenyl, or benzyl;

Z is hydrogen; a mono-peptide composed of D or L -amino
 10 acids with the terminal amino group optionally acylated by
 -C(O)R₁ or -C(O)OR₁; or a di-peptide composed of D or L
 -amino acids with the terminal amino group optionally
 acylated by -C(O)R₁ or -C(O)OR₁; or a tripeptide composed of
 D or L -amino acids with the terminal amino group optionally
 15 acylated by -C(O)R₁ or -C(O)OR₁;

Het is a heterocyclic ring;

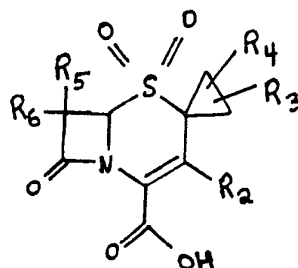
m is 0, 1, 2 and 3; and

n is 0, 1, or 2.

In another aspect, the present invention relates to a
 20 process for preparing a compound of formula (I) as defined
 above comprising:

i) providing a compound having the formula (II)

25

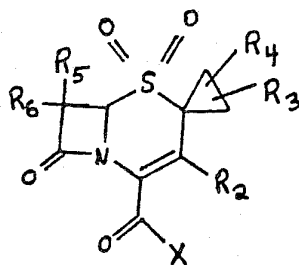


(II)

ii) converting the carboxyl group at the 4-position of
 the cephem nucleus of the formula (II) into an activated

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acid derivative having the formula (III)



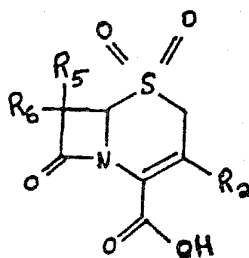
(III)

5

iii) treating the activated acid derivative of formula (III) with an organometallic derivative of R_1 to provide a compound having the formula (I).

10 In another aspect, the present invention relates to an alternative process for preparing a compound of Formula (I), comprising:

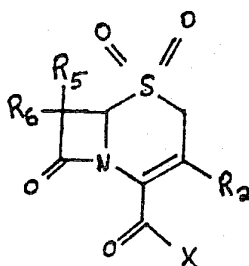
i) providing a compound having the formula (IV)



(IV)

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20 ii) converting the carboxyl group at the 4-position of the cephem nucleus of formula (IV) into an activated acid derivative having the formula (V)



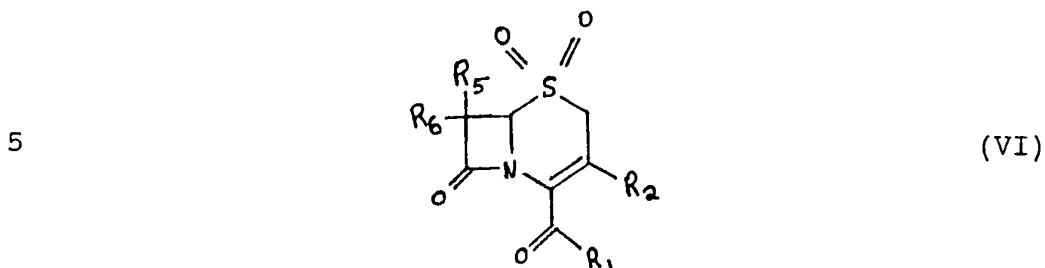
(V)

25

iii) treating the activated acid derivative of

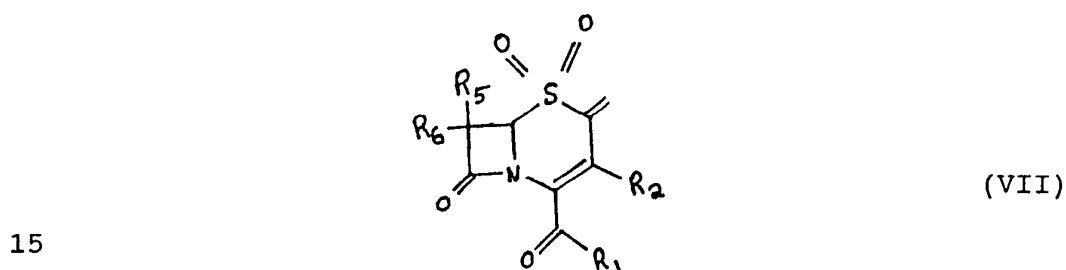
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formula (V) with an organometallic derivative of R_1 to provide a compound of the formula (VI)



iv) aminomethylating the compound of formula (VI) to provide a compound having the formula (VII)

10



v) carrying out a cycloaddition reaction to the compound of formula (VII) with $R_3R_4CN_2$ to provide a compound of the formula (I).

20

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS:

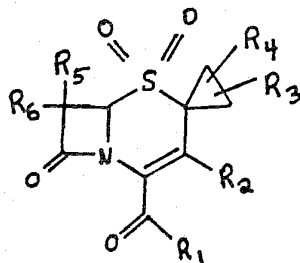
As summarized above, the present invention relates to 2-spirocyclopropyl 4-acylcephem sulfones which are potent elastase inhibitors, their preparation and to pharmaceutical and veterinary compositions containing them. More specifically, a 2-spirocyclopropyl 4-acylcephem sulfone of the structural formula (I) is

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them. More specifically, a 2-spirocyclopropyl 4-acylcephem sulfone of the structural formula (I) is provided:

5



(I)

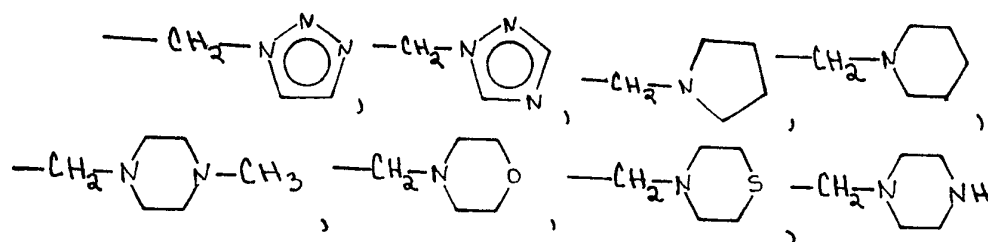
wherein R_1 in formula (I) represents a hydrogen atom; C_{1-12} straight or branched alkyl; C_{2-10} alkenyl; C_{2-10} alkynyl; C_{3-8} cycloalkyl; C_{5-8} cycloalkenyl; C_{6-10} aryl; aralkyl; aralkenyl; aralkynyl; (cycloalkyl) alkyl; a monocyclic or fused polycyclic, saturated or unsaturated heterocyclic group containing from 1 to 4 of any one or more of the heteroatoms N, S or O in each heterocyclic ring; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl, wherein the heterocycl, alkyl, alkenyl, and alkynyl groups are as defined above; wherein each of the above organic radicals is unsubstituted or substituted by one or more atoms or groups selected from halogen; cyano; azido; nitro; formyl; C_{1-4} alkyl; trifluoromethyl; C_{2-4} alkenyl; C_{2-4} alkynyl; C_{3-6} cycloalkyl; hydroxy or alkoxy; carboxy; $-(CH_2)_mCOOH$ or $-(CH_2)_mCOOR_{10}$; $-COR_{10}$ or $-COCF_3$; $-CONH_2$, $-CONHR_{10}$ or N-(carboxymethyl) carbamoyl ($-CONHCH_2COOH$); or $-NH_2$, $-NHR_{10}$ or $-NR_{10}R_{11}$; $-NHSO_2R_{10}$; $-NHCOR_{10}$; $-NHC(=NH)NH_2$; $-OCOR_{10}$; $-OC(O)NH_2$; or $-SH$ or $-SR_{10}$; $-S(O)R_{10}$; $-S(O)_2R_{10}$; $-SO_3H$; mono-, di-, or tri-substituted halomethyl, amino-

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methyl, hydroxymethyl, and cyanomethyl; wherein m is 0, 1, 2, and 3; R_{10} and R_{11} may be the same or different and represent C1-6 straight or branched alkyl, phenyl, or benzyl.

5 The preferred groups representing R_1 include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, neo-pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, ethenyl, propenyl, ethynyl, phenyl, benzyl,
 10 thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, pyrolyl, imidazolyl, furyl, thienyl, pyridyl and pyrimidinyl. Of these, the most preferred groups representing R_1 are hydrogen, methyl, ethyl, butyl, tert-butyl, neo-pentyl, cyclopropyl, phenyl, benzyl,
 15 dimethylphenyl, diphenylmethyl and propenyl.

