CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-785

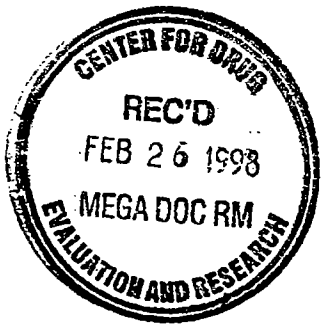
Administrative Reviews

Celgene

NC
NEW CORRES

ORIGINAL

Celgene Corporation
[illegible]



26 February 1998

Michael Weintraub, M.D.
Director, Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
THALOMID™ (thalidomide) Capsules
Amendment to Pending Application
Serial No.: 044
CONFIDENTIAL
Patent Certification Statement

Dear Dr. Weintraub:

In order to comply with Section 505.(b)(2) of the Food, Drug and Cosmetic Act, Celgene Corporation submits the following certification in accord with 21 CFR 314.50 (i) (ii):

In the opinion and to the best knowledge of Celgene Corporation, there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Furthermore, there is no listed drug in the book of "Approved Drug Products with Therapeutic Equivalence Evaluations-17 Edition" and therefore there are no patents for which certification is necessary.

Please do not hesitate to contact me with any questions or comments.

Sincerely,

Steve Thomas

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

014362

The following information is submitted as called for by 21 C.F.R. §314.53(c):

(i) Patent number and date patent will expire:

5,385,901 -- Expires Oct. 2, 2012
5,463,063 -- Expires Oct. 20, 2013

(ii) Type of patent (i.e., drug, drug product (formulation and composition)), or method of use:

5,385,901 -- composition and method of use
5,463,063 -- method of use

(iii) Name of patent owner

5,385,901 -- The Rockefeller University
New York, New York

5,463,063 -- Celgene Corporation
Warren, New Jersey

The undersigned declares that Patent Nos. 5,385,901 and 5,463,063 cover the formulation, composition, and/or method of use of Synovir (thalidomide). This product is the subject of this application for which approval is being sought.

Applicant's Agent

United States Patent [19]
Kaplan et al.

[11] Patent Number: 5,385,901
[45] Date of Patent: Jan. 31, 1995

[54] METHOD OF TREATING ABNORMAL CONCENTRATIONS OF TNF α

[75] Inventors: Gilla Kaplan, New York, N.Y.; Elisabeth P. Sampaio, Rio de Janeiro, Brazil

[73] Assignee: The Rockefeller University, New York, N.Y.

[21] Appl. No.: 955,936

[22] Filed: Oct. 2, 1992

Related U.S. Application Data

[60] Division of Ser. No. 834,588, Feb. 12, 1992, abandoned, which is a continuation of Ser. No. 655,087, Feb. 14, 1991, abandoned.

[51] Int. Cl.[6] A61K 31/535; A61K 31/44; A61K 31/445

[52] U.S. Cl. 514/231.5; 514/231.2; 514/282; 514/327; 514/331; 514/348

[58] Field of Search 514/327, 348, 282, 231.2, 514/231.5, 331

[56] References Cited

U.S. PATENT DOCUMENTS

2,830,991 4/1958 Keller et al. 260/231

FOREIGN PATENT DOCUMENTS

1185273 3/1970 United Kingdom .
WO92/09203 6/1992 WIPO .

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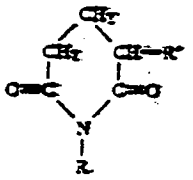
(List continued on next page.)

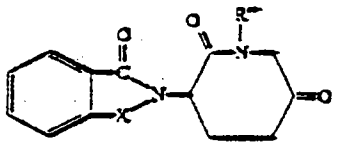
Primary Examiner—Raymond J. Henley, III
Assistant Examiner—T. J. Criares
Attorney, Agent, or Firm—Mathews, Woodbridge & Collins

[57] ABSTRACT

Compounds of the structure

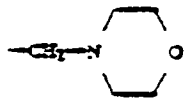


wherein R is selected from the group consisting of hydrogen, alkyl radicals of 1–6 carbon atoms, the phenyl radical, and the benzyl radical; and wherein R' is selected from the group consisting of the phthalimido radical and the succinimido radical and of the structure



II

wherein X is CH_2 or C=O; R'' is H, $-CH_2CH_3$, $-C_6H_5$, $-CH_2C_6H_5$, $-CH_2CH=CH_2$, or



and hydrolysis products of said compounds wherein R'' is H and the piperidino ring or both the piperidino and the imido ring are hydrolyzed are useful for the control of abnormal concentrations of TNF α manifested in septic shock, cachexia and HIV infection without substantially effecting the concentration of other cytokines.

