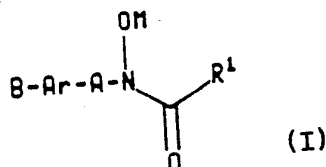




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(54) Title: HYDROXAMIC ACID DERIVATIVES WHICH INHIBIT LIPOXYGENASE



(57) Abstract

Certain novel hydroxamic acid derivatives having structure (I) inhibit the enzyme lipoxygenase. These compounds, and the pharmaceutically acceptable salts thereof, are useful in the treatment or alleviation of inflammatory diseases, allergic conditions and cardiovascular diseases in mammals and as the active ingredient in pharmaceutical compositions for treating such conditions.

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HYDROXAMIC ACID DERIVATIVES WHICH INHIBIT LIPOXYGENASE

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to novel hydroxamic acid derivatives. The
5 compounds of the present invention inhibit the enzyme lipoxygenase, and
are useful in the treatment or alleviation of inflammatory diseases, allergy and
cardiovascular diseases in mammals. This invention also relates to
pharmaceutical compositions comprising such compounds and to the use of
such compounds in treating inflammatory diseases, allergy and
10 cardiovascular diseases in mammals. This invention further relates to
methods of making such compounds.

Arachidonic acid is known to be the biological precursor of several
groups of endogenous metabolites, prostaglandins including prostacyclins,
thromboxanes and leukotrienes. The first step of arachidonic acid
15 metabolism is the release of arachidonic acid and related unsaturated fatty
acids from membrane phospholipids, via the action of phospholipase. Free
fatty acids are then metabolized either by cyclooxygenase to produce the
prostaglandins and thromboxanes or by lipoxygenase to generate
hydroperoxy fatty acids which may be further converted to the leukotrienes.
20 Leukotrienes have been implicated in the pathophysiology of inflammatory
diseases, including rheumatoid arthritis, gout, asthma, ischemia reperfusion
injury, psoriasis and inflammatory bowel disease. Any drug that inhibits
lipoxygenase is expected to provide significant new therapy for both acute
and chronic inflammatory conditions.

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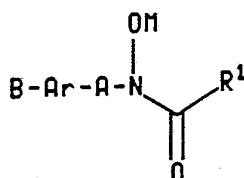
Description of the Related Art

Recently several review articles on lipoxygenase inhibitors have been reported (See H. Masamune et al., Ann. Rep. Med. Chem., **24**, 71-80 (1989) and B. J. Fitzsimmons et al., Leukotrienes and Lipoxygenases, 427-502
 5 (1989).

Compounds of the same general class as the compounds of the present invention are disclosed in EP 279263 A2, EP 196184 A2, JP 63502179 and U.S. patent No. 4,822,809.

SUMMARY OF THE INVENTION

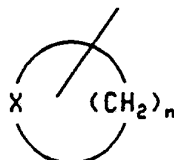
10 The present invention provides novel hydroxamic acid derivatives of the formula



wherein R¹ is hydrogen, C1 to C4 alkyl, C2 to C4 alkenyl, alkylthioalkyl, alkoxyalkyl or NR²R³; R² and R³ are each independently hydrogen, C1 to C4 alkyl, hydroxy, aryl, or aryl substituted with one or more substituents selected
 15 from the group consisting of halo, nitro, cyano, C1 to C12 alkyl, C1 to C12 alkoxy, C1 to C12 halosubstituted alkyl, C1 to C12 hydroxysubstituted alkyl, C1 to C12 alkoxy carbonyl, aminocarbonyl, C1 to C12 alkylaminocarbonyl, di C1 to C12 alkylaminocarbonyl and C1 to C12 alkylsulfonyl, with the proviso that R² and R³ are not both hydroxy; M is hydrogen, a pharmaceutically
 20 acceptable cation, aroyl or C1 to C12 alkoyl; A is alkynylene or alkynylene substituted with one or more substituents selected from the group consisting of C1 to C4 alkyl, C2 to C4 alkenyl, cyano, halo, C1 to C4 alkoxy, C1 to C4 halosubstituted alkyl and C1 to C4 hydroxysubstituted alkyl; Ar is phenyl or naphthyl; B is hydrogen, C1 to C12 alkyl, C2 to C12 alkenyl, C1 to C12
 25 halosubstituted alkyl, C1 to C12 hydroxysubstituted alkyl, OR⁴, NR⁴R⁵, aryl or aryl substituted with one or more substituents selected from the group

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- consisting of halo, nitro, cyano, C1 to C6 alkyl, C1 to C6 alkoxy, C1 to C6 halosubstituted alkyl, C1 to C6 hydroxysubstituted alkyl, C1 to C6 alkoxycarbonyl, aminocarbonyl, C1 to C6 alkylaminocarbonyl, di C1 to C6 alkylaminocarbonyl and C1 to C6 alkylsulfonyl; R⁴ and R⁵ are each
- 5 independently hydrogen, C1 to C12 alkyl, C3 to C12 alkenyl, C3 to C8 cycloalkyl, aryl or



n is 4 to 6; X is O, NR⁶ or S; and R⁶ is hydrogen or C1 to C4 alkyl.

- This invention also concerns pharmaceutical compositions comprising a pharmaceutically acceptable carrier or diluent and a compound of the
- 10 invention or a pharmaceutically acceptable salt thereof. This invention further concerns methods of treating inflammatory diseases, allergy and cardiovascular diseases in mammals comprising administration of such compounds or compositions.

DETAILED DESCRIPTION OF THE INVENTION

15 Definitions

As used herein, the following definitions are used.

"Halo" means radicals derived from the elements fluorine, chlorine, bromine and iodine.

- "Alkyl" means straight or branched saturated hydrocarbon radicals, for
- 20 example, methyl, ethyl, n-propyl and isopropyl.

"Alkenyl" means straight or branched unsaturated (double bonded) hydrocarbon radicals, for example, ethenyl, 1- or 2-propenyl, 2-methyl-1-propenyl and 1- or 2-butenyl.

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"Alkynylene" means straight or branched unsaturated (triple bonded) hydrocarbon radicals, for example, $-C\equiv C-$, $C\equiv CCH_2-$, $-C\equiv CHCH_2CH_2-$ and $-C\equiv CCH(CH_3)-$.