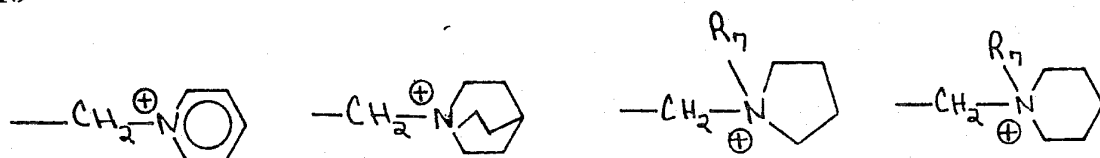
R_2 in the formula (I) may be selected from hydrogen, chloro, bromo or fluoro, C_{1-6} alkyl, trifluoromethyl, optionally substituted C_{2-6} -alkenyl, optionally substituted C_{2-6} alkynyl, C_{3-8} cycloalkyl, $-OR_7$, $-S(O)_nR_7$,
 20 $-CHO$, $-COOH$, $-C(O)R_7$, $-C(O)OR_7$, $-CH_2-O-R_7$, $-CH_2-S(O)_nR_7$, $-CH_2OC(O)R_7$, $-CH_2SC(O)R_7$, chloromethyl, bromomethyl, $-CH_2OC(O)NH_2$, $-CH_2NR_7R_8$, wherein R_7 and R_8 may be the same or different; R_7 and R_8 taken together with the nitrogen atom may represent a heterocyclic ring. Some
 25 representative examples include:



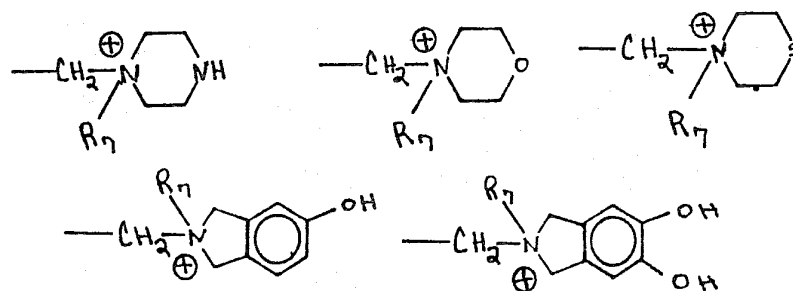
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R_2 may also be a quaternary ammonium group
 $-\text{CH}_2-\overset{\oplus}{\text{N}}\text{R}_7\text{R}_8\text{R}_9$, wherein R_7 and R_8 may be the same or
different; R_7 and R_8 taken together with the nitrogen atom
5 may represent a heterocyclic ring. R_8 and R_9 may be the
same or different; R_8 and R_9 taken together with the
nitrogen atom may represent a heterocyclic ring. R_7 and
 R_9 may be the same or different. R_7 and R_9 taken together
with the nitrogen atom may represent a heterocyclic ring.
10 R_7 , R_8 and R_9 taken together with the nitrogen atom to
which they are attached may represent an aromatic
heterocyclic ring. Some representative examples include:

15



20



wherein

25 R_7 is hydrogen, C_{1-6} lower straight or branched alkyl,
 C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{6-10} aryl,
aralkyl, aralkenyl, aralkynyl, heterocyclyl ring and
heterocyclylalkyl;

R_8 is R_7 ;

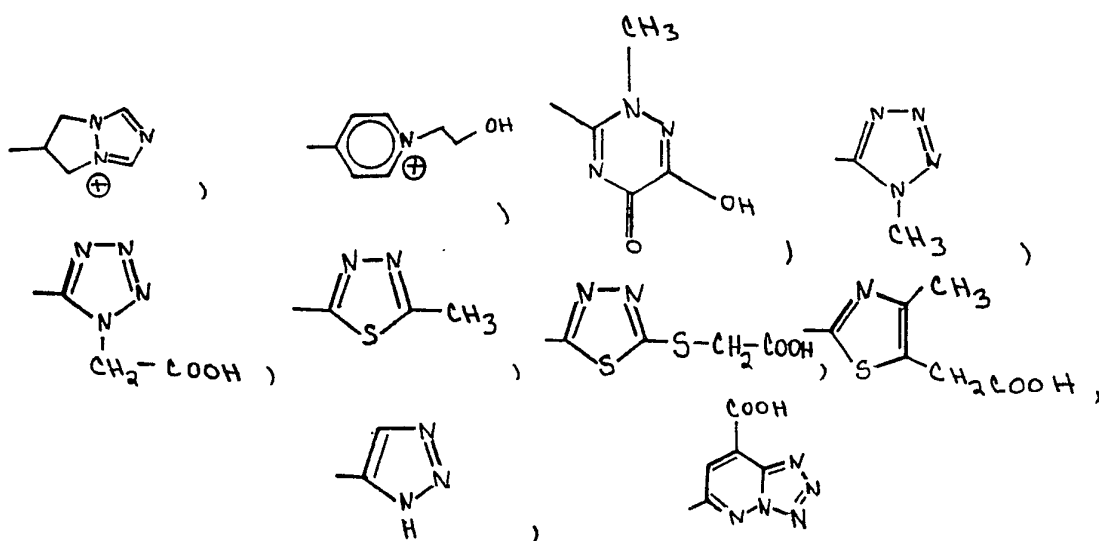
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R_9 is R_7 ;

"heterocyclyl" is a saturated or unsaturated monocyclic or fused polycyclic 3-8 membered heterocyclic group containing at least one heteroatom chosen from O, S and N;

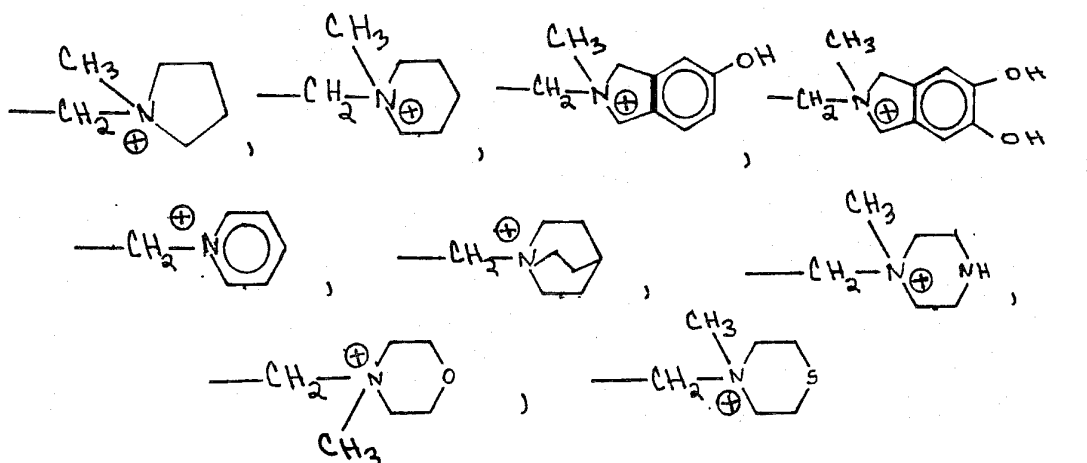
and n is either 0, 1 or 2.

R_2 may also be $NH-Z$, wherein Z is hydrogen, a mono, di- or tripeptide composed of D or L α -aminoacids with the terminal amino group either free or acylated by $-C(O)R_1$ or $-C(O)OR_1$; $-CH_2-NH-C(O)R_7$; $-CH_2-S(O)_nHet$, wherein n is either 0, 1 or 2 and Het is a heterocyclic ring. Het is preferably selected from:



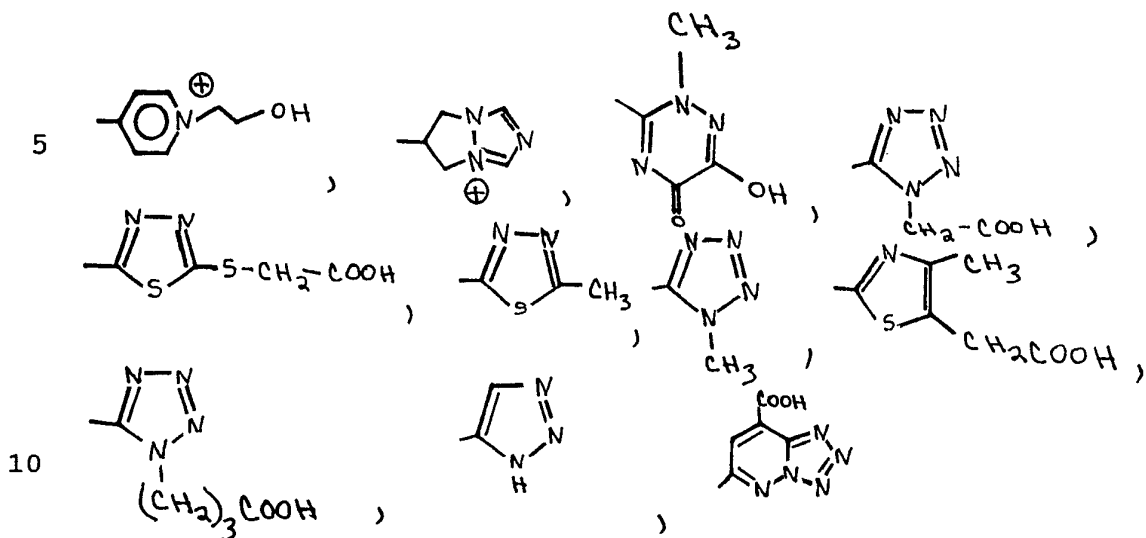
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- The preferred groups representing R_2 include
- hydrogen; chloro; methyl; trifluoromethyl; hydroxy;
methoxy; ethoxy; vinyl; cyclopropyl; acetoxymethyl;
hydroxymethyl; chloromethyl; bromomethyl;
- 5 carbamoyloxymethyl; methylthio; formyl; acetyl; benzoyl;
carboxy; methoxycarbonyl; ethoxycarbonyl; tert--
butoxycarbonyl; methoxymethyl; ethoxymethyl; isopropoxy-
methyl; phenoxymethyl; 3-pyridyloxymethyl, wherein the
phenyl and pyridyl rings may be unsubstituted or
- 10 substituted by one or two similar or two different groups
selected from hydroxy, carboxy, amino, and C_{1-4}
alkoxycarbonyl; methylthiomethyl; methylsulphonylmethyl;
phenylthiomethyl; phenylsulphonylmethyl;
(1,2,3-triazol-1-yl)methyl; (1,2,4-triazol-1-yl)methyl;
- 15 acetylthiomethyl; aminomethyl; $-CH_2-NH$ (C_{1-4} alkyl),
wherein the alkyl group is either unsubstituted or
substituted, preferably by a carboxy group;
trialkyl-ammonium methyl group wherein the alkyl group is
selected from methyl, ethyl and propyl; alkyl
- 20 (cycloalkyl) ammonium methyl, preferably selected from:

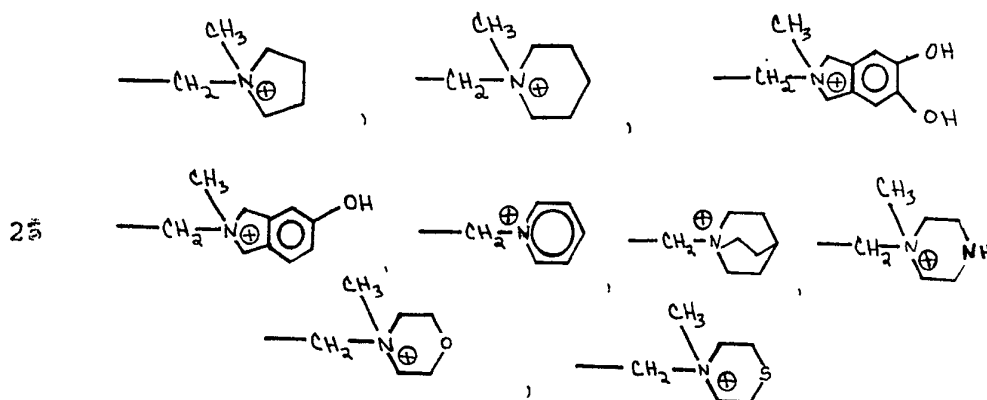


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R_2 may also preferably be $-\text{CH}_2-\text{S}(\text{O})$ Het, wherein Het is a heterocyclic ring preferably selected from



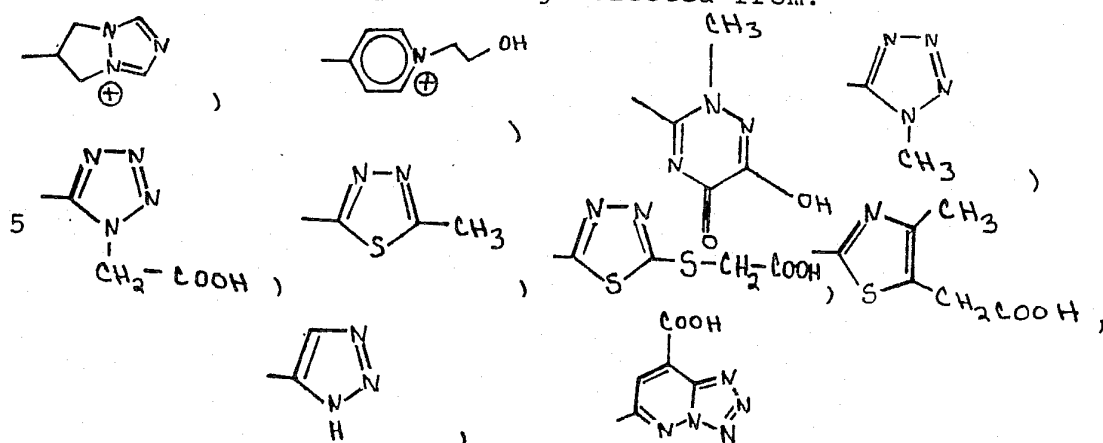
The most preferred groups representing R_2 include hydrogen, chloro, methyl, trifluoromethyl, hydroxy, methoxy, vinyl, cyclopropyl, methylthio, acetoxymethyl, hydroxymethyl, chloromethyl, bromomethyl, carbamoyloxymethyl, methoxymethyl, phenoxyethyl, 3-pyridyloxymethyl, methylthiomethyl, methylsulfonylmethyl, phenylthiomethyl, phenylsulfonylmethyl, (1,2,3-triazol-1-yl)methyl, (1,2,4-triazol-1-yl)methyl, acylthiomethyl, aminomethyl, a quaternary ammonium methyl group selected from:



R_2 is also most preferably selected from the group consisting of $\text{CH}_2-\text{S}(\text{O})_n$ Het, wherein n is 0, 1 or 2 and

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Het is a heterocyclic ring selected from:



R_3 and R_4 in the formula (I) may be the same or different and are selected from hydrogen, C_{1-6} straight or branched alkyl group, C_{6-10} aryl group, C_{3-8} cycloalkyl group, aralkyl group, saturated or unsaturated monocyclic or fused polycyclic 3 to 8 membered heterocyclic group containing at least one heteroatom selected from O, S and N; heteroarylalkyl group, $-COOH$, $-CH_2COOH$, $-COOC_{1-6}$ alkyl, and $-CH_2COOC_{1-6}$ alkyl.

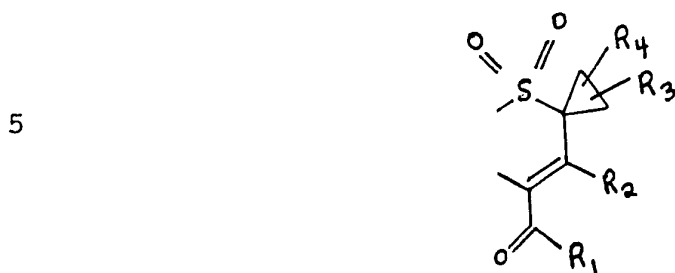
The above groups can be further substituted with one or more groups such as alkyl, hydroxy, halogen, amino, carboxy, cyano, haloalkyl, carboxamido, sulfinyl and sulfonyl.

R₃ and R₄ are preferably selected from hydrogen, methyl, ethyl, t-butyl, isopropyl, chloromethyl, fluoromethyl, cyclopropyl, phenyl, p-chlorophenyl, p-fluorophenyl, trifluoromethyl, 2-pyridylmethyl, 2-thienylmethyl, pyridyl, thienyl, furyl, -COOH, -CH₂COOH, -CH₂COOCH₃, and -CH₂COOCH₂CH₃, with hydrogen, methyl, trifluoromethyl, cyclopropyl, t-butyl, phenyl, p-chlorophenyl, p-fluorophenyl, thienyl, furyl, pyridyl, -COOH, -CH₂COOH,

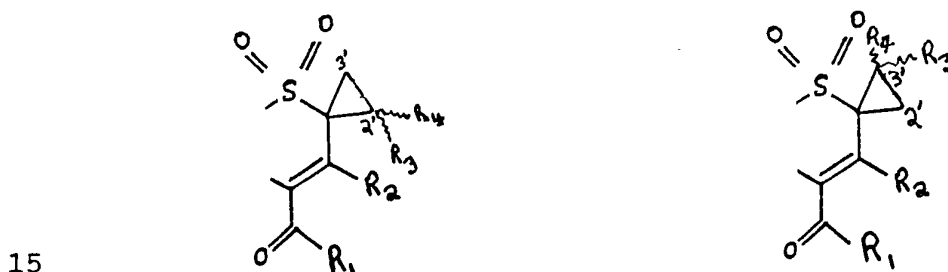
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$-\text{CH}_2\text{COOCH}_3$, and $-\text{CH}_2\text{COOCH}_2\text{CH}_3$ being most preferred.

The partial structure represented by the formula:



is to be understood to include both position isomers as
10 represented by the following formulae:



Furthermore it should be noted that when R_3 and R_4 in formula (I) are different they may be present in the form of an optical isomer, for example, l,d- or dl- forms.

R_5 in the formula (I) is hydrogen, chloro, fluoro,
20 bromo or iodo, R_1 , $-\text{OR}_1$, $-\text{S}(\text{O})_n\text{R}_1$ wherein n is either 0, 1 or 2, $-\text{OC}(\text{O})\text{R}_1$, $-\text{OSO}_2\text{R}_1$, $-\text{NHC}(\text{O})\text{R}_1$, $-\text{NH}-\text{Z}$, wherein Z is hydrogen, a mono-, di- or tripeptide composed of D or L α -amino acids with the terminal amino group either free or acylated by $-\text{C}(\text{O})\text{R}_1$ or $-\text{C}(\text{O})\text{OR}_1$.