18 Claims, 7 Drawing Sheets

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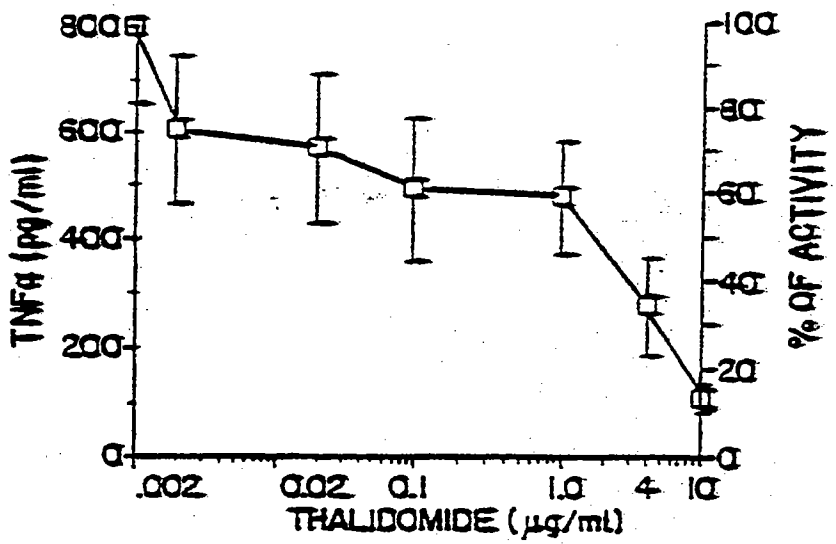