5 "Cycloalkyl" means carbocyclic radicals, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

"Alkoxy" means $-OR^7$ wherein R^7 is an alkyl radical, for example, methoxy, ethoxy, propoxy, isopropoxy and butoxy.

10 "Alkoxyalkyl" means $-R^8OR^9$ wherein R^8 and R^9 are independently alkyl radicals, for example, methoxymethyl, methoxyethyl, ethoxymethyl and ethoxyethyl.

"Alkylthioalkyl" means $-R^{10}SR^{11}$ wherein R^{10} and R^{11} are independently alkyl radicals, for example, methylthiomethyl, ethylthioethyl and methylthioethyl.

15 "Alkoyl" means $-COR^{12}$ wherein R^{12} is an alkyl radical, for example, formyl, acetyl, propionyl, butyryl and isobutyryl.

"Aryl" means aromatic radicals, for example, phenyl and naphthyl.

"Aroyl" means $-COR^{13}$ wherein R^{13} is an aryl radical, for example, benzoyl and naphthoyl.

20 "Aryloxy" means $-OR^{14}$ wherein R^{14} is an aryl radical, for example, phenoxy and naphthoxy.

"Alkoxycarbonyl" means $-C(=O)R^{15}$ wherein R^{15} is an alkoxy radical, for example, methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl.

25 "Alkylaminocarbonyl" means $-C(=O)NHR^{16}$ wherein R^{16} is an alkyl radical, for example, methylaminocarbonyl, ethylaminocarbonyl and propylaminocarbonyl.

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"Dialkylaminocarbonyl" means $-C(=O)N(R^{17})R^{18}$ wherein R^{17} and R^{18} are independently alkyl radicals, for example, dimethylaminocarbonyl, diethylaminocarbonyl and methylethylaminocarbonyl.

5 "Alkylsulfonyl" means $-SO_2R^{19}$ wherein R^{19} is an alkyl radical, for example, methanesulfonyl (mesyl) and ethanesulfonyl.

"Halosubstituted alkyl" means an alkyl radical as described above substituted with one or more halogens, for example, chloromethyl, trifluoromethyl and 2,2,2-trichloroethyl.

10 "Hydroxysubstituted alkyl" means an alkyl radical as described above substituted with one or more hydroxy radicals, for example, hydroxymethyl, dihydroxyethyl and trihydroxypropyl.

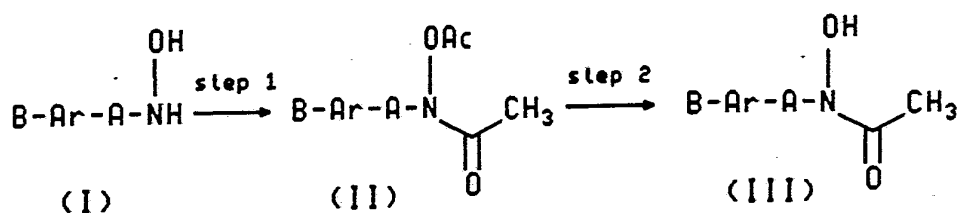
15 "Pharmaceutically acceptable cation" means non-toxic cations based on alkali and alkaline earth metals, for example, sodium, lithium, potassium, calcium and magnesium, as well as non-toxic ammonium, quaternary ammonium, and amine cations, for example, ammonium, tetramethylammonium, methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine and triethylamine.

Methods of Preparation

20 The compounds of the invention may be prepared by a number of synthetic methods. As used in the following reaction schemes, A, B and Ar are as defined above. Although in Schemes 1 and 2 R^1 is methyl and NH_2 , respectively, compounds wherein R^1 is otherwise, as defined above, may be prepared in a similar manner.

25 In one embodiment, compounds of the formula (III) are prepared according to the reaction steps outlined in Scheme 1.

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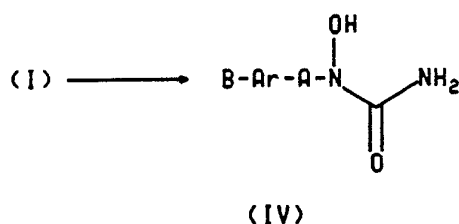
Reaction Scheme 1

In step 1, the diacetyl compound (II) is prepared by standard methods known in the art. For example, the hydroxylamine (I) is reacted with acetyl chloride or acetic anhydride in a reaction-inert solvent in the presence of a suitable base. Preferred bases are sodium hydride, triethylamine and pyridine, with the latter two being particularly preferred. Suitable reaction-inert solvents include methylene chloride, chloroform, tetrahydrofuran, benzene and toluene. The reaction is usually carried out in the temperature range of about 0°C through to ambient temperature, with reaction times from 30 minutes to a few hours being typical. The product can be isolated and purified by conventional procedures, such as recrystallization or chromatography.

Step 2 involves selective hydrolysis of the diacetyl (II) with an appropriate base. Typical bases include ammonium hydroxide, sodium hydroxide, potassium hydroxide and lithium hydroxide preferably in methanol, ethanol, isopropyl alcohol or water, though binary solvent systems such as alcohol-water, tetrahydrofuran-water and the like may also be employed. Reaction temperatures are usually in the range of about -10°C through to ambient temperature, with the reaction usually complete within a few minutes to several hours. The product of formula (III) is isolated by standard methods and purification can be achieved by conventional means, such as recrystallization and chromatography.

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In another embodiment, compounds of the formula (IV) are prepared as illustrated in Scheme 2.



Reaction Scheme 2

In this step the hydroxylamine (I) is treated with trimethylsilyl
5 isocyanate in a reaction-inert solvent usually at ambient through to reflux temperature. Suitable solvents which do not react with reactants and/or products include, for example, tetrahydrofuran, dioxane, methylene chloride and benzene. An alternative procedure employs treatment of (I) with
10 gaseous hydrogen chloride in a reaction-inert solvent such as benzene or toluene followed by treatment with phosgene. Reaction temperatures are usually in the range of ambient temperature through to boiling point of solvent. The intermediate carbamoyl chloride is not isolated but is subjected to (i.e. *in situ*) reaction with aqueous ammonia. The product of formula (IV) thus obtained is isolated by standard methods and purification can be
15 achieved by conventional means, such as recrystallization and chromatography.