25 R_5 is preferably selected from hydrogen, chloro, fluoro, bromo, methoxy, ethoxy, methyl, ethyl, formamido, acetamido, trifluoroacetamido, acetyloxy, chloroacetyloxy, bromoacetyloxy, dichloroacetyloxy, methylsulfonyloxy, phenylsulfonyloxy, and

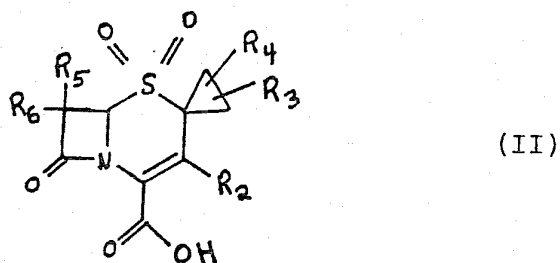
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tolylsulfonyloxy, with hydrogen, chloro, bromo, fluoro, methyl, ethyl, methoxy, ethoxy, methylsulfonyloxy, acetyloxy, and acetamido being most preferred.

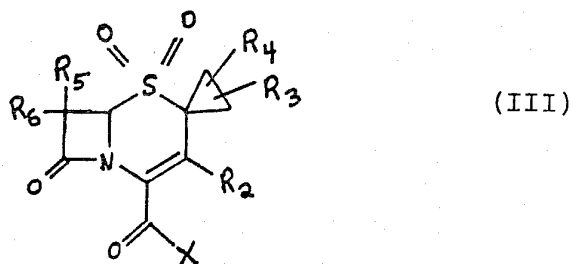
R_6 in formula (I) is selected from hydrogen, chloro, bromo, methoxy, and methylthio.

The compounds of the present invention can be prepared by a process which comprises the following steps:

(i) providing a compound having the formula (II)



(ii) converting the carboxyl group $-COOH$ at 4-position of the cephem nucleus of the formula (II) into an activated acid derivative having the formula (III)



(iii) treating the activated acid derivative (for example, acid chloride) of formula (III) with an organometallic derivative of R_1 to provide a compound having the formula (I).

The carboxylic acid group is typically activated as

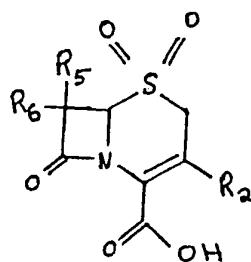
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the acyl halide, anhydride, mixed anhydride, thioester, etc.

The preferred organometallic derivatives of R_1 include Grignard reagents (R_1MgX), organolithium reagents (R_1Li), lithium dialkylcopper reagents $[(R_1)_2CuLi]$, organocadmium reagents $[(R_1)_2Cd]$, organozinc reagents (R_1ZnBr), and cuprous reagents (R_1Cu e.g. cuprous acetylides). Still other suitable reagents include organomanganese compounds, organotin reagents, lithium aryltrialkyl-borates, bis(triphenylphosphine)carbonylalkylrhodium(I), a magnesium dialkylcopper reagent (R_1CH_3CuMgX), and $PhS(R_1)CuLi$. Certain metallic halides, notably ferric and cuprous halides and AlX_3 , may be used as catalysts to improve the yields.

Alternatively, the compounds of the present invention can be prepared by a process which comprises the following steps:

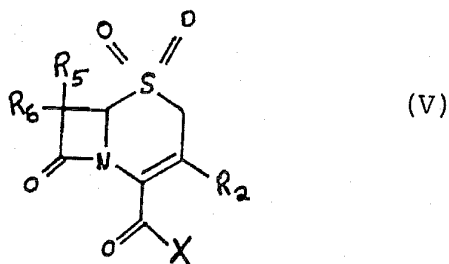
(iv) providing a compound having the formula (IV)



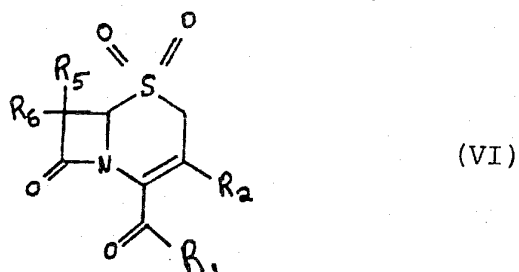
(IV)

(v) converting the carboxy group at 4-position of the cephem nucleus of formula (IV) into an activated acid derivative of the formula (V)

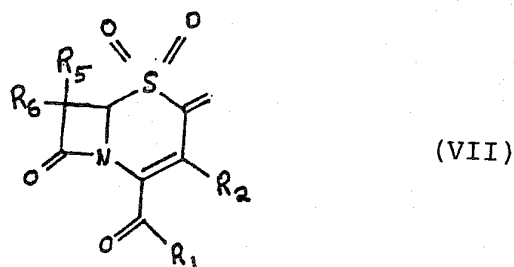
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(vi) treating the activated acid derivative of formula (V) with an organometallic derivative of R_1 to provide a compound of the formula (VI)



(vii) aminomethylating the compound of formula (VI) to provide a compound having the formula (VII); and



(viii) carrying out a cycloaddition reaction to the compound of formula (VII) with $R_3R_4CN_2$ to provide a compound of the formula (I).

The carboxyl group of compound (II) or compound (IV) can be converted to a suitable reactive derivative according to the conventional methods described in the cephalosporin or penicillin literature. For example, the

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carboxylic acid group can be converted to an acid halide by treatment with a halogenating agent such as phosphorus oxychloride, thionyl chloride, phosphorus pentachloride, oxalyl chloride, or oxalyl bromide. The reactions are usually carried out in a conventional solvent such as acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N, N-dimethyl formamide or any other organic solvent which does not adversely influence the reaction.

10

The present reaction is preferably carried out under mild conditions such as under cooling, at ambient, or slightly elevated temperature.

The reactions of activated acid derivatives of formula (III) and (V) with organometallic reagents can be carried out according to the conditions described in "Advanced Organic Chemistry", J. March, McGraw-Hill, incorporated herein by reference. The reactions are usually carried out in an inert solvent like ether, hexane, tetrahydrofuran and the like. The reaction is usually carried out at a low temperature, preferably between -78° to 10° C.

The introduction of an exocyclic double bond at the 2-position of compound (VI) can be carried out according to the procedure detailed in I. G. Wright et al., J. Med. Chem., 14, 420 (1971), incorporated herein by reference. The reaction is usually carried out in a solvent such as tert-butanol, methylene chloride, chloroform, carbon tetrachloride, dioxane, a mixed

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solvent thereof, or any other solvent which does not adversely affect the reaction. There is no particular limitation to the reaction temperature and the present reaction is usually carried out from room temperature to about 150° C with or without reflux until the reaction is complete.

The introduction of 2-spirocyclopropyl groups, which may be substituted with suitable substituents, may be performed by reacting the compound (VII) with a compound of the formula $R_3R_4CN_2$ wherein R_3 and R_4 may be the same or different and represent the groups as defined before. The reaction is usually carried out in a solvent such as methylene chloride, chloroform, carbon tetrachloride, benzene, ether, ethyl acetate, or any other solvent which does not adversely affect the reaction. The reaction is usually carried out under cooling to ambient temperature.

The most preferred embodiments of the present invention include the following compounds:

- 7 α -methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-ethylcarbonyl 1,1-dioxide;
- 7 α -methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-butylcarbonyl 1,1-dioxide;
- 7 α -methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-methylcarbonyl 1,1-dioxide;
- 7 α -methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-phenylcarbonyl 1,1-dioxide;
- 7 α -methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-tert-butylcarbonyl 1,1-dioxide;

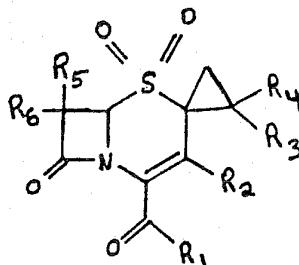
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7 α -chloro-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-phenylcarbonyl 1,1-dioxide; and
7 α -chloro-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-tert-butylcarbonyl 1,1-dioxide.

- 5 The compounds of the present invention are characterized by high inhibitory activity on HLE. The in vitro test data on anti-elastase activity of exemplary derivatives having the formula (I) are shown in the Table.

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Table
Activity of 2-spirocyclopropyl 4-acylcephem sulphones
against human leukocyte elastase (HLE).