FIG. 1A

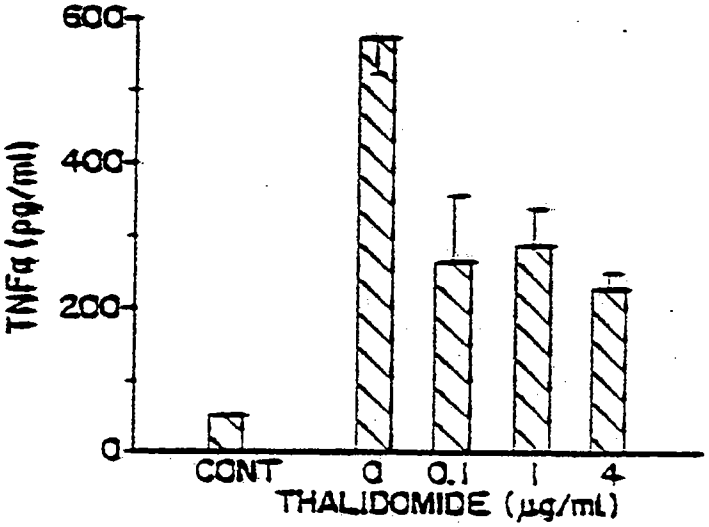


FIG. 1B

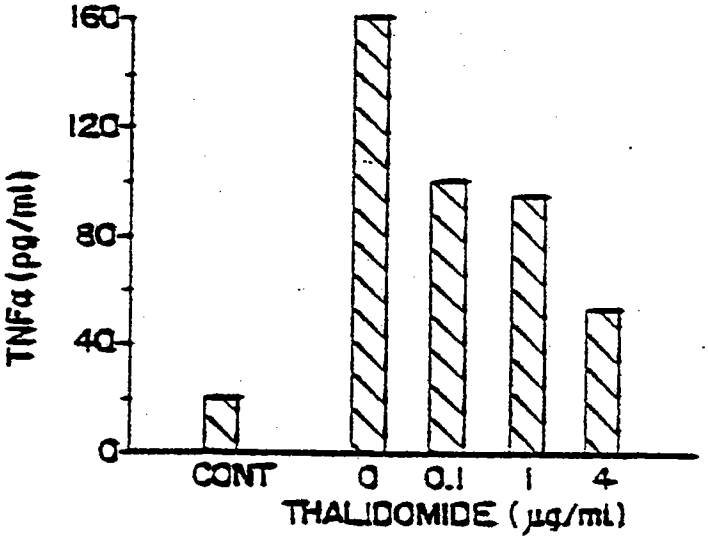


FIG. 1C

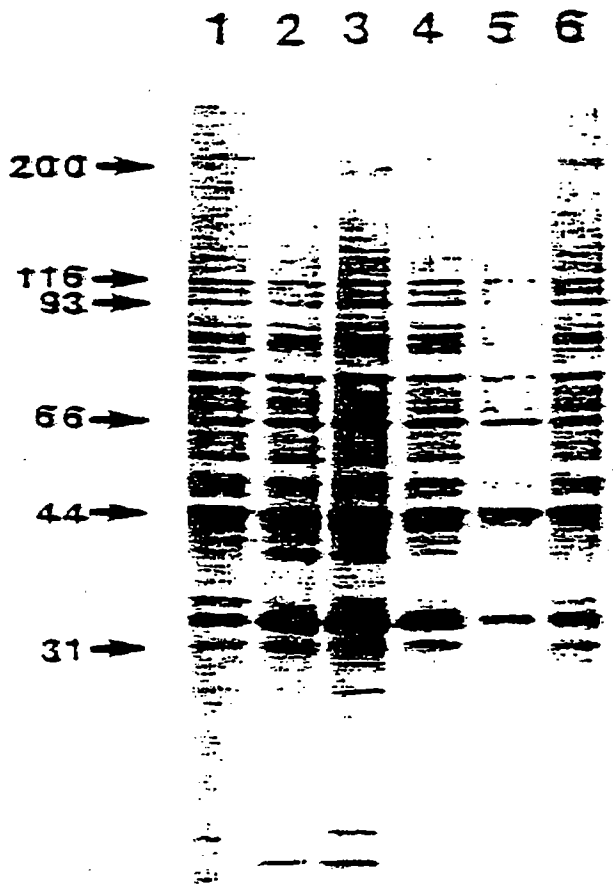


FIG. 2

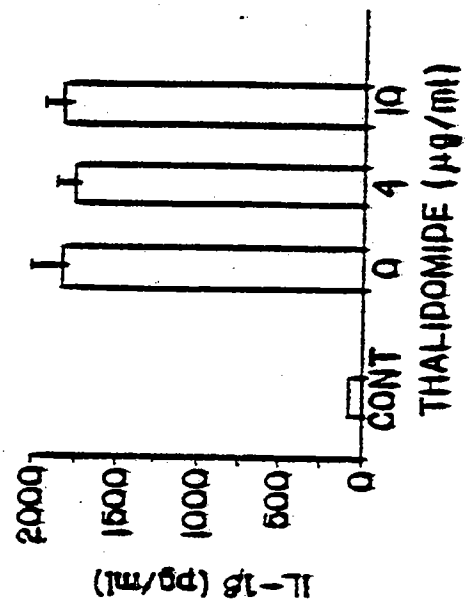