The aforementioned hydroxylamine (I) is easily prepared by standard synthetic procedures from readily available aldehyde. For example, the aldehyde is converted to its acetylene alcohol (see E.J. Corey et al.,
20 Tetrahedron Lett., 3769-3772 (1972)) and then the alcohol is treated with N,O-bis(*tert*-butoxycarbonyl)hydroxylamine under Mitsunobu-type reaction conditions followed by acid catalyzed hydrolysis of the N,O-protected intermediate product (see JP 1045344) to give the requisite hydroxylamine (I). N,O-diacetyl compound (II) can be prepared employing N,O-diacetyl

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hydroxylamine in place of N,O-bis(*tert*-butoxycarbonyl)hydroxylamine, thus providing a convenient route to the product of formula (III).

Alternatively, the hydroxylamine (I) can be prepared by direct coupling of the corresponding aryl bromide or aryl iodide and N,O-bis(*tert*-butoxycarbonyl)alkynylenehydroxylamine in the presence of $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ in a
5 reaction-inert solvent such as diethylamine or triethylamine, followed by acid-catalyzed hydrolysis of the N,O-protected intermediate product to afford the desired hydroxylamine (I).

The hydroxylamine of formula (I) thus obtained by the aforementioned
10 representative procedures is isolated by standard methods and purification can be achieved by conventional means, such as recrystallization and chromatography.

The pharmaceutically acceptable salts of the novel compounds of the present invention are readily prepared by contacting said compounds with a
15 stoichiometric amount of, in the case of a non-toxic cation, an appropriate metal hydroxide or alkoxide or amine in either aqueous solution or a suitable organic solvent. In the case of non-toxic acid salt, an appropriate mineral or organic acid in either aqueous solution or a suitable organic solvent can be used. The salt may then be obtained by precipitation or by evaporation of
20 the solvent.

Biological Activity

The compounds of this invention inhibit lipxygenase. This inhibition has been demonstrated by an assay using rat peritoneal cavity resident cells which determines the effect of such compounds on the metabolism of
25 arachidonic acid.

The compounds of the examples were tested according to the methods described in "Synthesis of leukotrienes by peritoneal

macrophages", Jap. J. Inflammation, 7, 145-150 (1987), and were shown to be lipoxygenase inhibitors. In this test some preferred compounds exhibit low IC_{50} values, in the range of about 0.01 to about $30\mu M$, for lipoxygenase inhibition.

- 5 The ability of the compounds of the present invention to inhibit lipoxygenase makes them useful for controlling the symptoms induced by the endogenous metabolites arising from arachidonic acid in a mammalian subject. The compounds are therefore valuable in the prevention and treatment of such disease states in which the accumulation of arachidonic
- 10 acid metabolites is the causative factor, e.g., allergic bronchial asthma, skin disorders, rheumatoid arthritis, osteoarthritis and thrombosis.

The compounds of the formula and their pharmaceutically acceptable salts are of particular use in the prevention and treatment of inflammatory diseases, allergy and cardiovascular diseases in a human subject.

15 Methods of Administration

- For treatment of the various conditions described above, the compounds of the invention and their pharmaceutically acceptable salts can be administered to a human subject either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents in a
- 20 pharmaceutical composition, according to standard pharmaceutical practice. A compound can be administered via a variety of conventional routes of administration including orally, parenterally and by inhalation. When the compounds are administered orally, the dose range will generally be from about 0.1 to about 20 mg/kg/day, based on the body weight of the subject
- 25 to be treated, preferably from about 0.1 to about 1.0 mg/kg/day in single or divided doses. If parenteral administration is desired, then an effective dose will generally be from about 0.1 to about 1.0 mg/kg/day. In some instances it may be necessary to use dosages outside these limits, since the dosage will necessarily vary according to the age, weight and response of the

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individual patient as well as the severity of the patient's symptoms and the potency of the particular compound being administered.

For oral administration, the compounds of the invention and their pharmaceutically acceptable salts can be administered, for example, in the form of tablets, powders, lozenges, syrups or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are commonly added. In the case of capsules, useful diluents are lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents can be added.

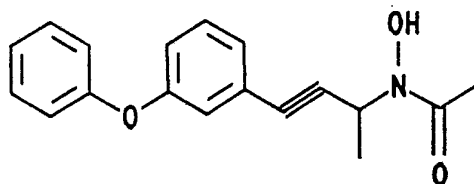
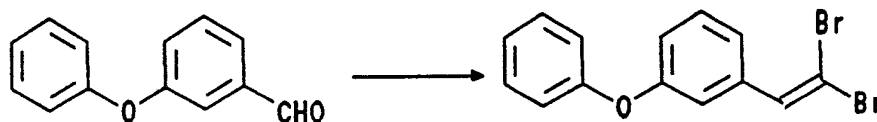
For intramuscular, intraperitoneal, subcutaneous and intravenous use, a sterile solution of the active ingredient is usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solute should be controlled to make the preparation isotonic.

Examples

The present invention is illustrated by the following examples.

However, it should be understood that the invention is not limited to specific details of these examples. Proton nuclear magnetic resonance (NMR) spectra were measured at 270 MHz unless otherwise indicated and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane. The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

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Example 1 N-Hydroxy-N-[4-(3-phenoxyphenyl)-3-butyn-2-yl]acetamideStep 1, 3-phenoxyphenylethylene-1,1-dibromide

To a mixture of zinc (2.90 g, 0.044 mol), triphenylphosphine (Ph_3P , 11.6 g, 0.044 mol) in CH_2Cl_2 (100 ml) was added CBr_4 (14.7 g, 0.044 mol) at 0°C. After stirring for 30 minutes, 3-phenoxybenzaldehyde (4.39 g, 0.022 mol) was added and stirred at room temperature overnight. The mixture was extracted with hexane/ethyl acetate (1:1), dried over magnesium sulfate and concentrated *in vacuo* to give a white precipitate which was suspended in ether/hexane (1:1) and filtered. The filtrate was concentrated *in vacuo* to afford 7.67 g of the title compound as a pale yellow oil.

^1H NMR (CDCl_3) δ 7.43 (s, 1H), 7.28-7.38 (m, 3H), 7.18-7.25 (m, 2H), 7.12 (tt, $J=7.0, 1.1$ Hz, 1H), 6.97-7.05 (m, 3H).