10	Compd	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	IC ₅₀ , nM
	1	CH ₃	CH ₃	Ph	Ph	CH ₃ O	H	
	2	CH ₂ CH ₃	CH ₃	Ph	Ph	CH ₃ O	H	10.3
	3	Bu ⁿ	CH ₃	Ph	Ph	CH ₃ O	H	7.4
15	4	Ph	CH ₃	Ph	Ph	Cl	H	8.9
	5	Bu ^t	CH ₃	Ph	Ph	Cl	H	6.3
	6	Bu ^t	CH ₃	Ph	Ph	CH ₃ O	H	12.0

Owing to their high anti-elastase activity and quite negligible toxicity, the compounds of the present invention can be used in the treatment of inflammatory or degenerative diseases caused by proteolytic enzymes in mammals, including humans. The compounds of the present invention may be administered to a warm-blooded mammalian in need thereof, particularly a human, to prevent or arrest the progression of diseases such as emphysema, pulmonary emphysema, lupus, rheumatoid arthritis, osteoarthritis, cystic fibrosis, spondylitis, gout, psoriasis, chronic bronchitis, and acute respiratory distress syndrome caused by proteolytic degradation of lungs and other connective tissues.

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The mode of administration may be oral, parenteral, topical, rectal or by inhalation. The compounds may be conventionally formulated in an oral or parenteral dosage form by compounding about 10 to 250 mg per unit of dosage with conventional vehicle excipients, binders, preservatives, stabilizers, flavoring agents, coloring agents, and sweetening agents or the like as called for by accepted pharmaceutical or veterinary practice.

For parenteral administration, a 1 to 10 ml intravenous, intramuscular or subcutaneous injection would be given containing about 0.02 to 10 mg/kg of body weight of a compound of the present invention three to four times daily. The injection would contain a compound of the present invention in an aqueous isotonic sterile solution or suspension, optionally with a preservative such as phenol or a solubilizing agent such as ethylenediaminetetraacetic acid (EDTA). 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. Synthetic monoglycerides, diglycerides, and fatty acids such as oleic acid find use as fixed oil in the preparation of injectables.

For rectal administration, the compounds of the present invention can be prepared in the form of suppositories by mixing with a suitable non-irritating excipient such as cocoa butter or polyethylene glycols.

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For topical use, the compounds of the present invention can be prepared in the form of ointments, jellies, solutions or suspensions.

The compounds of the invention may be administered as
5 a powdered aerosol by a Spinhaler turbo-inhaler device commercially available from Fisons Corp. of Bedford, Massachusetts at a rate of about 0.1 to 50 mg per capsule, 1 to 8 capsules being administered daily for an average human. In a liquid aerosol, the compounds of the
10 present invention are administered at the rate of about 100 to 1000 micrograms per "puff" or activated release of a standard volume of propellant. The liquid aerosol would be given at the rate of 1 to 8 puffs per day with variation in dosages due to the severity of the condition
15 being treated, the weight of the patient and the particle size distribution of the aerosol. A fluorinated hydrocarbon or isobutane may find use as propellants for liquid aerosols.

Daily dose are in the range of about 0.01 to about
20 100 mg per kg of body weight, depending on the activity of the specific compound, the age, weight, sex and condition of the subject to be treated, the type and severity of the disease, and the frequency and route of administration. The amount of active ingredient that may
25 be combined with the carrier materials to produce a single dosage will vary depending upon the host treated and the particular mode of administration.

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EXAMPLESExample 17 α -Methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-5 4-ethylcarbonyl 1,1-dioxide

To a suspension of 7-methoxy-2-spiro(2',2'-diphenyl)-cyclopropyl-3-methyl-3-cephem-4-carboxylic acid 1,1-dioxide (360 mg, 0.8191 mmol) in dry methylene chloride (15 ml) cooled in an ice-bath was added oxalyl chloride (135 mg, 1.065 mmol) followed by one drop of dimethyl formamide. The mixture slowly went into solution (still some solid left). After 5 min another drop of dimethyl formamide was added, ice-bath was removed and the reaction mixture went into solution completely within 10 min; the mixture was stirred at room temperature for 40 min, solvent was removed under reduced pressure. The residue was dissolved in dry THF (10 ml), cooled to -70° C, cuprous iodide (164 mg, 0.8601 mmol) was added followed by ethyl magnesium bromide [0.532 ml, 2 (M) solution in THF] and the reaction mixture was stirred at -70°C for 15 min; poured into ice-cold water, extracted with methylene chloride, washed with aqueous sodium bicarbonate solution, brine, dried and concentrated to give a light yellow solid which was purified over a silica gel column using hexane-ethyl acetate (7:3) as eluant, 190 mg.

Crystallization from methylene chloride-ether gave pure white solid, m.p. 206-208° C, decomp. IR(KBR) 1777, 1695, 1617 cm⁻¹.

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¹H NMR (200 MHz, CDCl₃): δ 0.975 (s, 3H, CH₃), 1.19 (t, 3H, CH₂CH₃), 2.34 (d, 1H, J = 7.1 Hz, cyclopropyl), 2.67 (dq, 1H, CH₂CH₃), 2.97 (dq, 1H, CH₂CH₃), 2.94 (d, 1H, J = 7.1 Hz, cyclopropyl), 3.48 (s, 3H, OCH₃), 4.97 (d, 1H, J = 1.7 Hz), 5.05 (d, 1H, J = 1.7 Hz), 7.18 - 7.49 (m, 10H, aromatic).

Example 2

7α-Methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-butylcarbonyl 1,1-dioxide

10 To a suspension of 7α-methoxy-2-spiro(2',2'-diphenyl)-cyclopropyl-3-methyl-3-cephem-4-carboxylic acid 1,1-dioxide (700 mg, 1.5928 mmol) in dry DCM (25 ml) cooled in an ice-bath was added oxalyl chloride (263 mg, 2.0706 mmol) followed by two drops of N,N-dimethylformamide, the reaction
15 mixture was stirred at ice-temperature for 15 minutes and then at room temperature for 45 min; solvent was removed under reduced pressure. The residue was dissolved in dry THF (15 ml), cooled to -70° C, cuprous iodide (319 mg, 1.6724 mmol) was added followed by n-butyl magnesium
20 chloride (1.035 ml, 2 (M) in THF) and the reaction mixture was stirred at -70° C for 15 min; poured into ice-cold water, extracted with methylene chloride, the aqueous layer was saturated with sodium chloride and re-extracted with methylene chloride. The combined organic layers were washed
25 with aqueous sodium bicarbonate solution, brine, dried and concentrated to give a light yellow foam (600 mg) which was purified over a silica gel column using hexane-ethyl acetate mixture as eluant (520 mg).

Crystallization from methylene chloride-ether gave pure

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compound as white crystals, m.p. 170° - 175° C. IR (KBr) 1779, 1694, 1609 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ 6.098 (s, 3H, CH₃), 0.98 (t, 3H, CH₃), 1.33 - 1.72 (m, 4H), 2.34 (d, 1H, J = 6.8 Hz, cyclopropyl), 2.73 - 2.95 (m, 2H, -COCH₂-), 2.93 (d, 1H, J = 6.8 Hz, cyclopropyl), 3.49 (s, 3H, OCH₃), 4.97 (d, 1H, J = 2.0 Hz), 5.04 (d, 1H, J = 2.0 Hz), 7.22 - 7.48 (m, 10H, aromatic).

Example 3

10 7α-Methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-methylcarbonyl 1,1-dioxide

To a suspension of 7α-methoxy-2-spiro (2',2'-diphenyl) cyclopropyl-3-methyl-3-cephem-4-carboxylic acid 1,1-dioxide (500 mg, 1.138 mmol) in dry methylene chloride (18 ml) cooled to 0° C, was added oxalyl chloride (188 mg, 1.479 mmol) followed by two drops of DMF. The mixture was stirred at ice-temperature for 15 min and then at room temperature for 45-min; solvent was removed under reduced pressure. The residue was redissolved in dry THF (10 ml), cooled to -70° C, cuprous iodide (228 mg, 1.195 mmol) was added followed by methyl magnesium bromide (0.49 ml, 3(M) in ether) and the reaction mixture was stirred at -70° C for 15 min; poured into ice-cold water, extracted with methylene chloride, washed with aqueous sodium bicarbonate solution, brine, dried and concentrated to give a light yellow foam (300 mg) which was purified over silica gel column using hexane-ethyl acetate (3:1) as eluant to give pure compound (150 mg) which was crystallized from methylene chloride-ether (88 mg), m.p. 196° - 198° C, decomp. IR (KBr) 1778, 1695, 1594 cm⁻¹.

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^1H NMR(200 MHz, CDCl_3): 1.02 (s, 3H, CH_3), 2.35 (d, 1H, $J = 6.84$ Hz), 2.52 (s, 3H, COCH_3), 2.95 (d, 1H, $J = 7.2$ Hz), 3.49 (s, 3H, OCH_3), 4.98 (d, 1H, $J = 1.59$ Hz), 5.05 (d, 1H, $J = 1.94$ Hz), 7.22 - 7.49 (m, 10H, aromatic).