FIG. 3B

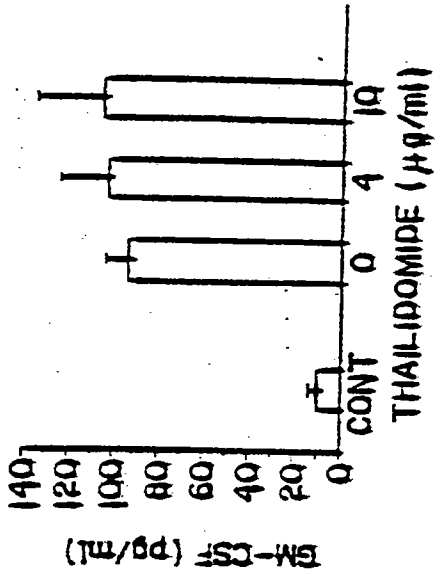


FIG. 3D

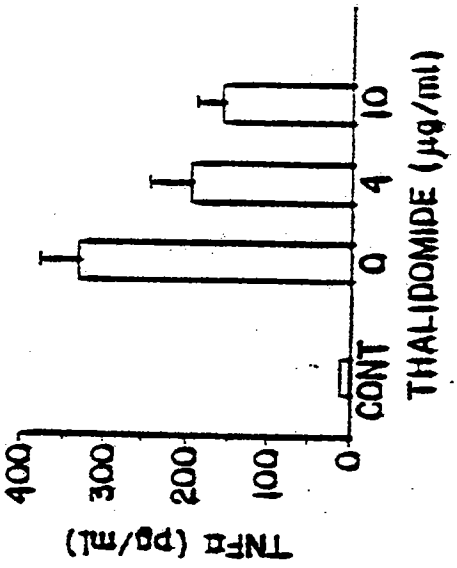


FIG. 3A

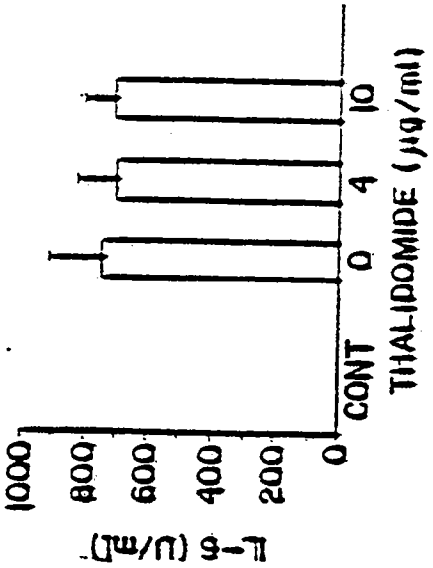
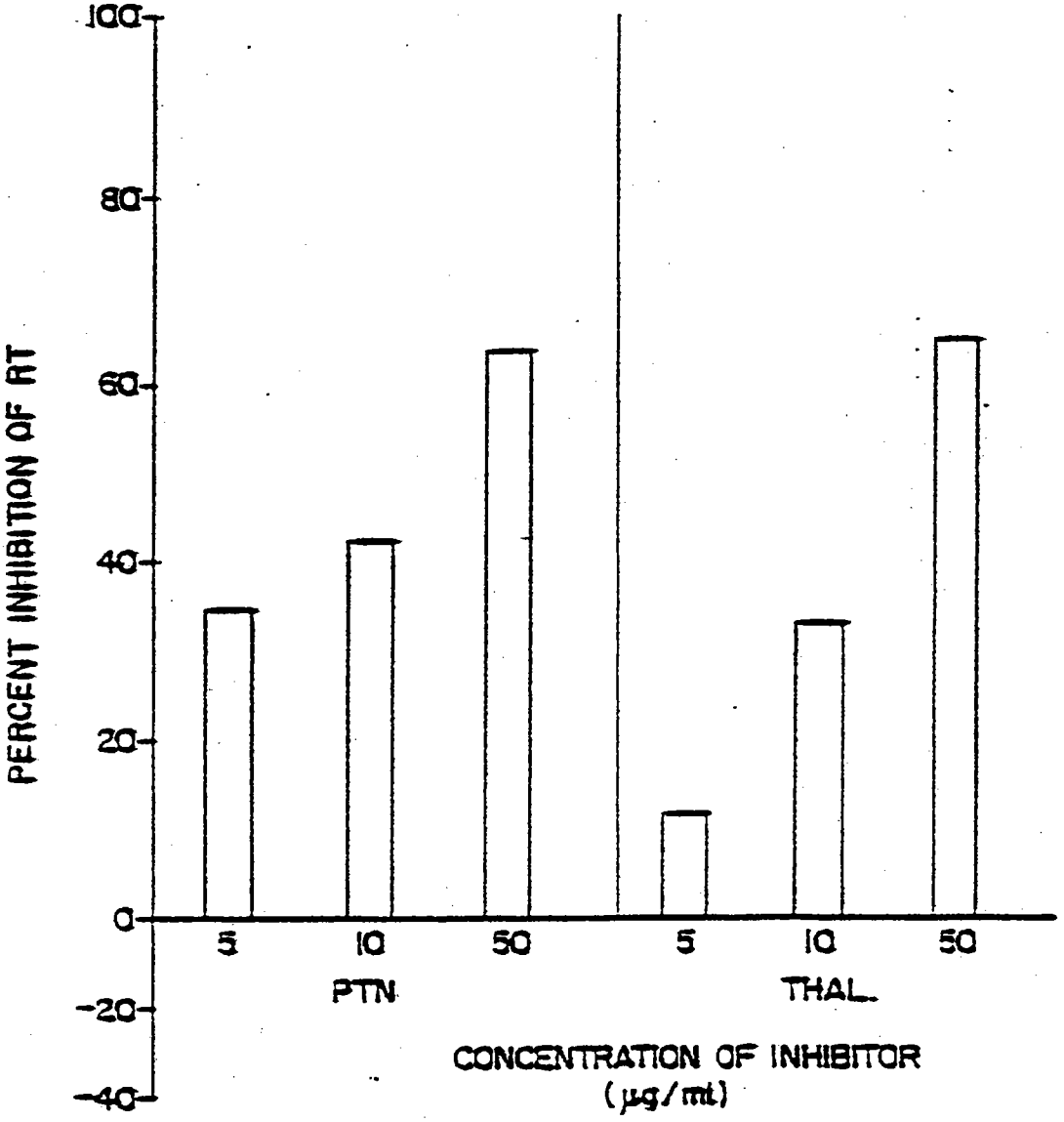