Step 2, 4-(3-phenoxyphenyl)-3-butyn-2-ol

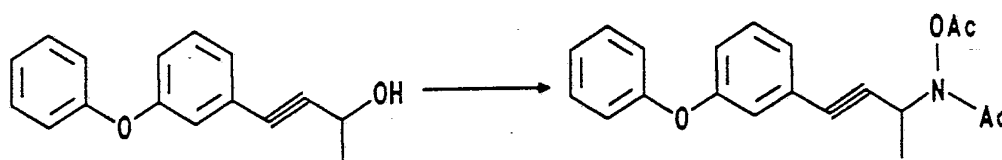
To a solution of the dibromide prepared in Step 1, above, (3.557 g, 10 mmol) in tetrahydrofuran (THF, 20 ml) was added *n*-butyllithium (*n*-BuLi, 13.4 ml, 21 mmol) at -78 to -45°C under nitrogen atmosphere. The reaction mixture was stirred at -78°C for 45 minutes and then at room temperature for 1 hour under nitrogen atmosphere. To the mixture was added dry acetaldehyde (about 2 ml) at 0°C and the mixture was stirred at room

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temperature for 5 minutes. The mixture was combined with 2N HCl (11 ml, 22 mmol), extracted with ethyl acetate and washed with brine, NaHCO₃ solution and then brine again. The solution was dried over magnesium sulfate and concentrated (3.84 g). Chromatography on silica gel eluted with
5 hexane/ethyl acetate (4:1) afforded 2.34 g (75.6% yield) of the title compound as a colorless oil.

¹H NMR (CDCl₃) δ 7.31-7.39 (m, 2H), 7.27 (t, J=7.9 Hz, 1H), 7.09-7.18 (m, 2H), 7.69-7.05 (m, 4H), 4.73 (qd, J=6.6, 5.5 Hz, 1H), 1.86 (d, J=5.5 Hz, 1H), 1.53 (d, J=6.6 Hz, 3H).

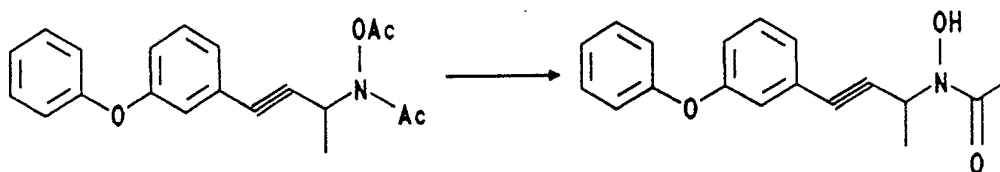
10 Step 3. N-acetoxy-N-[4-(3-phenoxyphenyl)-3-butyn-2-yl]acetamide



To a solution of the alcohol prepared in Step 2, above, (2 g, 8.4 mmol), N,O-diacetylhydroxylamine, Ph₃P (3.3 g, 12.6 mmol) in toluene (50 ml) and diethyl azodicarboxylate (DEAD, 2.19 g, 12.6 mmol) were added at -78°C under nitrogen atmosphere. The reaction mixture was stirred at room
15 temperature overnight, the resultant precipitate was filtered off and the filtrate was concentrated *in vacuo*. Chromatography on silica gel eluted with hexane/ethyl acetate (4:1) afforded 1.23 g (43% yield) of the title compound as a colorless oil.

20 ¹H NMR (CDCl₃) δ 7.32-7.39 (m, 2H), 7.25 (t, J=7.7 Hz, 1H), 7.09-7.16 (m, 2H), 6.95-7.03 (m, 4H), 5.58 (q, J=6.6 Hz, 1H), 2.23 (s, 3H), 2.05 (s, 3H), 1.48 (d, J=6.6 Hz, 3H).

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Step 4. N-hydroxy-N-[4-(3-phenoxyphenyl)-3-butyn-2-yl]acetamide

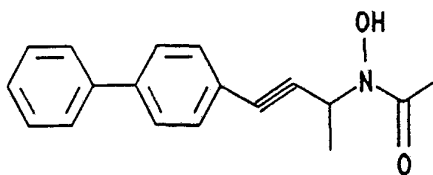
To a solution of the diacetate prepared in Step 3, above, (1.15 g, 3.41 mmol) in methanol (10 ml) was added NH_4OH (2 ml) at room temperature.

The mixture was concentrated *in vacuo* and extracted with ethyl acetate.

- 5 The extract was washed with water and dried over magnesium sulfate. The solution was concentrated to give a colorless oil (1.09 g). Chromatography on silica gel eluted with hexane/ethyl acetate (2:1) afforded the title compound as a white powder. Recrystallization from ethyl acetate/hexane gave 787 mg (78% yield) of product as a white powder.

10 IR (film) ν 3170, 2230, 1600 cm^{-1} .

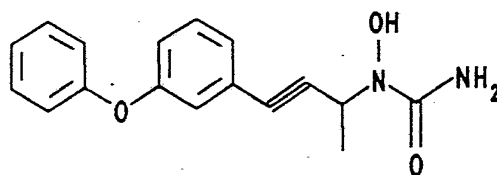
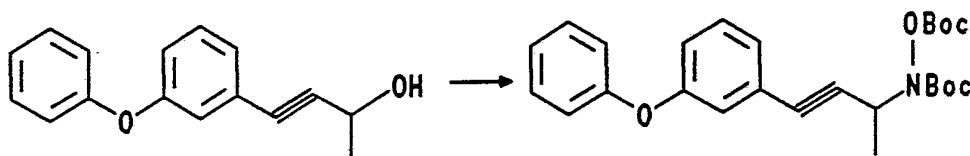
^1H NMR ($\text{DMSO}-d_6$) δ 7.35-7.46 (m, 3H), 7.15-7.22 (m, 2H), 7.02-7.07 (m, 3H), 6.94-6.97 (m, 1H), 5.47 (q, $J=6.9$ Hz, 1H), 2.01 (s, 3H), 1.37 (d, $J=6.9$ Hz, 3H).