5 Example 4

7 α -Methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-phenylcarbonyl 1,1-dioxide

To a suspension of 7 α -methoxy-2-spiro(2',2'-diphenyl)-cyclopropyl-3-methyl-3-cephem-4-carboxylic acid 1,1-dioxide
10 (500 mg, 1.138 mmol) in dry methylene chloride (18 ml) cooled to 0° C, was added oxalyl chloride (188 mg, 1.479 mmol) followed by two drops of DMF. The mixture was stirred at 0° C for 15 min and then at room temperature for 45 min; solvent was removed under reduced pressure. The residue was
15 redissolved in dry THF (10 ml), cooled to -70°C, cuprous iodide (228 mg, 1.195 mmol) was added followed by phenyl magnesium bromide (1.48 ml, 1(M) in THF) and the reaction mixture was stirred at -70° C for 15 min; poured into ice-cold water, extracted with methylene chloride, washed with
20 aqueous sodium bicarbonate solution, brine, dried and concentrated to give a light yellow foam (370 mg) which was purified over a silica gel column using hexane-ethyl acetate mixture (3:1) as eluant to give the desired compound (80 mg). Crystallization from methylene chloride - ether
25 afforded shiny crystals (36 mg), mp. 180° - 182° C, decomp. IR (KBr) 1786, 1594 cm^{-1} . ^1H NMR(CDCl_3): δ 1.11 (s, 3H, CH_3), 2.414 (d, 1H, $J = 7.2$ Hz), 3.02 (d, 1H, $J = 7.2$ Hz), 3.52 (s, 3H, OCH_3), 5.02 (d, 1H, $J = 1.42$ Hz), 5.10 (d, 1H, $J = 1.48$ Hz), 7.26 -

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7.50 (m, 15H, aromatic).

Example 5

7 α -Methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-t-butylcarbonyl 1,1-dioxide

5 To a suspension of 7 α -methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-carboxylic acid 1,1-dioxide (300 mg, 0.6826 mmol) in dry methylene chloride (10 ml) cooled to 0°C, was added oxalyl chloride (113 mg, 0.8874 mmol) followed by two drops of DMF. The mixture was stirred
10 at 0° C for 15 min and then at room temperature for 45 min; solvent was removed under reduced pressure. The residue was redissolved in dry THF (5 ml), cooled to -70°C, cuprous iodide (136 mg, 0.71677 mmol) was added followed by t-butyl magnesium chloride (0.44 mol, 0.8874 mmol, 2.0 (M) in THF)
15 and the reaction mixture was stirred at at -70° C for 15 min; poured into ice-cold water, extracted with methylene chloride, washed with aqueous sodium bicarbonate solution, dried and concentrated to give a crude product (250 mg) which was purified over a silica gel column using hexane-
20 ethyl acetate mixture as the eluant. The product (122 mg) obtained was repurified over a silica column using 5% ethyl acetate in methylene chloride. The product (45 mg) obtained on treatment with ether gave a white solid (25 mg) which was crystallized from methylene chloride-ether, m.p. 222° C,
25 decomp. IR (KBr) 1779. 1685, 1610 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ 0.873 (s, 3H, CH₃), 1.2969 (s, 9H, Bu^t), 2.32 (d, 1H, J = 6.8 Hz), 2.88 (d, 1H, J = 6.8 Hz), 3.48 (s, 3H, OCH₃), 4.96 (d, 1H, J = 1.6 Hz), 5.06 (d, 1H, J = 1.6 Hz), 7.16 - 7.52 (m, 10H, aromatic).

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Example 6

7 α -chloro-2-spiro (2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-phenylcarbonyl 1,1-dioxide

Step A: 7 α -Chloro-3-methyl-3-cephem-4-phenylcarbonyl 1,1-dioxide

5 A solution of 7 α -chloro-3-methyl-3-cephem-4-carboxylic acid 1,1-dioxide (934 mg, 0.0035 mol) in dry methylene chloride (25 ml) was treated at ice-temperature with oxalyl chloride (592 mg) and two drops of DMF. The reaction
10 mixture was stirred at ice-temperature for 15 min and at room temperature for 30 min; solvent was removed under reduced pressure. The residue was dissolved in dry THF (25 ml) cooled to -70° C, anhydrous aluminium trichloride (327 mg, 0.00245 mol) was added and then phenyl magnesium bromide
15 (4.5 ml, 1(M) THF solution). The reaction mixture was stirred for 5 min and poured into ice-water extracted with ethyl acetate, washed with brine, dried and concentrated (600 mg) which was purified over a silica gel column using hexane-ethyl acetate (3:2) as eluant to give the pure
20 compound (103 mg) as a white solid. This product was directly used for the next step.

Step B: 7 α -Chloro-2-exomethylene-3-methyl-3-cephem-4-phenylcarbonyl 1,1-dioxide

7 α -Chloro-3-methyl-3-cephem-4-phenylcarbonyl
25 1,1-dioxide (103 mg, 0.000316 mol) was dissolved in a mixture of 1,4-dioxane (6 ml) and t-BuOH (1 ml). To this mixture formaldehyde solution (37%, 0.1 ml and dimethylamine hydrochloride (77 mg, 0.000948 mol) were added and the mixture was heated to reflux at 90° C for 2.5 h. The

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progress of the reaction was monitored by tlc. After the reaction was over the mixture was cooled to room temperature, diluted with 60 ml of methylene chloride, washed with water (4 x 10 ml), dried and concentrated to
5 give a white solid (108 mg).

A portion of the above compound was crystallized from methylene chloride-ether, m.p. 245° C, decomp.

¹H NMR (200 MHz, CDCl₃): δ 1.85 (s, 3H), 5.34 (d, 1H, J = 2.0 Hz), 5.49 (d, 1H, J = 2.0 Hz), 6.17 (d, 1H, J = 2.0
10 Hz), 6.66 (d, 1H, J = 2.0 Hz), 7.51 - 7.97 (m, 5H, aromatic).

Step C: 7α-Chloro-2-spiro (2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-phenylcarbonyl 1,1-dioxide

To a stirred solution of 7α-chloro-2-exomethylene-3-methyl-3-cephem-4-phenylcarbonyl 1,1-dioxide (70 mg,
15 0.000207 mol) in dry methylene chloride (10 ml) at room temperature was added diphenyldiazomethane (48 mg, 0.000249 mol) and the reaction mixture was stirred at room temperature for 1 h, solvent was removed under reduced
20 pressure and the crude product (123 mg) was purified over a silica gel column using hexane-ethyl acetate (3:2) mixture, the product obtained (105 mg) was further purified by preparative tlc, 50 mg; mp 145 - 147° C (ethyl acetate-hexane).

25 IR (KBr) 1793, 1664 cm⁻¹.

¹H NMR (200 MHz, CDCl₃): δ 0.77 (s, 3H, CH₃), 2.33 (d, 1H, J = 7.0 Hz, cyclopropyl), 3.0 (d, 1H, J = 7.0 Hz, cyclopropyl), 5.08 (d, 1H, J = 2.0 Hz), 5.25 (d, 1H, J = 2.0 Hz), 7.18 - 7.80 (m, 15H, aromatic).

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Example 77 α -Chloro-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-oxo-4-(4-oxo-4-butyl)-1,1-dioxane

To a stirred solution of 7 α -chloro-2-exomethylene-3-methyl-3-oxo-4-(4-oxo-4-butyl)-1,1-dioxane (73 mg, 0.00023 mol, prepared according to Step B, Example 6) in dry methylene chloride (10 ml) at room temperature was added diphenyldiazomethane (54 mg, 0.000276 mol) and the reaction mixture was stirred at room temperature for a period of 3 hours. Solvent was removed under reduced pressure and the product (130 mg) was purified over a silica gel column using hexane-ethyl acetate mixture (8:2). The pure compound obtained (22 mg) was crystallized from ethyl acetate-hexane, m. p. 185-187° C, decomp.

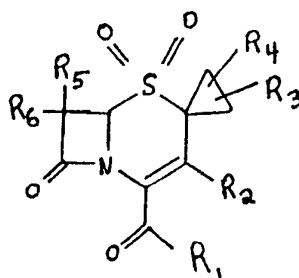
IR(KBr) 1797, 1715, 1615 cm^{-1} .

^1H NMR (200 MHz, CDCl_3): δ 1.10 (s, 3H, CH_3), 1.56 (s, 9H, Bu^t), 2.37 (d, 1H, $J = 7.1$ Hz, cyclopropyl), 2.96 (d, 1H, $J = 7.1$ Hz, cyclopropyl), 5.0 (d, 1H, $J = 2.0$ Hz), 5.20 (d, 1H, $J = 2.0$ Hz), 7.23-7.49 (m, 10H, aromatic).