FIG. 3C


100
80
60
40
20
0
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PERCENT INHIBITION OF RT
5
10
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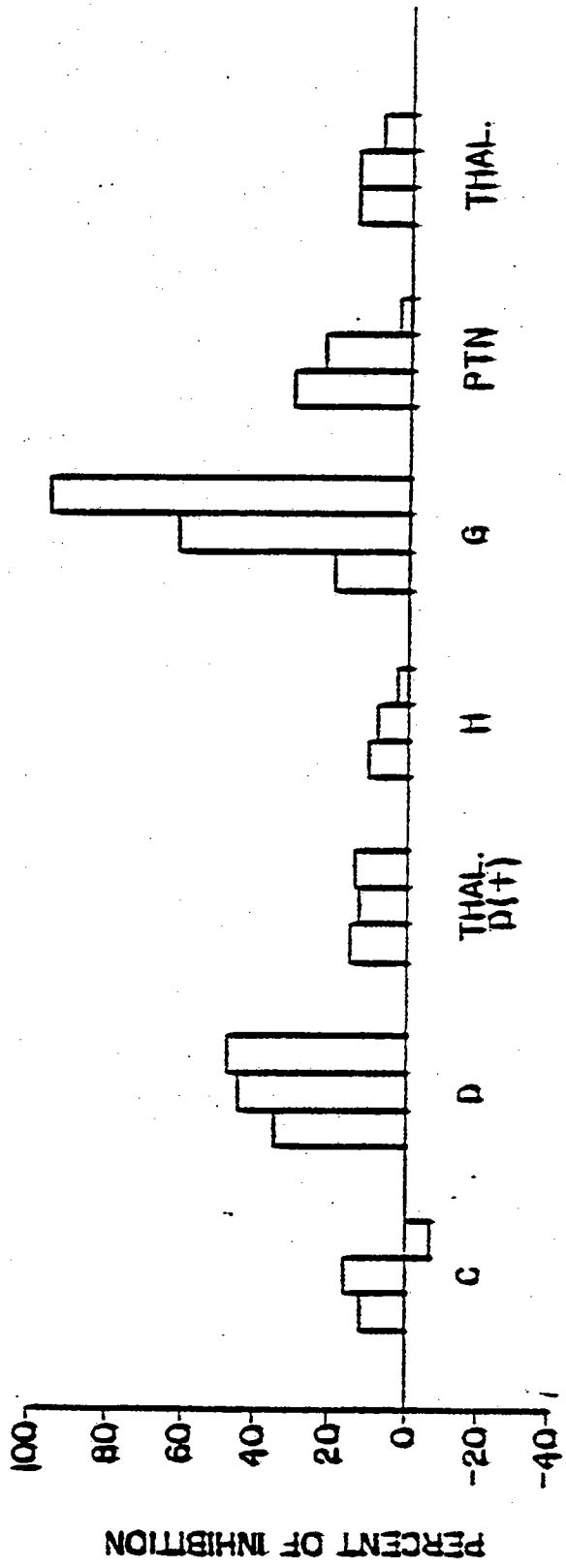
5
10
50
PTN
THAL
CONCENTRATION OF INHIBITOR
(μg/ml)