Example 2 N-Hydroxy-N-[4-(4-biphenyl)-3-butyn-2-yl]acetamide

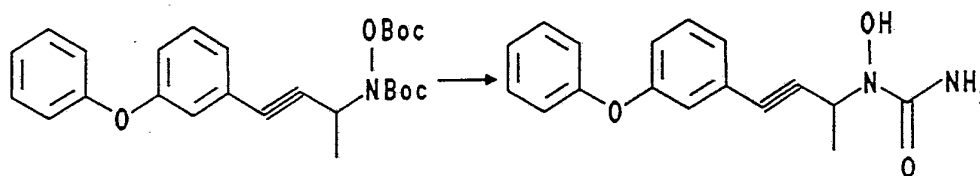
- 15 The title compound (m.p. 152.9-153.8°C) was prepared from 4-phenylbenzaldehyde using the same procedure as Example 1.

IR (KBr) ν 3450, 1612 cm^{-1} .

^1H NMR ($\text{DMSO}-d_6$) δ 9.90 (s, 1H), 7.66-7.72 (m, 4H), 7.33-7.54 (m, 5H), 5.53 (q, $J=7$ Hz, 1H), 2.04 (s, 3H), 1.42 (d, $J=7$ Hz, 3H).

Example 3 N-Hydroxy-N-[4-(3-phenoxyphenyl)-3-butyn-2-yl]ureaStep 1. N,O-bis-Boc-(4-phenoxyphenyl-3-butyn-2-yl)hydroxylamine

To a solution of 4-phenoxyphenyl-3-butyn-2-ol (1.2 g, 5.04 mmol), Ph_3P (1.98 g, 7.56 mmol) and BocNH-OBoc (1.23 g, 5.29 mmol) in toluene (10 ml) was added DEAD (1.32 g, 7.56 mmol) in toluene (3 ml) at -78°C under nitrogen atmosphere. The mixture was concentrated *in vacuo* and a mixture of hexane/toluene (1:1, 30 ml) was added. The resulting precipitate was separated off by suction filtration and the filtrate was concentrated to give a yellow oil. Chromatography on silica gel eluted with hexane/ethyl acetate (8:1) afforded 1.77 g (77.5% yield) of the desired product as a pale yellow oil. A less pure fraction of the desired product was also obtained (579 mg, 25% yield).

Step 2. N-hydroxy-N-[4-(3-phenoxyphenyl)-3-butyn-2-yl]urea

To a solution of the hydroxylamine prepared in Step 1 in CH_2Cl_2 (10 ml) was added trifluoroacetic acid (TFA, 3 ml). The resulting mixture was stirred at room temperature for 1 hour under nitrogen atmosphere, then was washed with small amount of saturated NaHCO_3 solution in brine. The solution was dried over magnesium sulfate and concentrated *in vacuo* to give a pale yellow oil. Without purification, the product was dissolved in THF

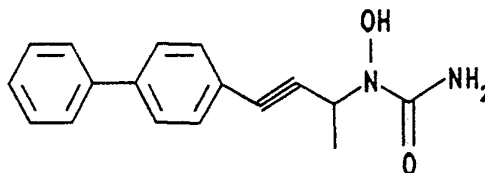
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(10 ml), added to TMS-NCO (731 μ l, 5.4 mmol), stirred for 1 hour and concentrated *in vacuo*. Chromatography on silica gel eluted with CH_2Cl_2 /acetone (10:1) afforded 610 mg of product as a white powder. This was recrystallized from ethyl acetate/hexane-IPE (1:1:1) to give 456 mg (42.7% yield) of the desired product as a white powder, m.p. 120.0-120.8°C.

IR (KBr) ν 3150, 1670, 1580 cm^{-1} .

^1H NMR (CDCl_3) δ 7.31-7.39 (m, 2H), 7.25 (t, $J=7.7$ Hz, 1H), 7.09-7.18 (m, 2H), 7.04-7.06 (m, 1H), 6.95-7.02 (m, 3H), 6.22 (s, 1H), 5.39 (br s, 2H), 5.34 (q, $J=6.9$ Hz, 1H), 1.50 (d, $J=6.9$ Hz, 3H).

10 Example 4 N-Hydroxy-N-[4-(4-biphenyl)-3-butyn-2-yl]urea

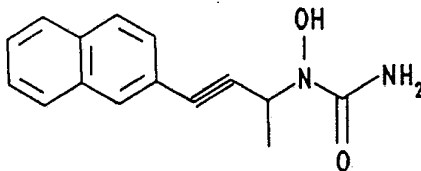


The title compound (m.p. 170.3-171.2°C) was prepared from 4-phenylbenzaldehyde using the same procedure as Example 3.

IR (KBr) ν 3460, 1610, 1575 cm^{-1} .

15 ^1H NMR ($\text{DMSO}-d_6$) δ 9.36 (s, 1H), 7.65-7.72 (m, 4H), 7.44-7.52 (m, 4H), 7.38 (tt, $J=7.3, 1.5$ Hz, 1H), 6.55 (s, 1H), 5.16 (q, $J=7.3$ Hz, 1H), 1.38 (d, $J=6.9$ Hz, 3H).

Example 5 N-Hydroxy-N-[4-(2-naphthyl)-3-butyn-2-yl]urea



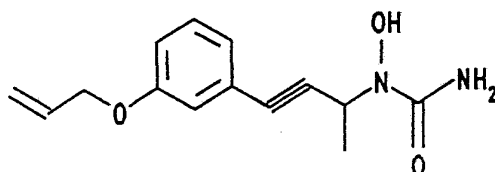
The title compound (m.p. 137.6-138.6°C) was prepared from 2-naphthaldehyde using the same procedure as Example 3.

-16-

IR (KBr) ν 3450, 3250, 1630 cm^{-1} .

^1H NMR (CDCl_3 -DMSO- d_6) δ 9.24 (s, 1H), 7.96 (s, 1H), 7.67-7.87 (m, 3H), 7.38-7.55 (m, 3H), 5.78 (s, 2H), 5.38 (q, $J=6.8$ Hz, 1H), 1.54 (d, $J=6.9$ Hz, 3H).

5 Example 6 N-Hydroxy-N-[4-(3-allyloxyphenyl)-3-butyn-2-yl]urea

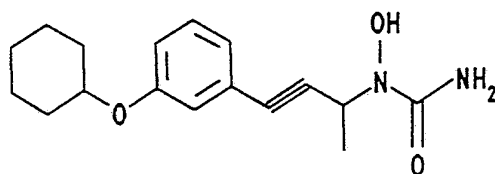


The title compound (m.p. 116.3-116.7°C) was prepared from 3-allyloxybenzaldehyde using the same procedure as Example 3.