CLAIMS:

What is claimed is:

1. A 2-spirocyclopropyl 4-acylcephem sulfone of the
5 formula



(I)

wherein

- R_1 is hydrogen; or C_{1-12} straight or branched alkyl; or
 C_{2-10} alkenyl; or C_{2-10} alkynyl; or C_{3-8} cycloalkyl; or C_{5-8}
15 cyclo-alkenyl; or C_{6-10} aryl; or aralkyl; or aralkenyl; or
aralkynyl; or (cycloalkyl)alkyl; or a monocyclic or
polycyclic, saturated or unsaturated heterocyclic group
containing from 1 to 4 of any one or more of the heteroatoms
N, S, or O in each heterocyclic ring; or a fused polycyclic
20 saturated or unsaturated heterocyclic group containing from
1 to 4 of any one or more of the heteroatoms N, S, or O in
each heterocyclic ring; or heterocyclylalkenyl; or hetero-
cyclylalkynyl; wherein the heterocyclyl, alkyl, alkenyl, and
alkynyl groups are as defined above; wherein each of the
25 above organic radicals is unsubstituted or substituted by
one or more atoms or groups selected from chloro, bromo,
fluoro, cyano, azido, nitro, formyl, C_{1-4} alkyl,
trifluoromethyl, C_{2-4} alkenyl, alkynyl, C_{3-6} cycloalkyl,
hydroxy, alkoxy, carboxy, $-(CH_2)_mCOOH$, $-(CH_2)_mCOOR_{10}$, $-COR_{10}$,

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-COCF₃, -CONH₂, -CONHR₁₀, -NH₂, -NHR₁₀, -NR₁₀R₁₁, -NHSO₂R₁₀,
 -NHCOR₁₀, -NHC(=NH)NH₂, -OCOR₁₀, -OC(O)NH₂, -SH, -SR₁₀,
 -S(O)R₁₀, -S(O)₂R₁₀, or -SO₃H

R₂ is selected from hydrogen; or chloro, bromo, or
 5 fluoro; or -C₁₋₆ alkyl; or -trifluoromethyl; or -C₂₋₆ alkenyl
 (substituted or unsubstituted); or -C₂₋₆ alkynyl
 (substituted or unsubstituted); or -C₃₋₈ cycloalkyl, or
 -OR₇; or -S(O)_nR₇; or -CHO; or -COOH; or -CH₂-O-R₇; or
 -CH₂-S(O)_nR₇; or -C(O)R₇; or -C(O)OR₇; or -CH₂OC(O)R₇; or
 10 -CH₂SC(O)R₇; or -CH₂Cl; or -CH₂Br; or -CH₂OC(O)NH₂; or
 -CH₂NR₇R₈; or -CH₂-NH(C₁₋₄ alkyl), wherein the alkyl is
 either unsubstituted or substituted; or -CH₂-NHC(O)R₇; or
 -CH₂-[⊕]NR₇R₈R₉; or -CH₂-S(O)_nHet;

R₃ and R₄ are the same or different and may be hydrogen;
 15 or C₁₋₆ straight or branched alkyl group; or C₆₋₁₀ aryl
 group; or C₃₋₈ cycloalkyl group; or aralkyl group; or
 saturated or unsaturated monocyclic or fused polycyclic 3-8
 membered heterocyclic group containing at least one
 heteroatom chosen from O, S, and N; or a halogenated C₁₋₆
 20 alkyl; or a hydroxy C₁₋₆ alkyl; or -CH₂COOH; or -COOH; or
 -COOC₁₋₆ alkyl group; or -CH₂COOC₁₋₆ alkyl;

R₅ is R₁; or -O-R₁; or -S(O)_nR₁; -OC(O)R₁; -OSO₂R₁; or
 -NHC(O)R₁; or -NH-Z; or halogen;

R₆ is hydrogen; or C₁₋₄ alkyl; or C₁₋₄ alkoxy; or
 25 halogen;

R₇, R₈ and R₉ are the same or different, and may be
 hydrogen; or C₁₋₆ lower straight or branched alkyl; or C₂₋₆
 alkenyl; or C₂₋₆ alkynyl; or C₃₋₈ cycloalkyl; or C₆₋₁₀ aryl;
 or aralkyl; or saturated or unsaturated monocyclic or fused

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polycyclic 3 to 8 membered heterocyclic ring containing at least one heteroatom chosen from O, S, and N; or, at least two of them, taken together with the nitrogen atom to which they are attached, form a heterocyclic ring;

- 5 R_{10} and R_{11} may be the same or different and represents C_{1-6} straight or branched alkyl, phenyl, or benzyl;

Z is hydrogen; a mono-peptide composed of D or L -amino acids with the terminal amino group optionally acylated by $-C(O)R_1$ or $-C(O)OR_1$; or a di-peptide composed of D or L
 10 -amino acids with the terminal amino group optionally acylated by $-C(O)R_1$ or $-C(O)OR_1$; or a tripeptide composed of D or L -amino acids with the terminal amino group optionally acylated by $-C(O)R_1$ or $-C(O)OR_1$;

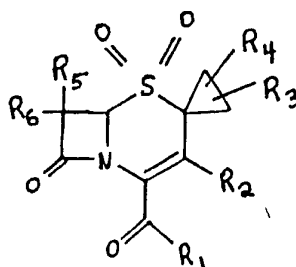
Het is a heterocyclic ring;

- 15 m is 0, 1, 2 or 3; and

n is 0, 1, or 2.

2. A compound according to claim 1 of the formula (I)

20



wherein

- 25 R_1 is hydrogen; or methyl; or ethyl; or tert-butyl; or n-butyl; or phenyl; or benzyl; or dimethylphenyl; or diphenyl-methyl; or propenyl;

R_2 is selected from hydrogen; or chloro; or methyl; or trifluoromethyl; or chloromethyl; or bromomethyl; or

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hydroxymethyl; or acetoxymethyl; or acetylthiomethyl; or carbamoyloxymethyl; or hydroxy, methoxy, vinyl (substituted or unsubstituted), cyclopropyl; or formyl; or carboxy, methoxycarbonyl; or ethoxycarbonyl; or methoxymethyl; or
5 ethoxymethyl; or phenoxymethyl; or 3-pyridyloxymethyl; or methylthiomethyl; or phenylthiomethyl; or methylsulphonylmethyl; or phenylsulphonylmethyl; or aminomethyl; or C₁₋₄ alkylamino methyl wherein the alkyl is either unsubstituted or substituted by a carboxy group; or
10 a quaternary ammonium group; or CH₂-S(O)_nHet;

R₃ and R₄ are the same or different and are hydrogen; or methyl; or ethyl; or phenyl; or cycloalkyl; or aralkyl; or saturated or unsaturated monocyclic or fused polycyclic 3-8 membered heterocyclic groups containing at least one
15 heteratom chosen from O, S, and N; or -COOH; or -CH₂COOH; or -COOC₁₋₆ alkyl; or -CH₂COOC₁₋₆ alkyl;

R₅ is selected from hydrogen; or chloro; or fluoro; or bromo; or C₁₋₄ alkyl; or methoxy; or ethoxy; or isopropoxy or phenoxy; or methylthio; or formyloxy; or acetoxy; or
20 phenylacetoxy; or mesyloxy; or tosyloxy; or formamido; or acetamido; or trifluoro-acetamido; or chloroacetamido; and

R₆ is hydrogen; or chloro; or bromo; or fluoro; or C₁₋₄ alkyl; or C₁₋₄ alkoxy.

3. A compound according to claim 2, which is selected
25 from the group consisting of:

7 α -methoxy-2-spiro(2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-ethylcarbonyl 1,1-dioxide;

7 α -methoxy-2-spiro (2',2'-diphenyl)cyclopropyl-3-methyl-3-cephem-4-butylcarbonyl 1,1-dioxide;

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7 α -methoxy-2-spiro (2',2'-diphenyl)cyclopropyl-3-methyl-3-
cephem-4-methylcarbonyl 1,1-dioxide;

7 α -methoxy-2-spiro (2',2'-diphenyl)cyclopropyl-3-methyl-3-
cephem-4-phenylcarbonyl 1,1-dioxide;

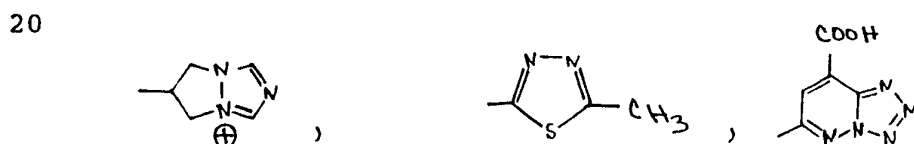
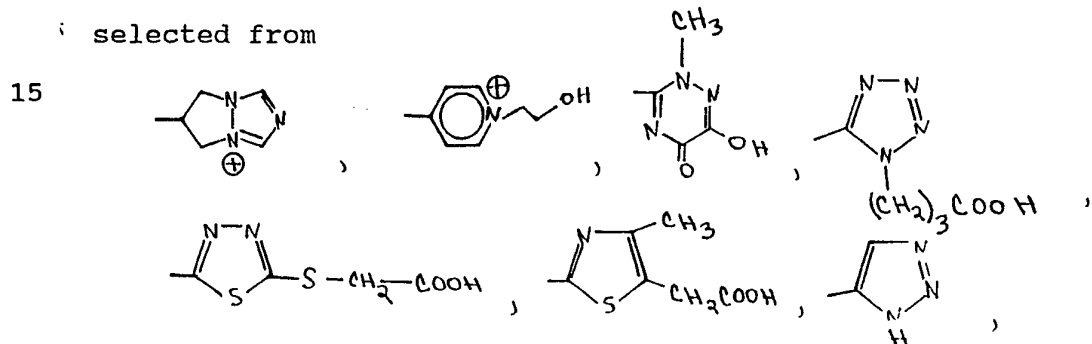
5 7 α -methoxy-2-spiro (2',2'-diphenyl)cyclopropyl-3-methyl-3-
cephem-4-tert-butylcarbonyl 1,1-dioxide;