IR (KBr) ν 3450, 3330, 1630, 1595 cm^{-1} .

10 ^1H NMR (DMSO- d_6) δ 7.26 (t, $J=8.4$ Hz, 1H), 6.90-6.99 (m, 2H), 6.52 (br s, 2H), 5.95-6.10 (m, 1H), 5.38 (dq, $J=16$, 1 Hz, 1H), 5.26 (dq, $J=9.5$, 1 Hz, 1H), 4.54-4.60 (m, 2H), 1.35 (d, $J=7$ Hz, 3H).

Example 7 N-Hydroxy-N-[4-(3-cyclohexyloxyphenyl)-3-butyn-2-yl]urea



Step 1, 3-cyclohexyloxy-1-iodobenzene

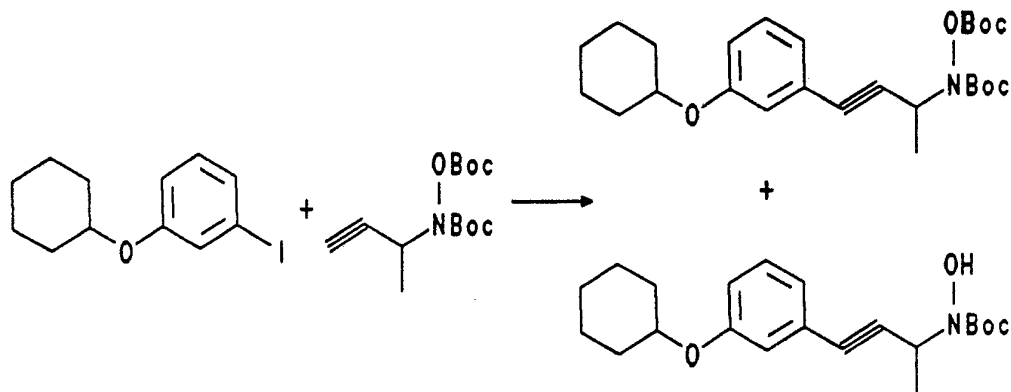
15 A solution of cyclohexanol (6.0 g), 3-iodophenol (13.2 g) and triphenylphosphine (15.7 g) in THF (150 ml) was stirred at room temperature under nitrogen atmosphere. Diethyl azodicarboxylate (10.45 g) was added dropwise and the resulting solution was stirred for 7 days. The reaction mixture was evaporated to dryness under reduced pressure, hexane/ether (2:1) mixture (400 ml) was added to the precipitate, the undissolved
20 precipitate was filtered off and the filtrate was concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (ether/hexane,

-17-

1:4), and distillation (200°C, 0.4 mmHg, bath temp.) to provide 7.46 g (41% yield) of title product.

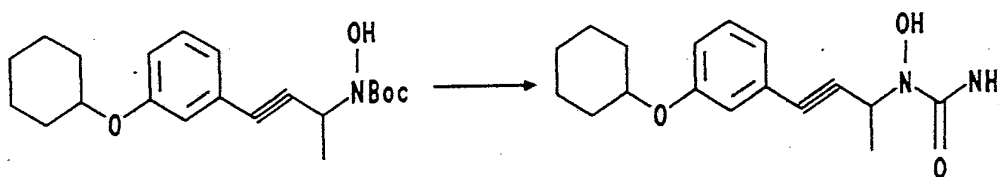
5

Step 2, N,O-bis-*tert*-butoxycarbonyl-N-[4-(3-cyclohexyloxyphenyl)-3-butyn-2-yl]hydroxylamine and N-*tert*-butoxycarbonyl]-N-[4-(3-cyclohexyloxyphenyl)-3-butyn-2-yl]hydroxylamine



- Diethylamine (25 ml), suspension of CuI (0.043 g) and $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (0.33 g) was stirred at room temperature under argon atmosphere. Diethylamine solution of N,O-bis-*tert*-butoxycarbonyl-N-(3-butyn-2-yl)hydroxylamine (5.42 g) was added to the suspension, then the 3-cyclohexyloxy-1-iodobenzene (4.53 g) prepared in Step 1 was added. The resulting mixture was stirred for 17 hours. Solvent was removed under reduced pressure and ether (200 ml) and water (100 ml) were added. Undissoluble red grease was filtered off (celite). Ethereal layer of the filtrate was collected, dried (MgSO_4), and concentrated under reduced pressure.
- The crude product was purified by silica gel column chromatography (ether/hexane, 15:85), providing 4.0 g (59 % yield) of N,O-bis-*tert*-butoxycarbonyl-N-[4-(3-cyclohexyloxyphenyl)-3-butyn-2-yl]hydroxylamine and 1.6 g (30% yield) of N-*tert*-butoxycarbonyl]-N-[4-(3-cyclohexyloxyphenyl)-3-butyn-2-yl]hydroxylamine.

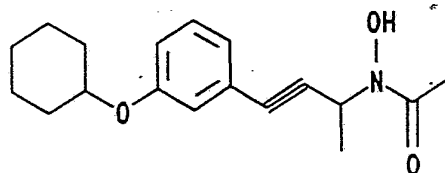
-18-

Step 3, N-hydroxy-N-[4-(3-cyclohexyloxyphenyl)-3-butyn-2-yl]urea

The N-*tert*-butoxycarbonyl (1.51 g) prepared in Step 2 was dissolved in CH_2Cl_2 (30 ml). $\text{CF}_3\text{CO}_2\text{H}$ (4 ml) was added to the solution at room temperature and the reaction mixture was stirred for 4 hours and concentrated under reduced pressure. NaHCO_3 solution was added and extracted with CH_2Cl_2 . The organic layer was dried (MgSO_4) and concentrated *in vacuo*. The resulting crude product was dissolved in dry THF (10 ml). Trimethylsilylisocyanate (1.09 g) was added to the solution, the mixture was stirred for 3 hours and the solvent was removed *in vacuo*. The resulting crude product was recrystallized with CHCl_3 /hexane, affording 0.62 g (45% yield) of the title compound (m.p. 95-95.5°C).

IR. (KBr) ν 3405, 1668 cm^{-1} .

^1H NMR (CDCl_3) δ 7.17 (dd, $J=7.7, 7.7$ Hz, 1H), 6.9-7.0 (m, 2H), 6.86 (ddd, $J=8.4, 2.6, 1.1$ Hz, 1H), 5.35 (q, $J=7.0$ Hz, 1H), 4.17-4.25 (m, 1H), 1.92-1.98 (m, 2H), 1.77-1.80 (m, 2H), 1.50 (d, $J=7.0$ Hz, 3H), 1.31-1.58 (m, 6H).

Example 8 N-Hydroxy-N-[4-(3-cyclohexyloxyphenyl)-3-butyn-2-yl]acetamideStep 1, N,O-diacetyl-N-[4-(3-cyclohexyloxyphenyl)-3-butyn-2-yl]hydroxylamine

N,O-Di-*tert*-butoxycarbonyl-N-[4-(3-cyclohexyloxyphenyl)-3-butyn-2-yl]hydroxylamine (2.0 g) was dissolved in CH_2Cl_2 (15 ml). $\text{CF}_3\text{CO}_2\text{H}$ (4 ml) was added to the solution at room temperature and the reaction mixture was

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stirred for 2 hours and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (20 ml) and stirred, then pyridine (5 ml) and AcCl (2.5 ml) were added at 0°C and stirred for 2 hours. The solvent was removed under reduced pressure, the residue was combined with 10% citric acid and extracted with ether. The organic layer was washed with NaHCO_3 solution, dried (MgSO_4) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (hexane/ EtOAc , 2:1), affording the title product as a colorless oil.

10 Step 2, N-hydroxy-N-[4-(3-cyclohexyl-oxyphenyl)-3-butyn-2-yl]acetamide

To a stirred solution of the product of Step 1, above (1.1 g), in MeOH (15 ml) was added 25% NH_3 solution (3 ml) at room temperature. The reaction mixture was stirred for 30 minutes and the solvent was evaporated off. To the resulting mixture water was added and the mixture was extracted with ether. The extract was dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (hexane/ EtOAc , 2:1), affording the title compound (0.412 g) as a colorless oil.

IR (neat) ν 2940, 1617, 1605, 1422, 1282 cm^{-1} .
20 ^1H NMR (DMSO) δ 9.9 (br, 1H), 7.25 (dd, $J=7.3, 8.8$ Hz, 1H), 6.93-6.98 (m, 3H), 5.48 (q, $J=7.0$ Hz, 1H), 4.35 (m, 1H), 2.03 (s, 3H), 1.24-1.87 (m, 10H), 1.36 (d, $J=7.0$ Hz, 3H).

$$\text{B-Ar-A-N} \begin{array}{l} \text{OH} \\ | \\ \text{C} \text{---} \text{R}^1 \\ || \\ \text{O} \end{array}$$

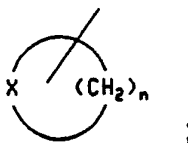
5 R^2 and R^3 are each independently hydrogen, C1 to C4 alkyl, hydroxy, aryl, or aryl substituted with one or more substituents selected from the group consisting of halo, nitro, cyano, C1 to C12 alkyl, C1 to C12 alkoxy, C1 to C12 halosubstituted alkyl, C1 to C12 hydroxysubstituted alkyl, C1 to C12 alkoxy carbonyl, aminocarbonyl, C1 to C12 alkylaminocarbonyl, di C1 to C12 alkylaminocarbonyl and C1 to C12 alkylsulfonyl, wherein R^2 and R^3 are not
10 both hydroxy;

A is alkynylene or alkynylene substituted with one or more substituents selected from the group consisting of C1 to C4 alkyl, C2 to C4 alkenyl, cyano, halo, C1 to C4 alkoxy, C1 to C4 halosubstituted alkyl and C1 to C4 hydroxysubstituted alkyl;

B is hydrogen, C1 to C12 alkyl, C2 to C12 alkenyl, C1 to C12
20 halosubstituted alkyl, C1 to C12 hydroxysubstituted alkyl, OR⁴, NR⁴R⁵, aryl or
aryl substituted with one or more substituents selected from the group
consisting of halo, nitro, cyano, C1 to C6 alkyl, C1 to C6 alkoxy, C1 to C6
halosubstituted alkyl, C1 to C6 hydroxysubstituted alkyl, C1 to C6
alkoxycarbonyl, aminocarbonyl, C1 to C6 alkylaminocarbonyl, di C1 to C6
25 alkylaminocarbonyl and C1 to C6 alkylsulfonyl;

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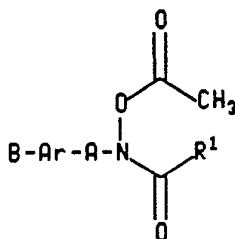
R^4 and R^5 are each independently hydrogen, C1 to C12 alkyl, C3 to C12 alkenyl, C3 to C8 cycloalkyl, aryl or



n is 4 to 6; X is O, NR^6 or S; and

5 R^6 is hydrogen or C1 to C4 alkyl; comprising:

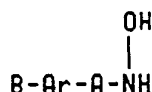
(I) selectively hydrolyzing a compound having the formula



wherein A, B, Ar and R^1 are as defined above, with a base selected from ammonium hydroxide, sodium hydroxide, potassium hydroxide and lithium hydroxide in a solvent system under conditions including a reaction

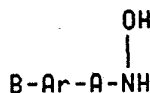
10 temperature of between -10°C and ambient temperature;

(II) reaction of a compound having the formula



wherein A, B, Ar and R^1 are as defined above, with trimethylsilyl isocyanate in a reaction-inert solvent under conditions including a reaction temperature of between ambient and reflux temperature; or

15 (III) reaction of a compound having the formula



wherein A, B, Ar and R^1 are as defined above, with gaseous hydrogen chloride in a reaction-inert solvent under reaction conditions including a reaction temperature of between ambient temperature and boiling point of the solvent, followed by treatment with phosgene.

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2. A process according to Claim 1 wherein:

when process (I) is used, said solvent system is selected from one or more of water, methanol, ethanol, propanol and tetrahydrofuran;

when process (II) is used; said reaction-inert solvent is selected from
5 tetrahydrofuran, dioxane, methylene chloride and benzene; and

when process (III) is used, said reaction-inert solvent is selected from benzene and toluene.