7 α -chloro-2-spiro (2',2'-diphenyl)cyclopropyl-3-methyl-3-
cephem-4-phenylcarbonyl 1,1-dioxide; and

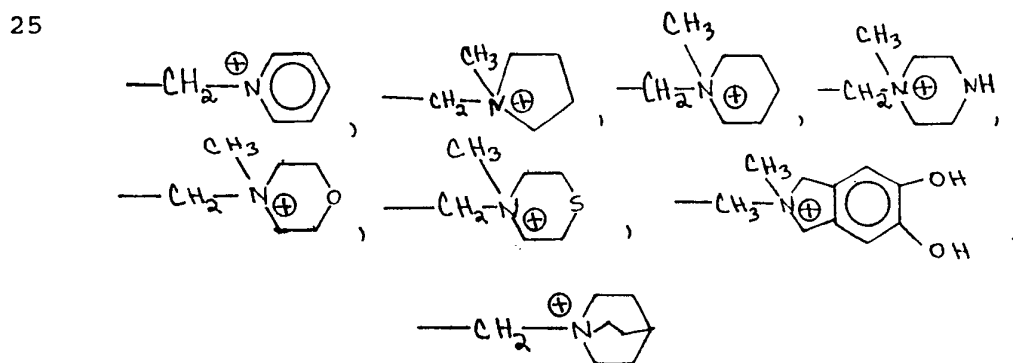
7 α -chloro-2-spiro (2', 2'-diphenyl)cyclopropyl-3-methyl-3-
10 cephem-4-tert-butylcarbonyl 1,1-dioxide.

4. The compound of claim 1, wherein R₂ is a carboxy-
substituted CH₂-NH(C₁₋₄alkyl) group.

5. The compound of claim 1, wherein R₂ is a Het
selected from



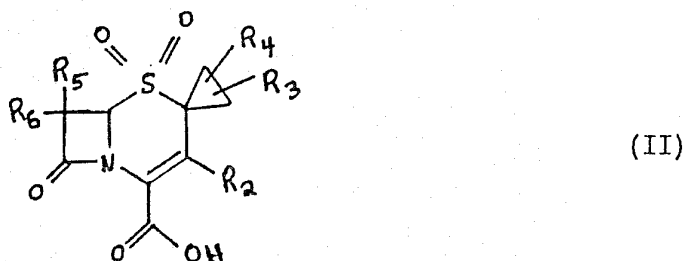
6. The compound of claim 2, wherein R₂ is a quaternary
ammonium group selected from the group consisting of:



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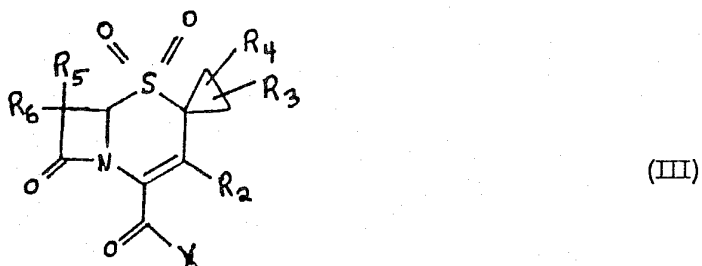
7. A process for preparing a compound of the formula (I) as defined in claim 1, comprising:

5 i) providing a compound having the formula (II)



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ii) converting the carboxyl group at the 4-position of the cephem nucleus of the formula (II) into an activated acid derivative having the formula (III)



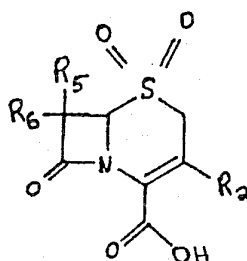
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iii) treating the activated acid derivative of formula (III) with an organometallic derivative of R_1 to provide a
20 compound having the formula (I).

8. A process for preparing a compound of the Formula (I) as defined in claim 1, comprising:

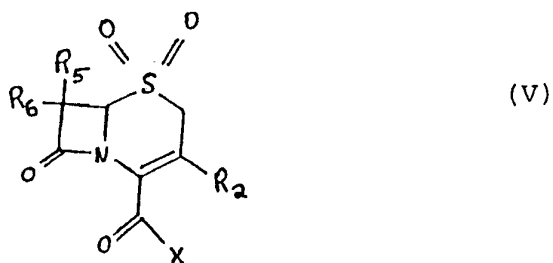
i) providing a compound having the formula (IV)

25



ii) converting the carboxyl group at the 4-position of the cephem nucleus of formula (IV) into an activated acid derivative having the formula (V)

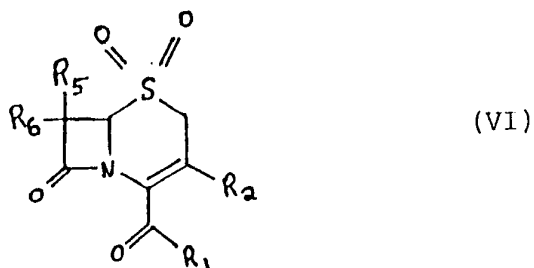
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iii) treating the activated acid derivative of formula (V) with an organometallic derivative of R_1 to provide a compound of the formula (VI)

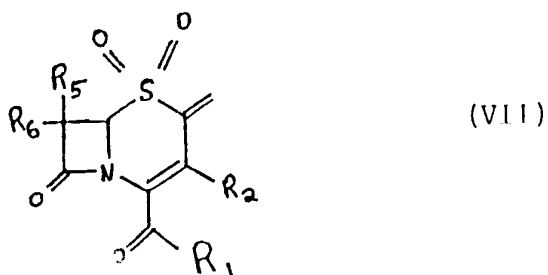
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iv) aminomethylating the compound of formula (VI) to provide a compound having the formula (VII)

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v) carrying out a cycloaddition reaction to the compound of formula (VII) with $R_3R_4CN_2$ to provide a compound of the formula (I).

9. The process of claim 7, further comprising
5 converting the resulting compound of formula (I) into a pharmaceutically or veterinarily acceptable salt.

10. The process of claim 8, further comprising converting the resulting compound of formula (I) into a pharmaceutically or veterinarily acceptable salt.

10 11. A pharmaceutical or veterinary composition comprising of an effective amount of a compound of claim 1 or a pharmaceutically or veterinarily acceptable salt thereof, in admixture with a pharmaceutically or veterinarily acceptable carrier.

15 12. A method of treatment for a mammal suffering from inflammatory or degenerative diseases and in need of such treatment, comprising administering an effective amount of the compound of claim 1 to said mammal.

13. The method of claim 12, wherein said disease is
20 selected from the group consisting of emphysema, pulmonary emphysema, lupus, rheumatoid arthritis, osteoarthritis, cystic fibrosis, spondylitis, gout, psoriasis, chronic bronchitis, and acute respiratory distress syndrome.

25 14. The method of claim 12, wherein said compound is administered orally in a unit-dose amount ranging from 10 to 250 mg.

15. The method of claim 12, wherein said compound is administered parenterally in a unit-dose amount ranging

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from 0.02 to 10 mg/kg of body weight of said mammal.

16. The method of claim 12, wherein said compound is administered rectally.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 92/00145

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl.5 C 07 D 501/00 A 61 K 31/545		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl.5	C 07 D 501/00	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ^o	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
1	A EP,A,0124081 (MERCK) 7 November 1984, see page 0; pages 87-100, claims ---	1-11
1	A US,A,4547371 (J.B. DOHERTY) 15 October 1985, see pag 0; columns 24-30 (cited in the application) ---	1-11
1	A EP,A,0267723 (MERCK) 18 May 1988, see page 1; pages 55-64, claims (cited in the application) ---	1-11
1	A EP,A,0337704 (FARMITALIA CARLO ERBA) 18 October 1989, see pages 1-2; pages 34-43, claims (cited in the application) ---	1-11
1	P,X WO,A,9104977 (SYNPHAR) 18 April 1991, see the whole document -----	1-11
^o Special categories of cited documents : ¹⁰ "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 "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		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
03-07-1992		05.08.92
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		Luyten W.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA92/00145

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. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 12-16 are directed to a method of treatment of
(diagnostic method practised on) the human/animal body the search
has been carried out and based on the alleged effects of the
compound/composition.
2. ☐ Claims Nos.:
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:
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.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

CA 9200145
SA 58067

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 16/07/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0124081	07-11-84	JP-A- 59206389	22-11-84
US-A- 4547371	15-10-85	None	
EP-A- 0267723	18-05-88	AU-B- 611104	06-06-91
		AU-A- 8062487	19-05-88
		JP-A- 63198688	17-08-88
EP-A- 0337704	18-10-89	AU-B- 615048	19-09-91
		AU-A- 3276289	19-10-89
		JP-A- 2028183	30-01-90
		US-A- 5077286	31-12-91
WO-A- 9104977	18-04-91	AU-A- 6513190	28-04-91