3. A process according to Claim 1 or 2 further comprising the step of isolating said prepared compound.

10 4. A process according to one of Claims 1 to 3 wherein:

when process (I) is used, R^1 is C1 to C4 alkyl; and

when process (II) or (III) is used, R^1 is NR^2R^3 .

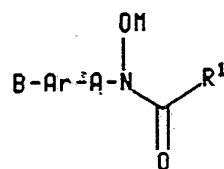
5. A process according to Claim 4 wherein:

when process (I) is used, R^1 is methyl; and

15 when process (II) or (III) is used, R^1 is NH_2 .

6. A process according to one of Claims 1 to 5, wherein process (III) is used, further comprising the step of treating the reaction mixture with aqueous ammonia.

7. A compound of the formula



20 wherein R^1 is hydrogen, C1 to C4 alkyl, C2 to C4 alkenyl, alkylthioalkyl, alkoxyalkyl or NR^2R^3 ;

R^2 and R^3 are each independently hydrogen, C1 to C4 alkyl, hydroxy, aryl, or aryl substituted with one or more substituents selected from the

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group consisting of halo, nitro, cyano, C1 to C12 alkyl, C1 to C12 alkoxy, C1 to C12 halosubstituted alkyl, C1 to C12 hydroxysubstituted alkyl, C1 to C12 alkoxycarbonyl, aminocarbonyl, C1 to C12 alkylaminocarbonyl, di C1 to C12 alkylaminocarbonyl and C1 to C12 alkylsulfonyl, with the proviso that R² and
 5 R³ are not both hydroxy;

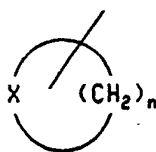
M is hydrogen, a pharmaceutically acceptable cation, aroyl or C1 to C12 alkoyl;

A is alkynylene or alkynylene substituted with one or more substituents selected from the group consisting of C1 to C4 alkyl, C2 to C4 alkenyl, cyano, halo, C1 to C4 alkoxy, C1 to C4 halosubstituted alkyl and C1
 10 to C4 hydroxysubstituted alkyl;

Ar is phenyl or naphthyl;

B is hydrogen, C1 to C12 alkyl, C2 to C12 alkenyl, C1 to C12 halosubstituted alkyl, C1 to C12 hydroxysubstituted alkyl, OR⁴, NR⁴R⁵, aryl or
 15 aryl substituted with one or more substituents selected from the group consisting of halo, nitro, cyano, C1 to C6 alkyl, C1 to C6 alkoxy, C1 to C6 halosubstituted alkyl, C1 to C6 hydroxysubstituted alkyl, C1 to C6 alkoxycarbonyl, aminocarbonyl, C1 to C6 alkylaminocarbonyl, di C1 to C6 alkylaminocarbonyl and C1 to C6 alkylsulfonyl;

20 R⁴ and R⁵ are each independently hydrogen, C1 to C12 alkyl, C3 to C12 alkenyl, C3 to C8 cycloalkyl, aryl or



n is 4 to 6;

X is O, NR⁶ or S; and

25 R⁶ is hydrogen or C1 to C4 alkyl.

8. A compound according to Claim 7 wherein:

A is alkynylene;

R¹ is C1 to C4 alkyl; and

B is hydrogen, aryl, or aryloxy.

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9. A compound according to Claim 7 wherein:

A is alkynylene;

R¹ is NR²R³; and

B is hydrogen, aryl, aryloxy or C3 to C12 alkenyloxy.

5 10. A compound according to one of Claims 7 to 9 wherein Ar is phenyl.

11. A compound according to Claim 7 or 8 wherein:

Ar is phenyl;

M is hydrogen; and

10 R¹ is methyl.

12. A compound according to Claim 7 or 9 wherein:

Ar is phenyl;

M is hydrogen; and

R¹ is amino.

15 13. A compound according to one of Claims 7 to 12 wherein B is phenyl or phenoxy.

14. A compound according to one of Claims 7, 9 and 12 wherein B is allyloxy.

15. A compound according to one of Claims 7 to 9 wherein:

20 Ar is naphthyl; and

B is hydrogen.

16. A pharmaceutical composition for the treatment of allergic or inflammatory conditions in a mammal comprising a therapeutically effective amount of a compound according to one of Claims 7 to 15, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

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17. A pharmaceutical composition for the treatment of cardiovascular diseases in a mammal comprising a therapeutically effective amount of a compound according to one of Claims 7 to 15, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

5 18. A method of inhibiting lipoxygenase in a mammal comprising administering to said mammal a lipoxygenase-inhibiting amount of a compound according to one of Claims 7 to 15 or a pharmaceutically acceptable salt thereof.

10 19. A method of treating allergy or inflammatory conditions in a mammal comprising administering to said mammal a lipoxygenase-inhibiting amount of a compound according to one of Claims 7 to 15 or a pharmaceutically acceptable salt thereof.

15 20. A method of treating cardiovascular diseases in a mammal comprising administering to said mammal a lipoxygenase-inhibiting amount of a compound according to one of Claims 7 to 15 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 91/07193

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.C1.5 C 07 C 275/64 C 07 C 259/06 C 07 C 273/18 A 61 K 31/17 A 61 K 31/16		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.C1.5	C 07 C	
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
A	EP,A,0351214 (THE WELLCOME RESEARCH LABORATORIES) 17 January 1990 -----	
A	EP,A,0384594 (THE WELLCOME RESEARCH LABORATORIES) 29 August 1990 -----	
A	WO,A,9012008 (ABBOTT LABORATORIES) 18 october 1990 -----	
^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	
12-03-1992	01.04.92	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	Els Vonk	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

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

1. ☒ Claim numbers 18-20 because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 18-20 are directed to a method of treatment if the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claim numbers 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. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

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 of the International application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:
3. ☐ 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 claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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

US 9107193

SA 54157

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 26/03/92
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- 0351214	17-01-90	JP-A- 2088553	28-03-90
EP-A- 0384594	29-08-90	AU-A- 4908890	09-08-90
		JP-A- 2270855	05-11-90
WO-A- 9012008	18-10-90	None	