FIG. 4


PERCENT OF INHIBITION
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D
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H
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FIG. 5

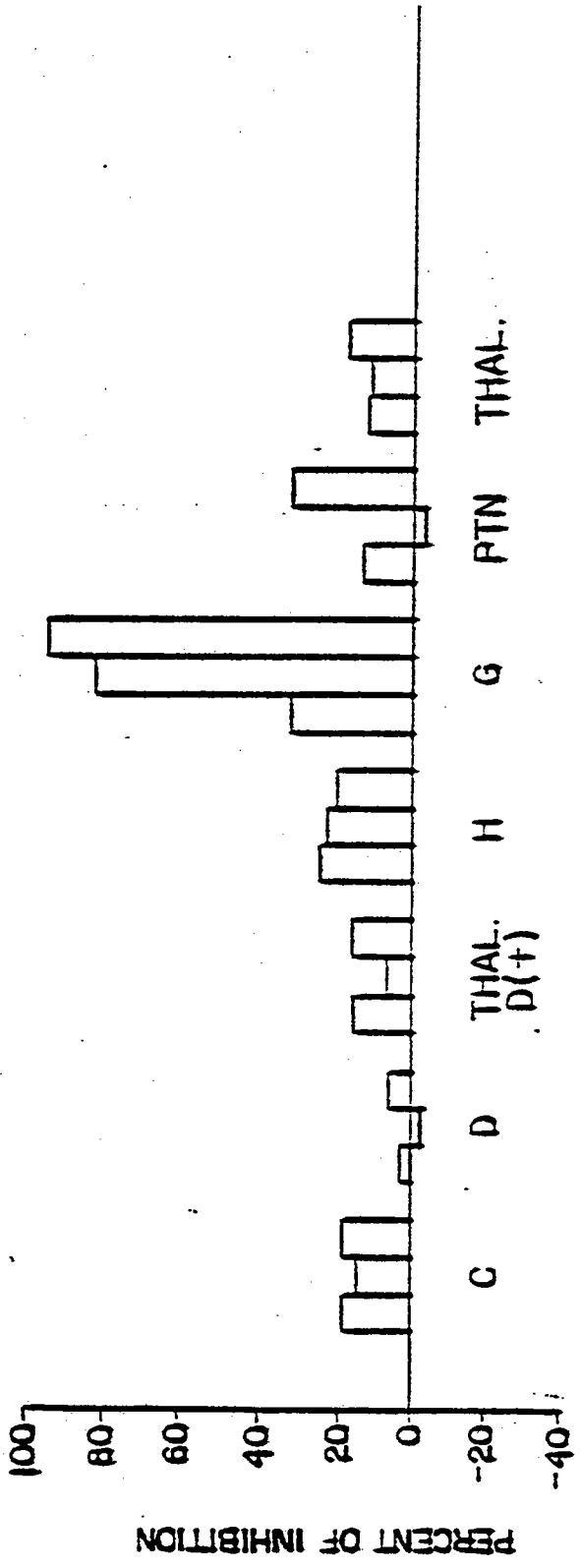
PERCENT OF INHIBITION
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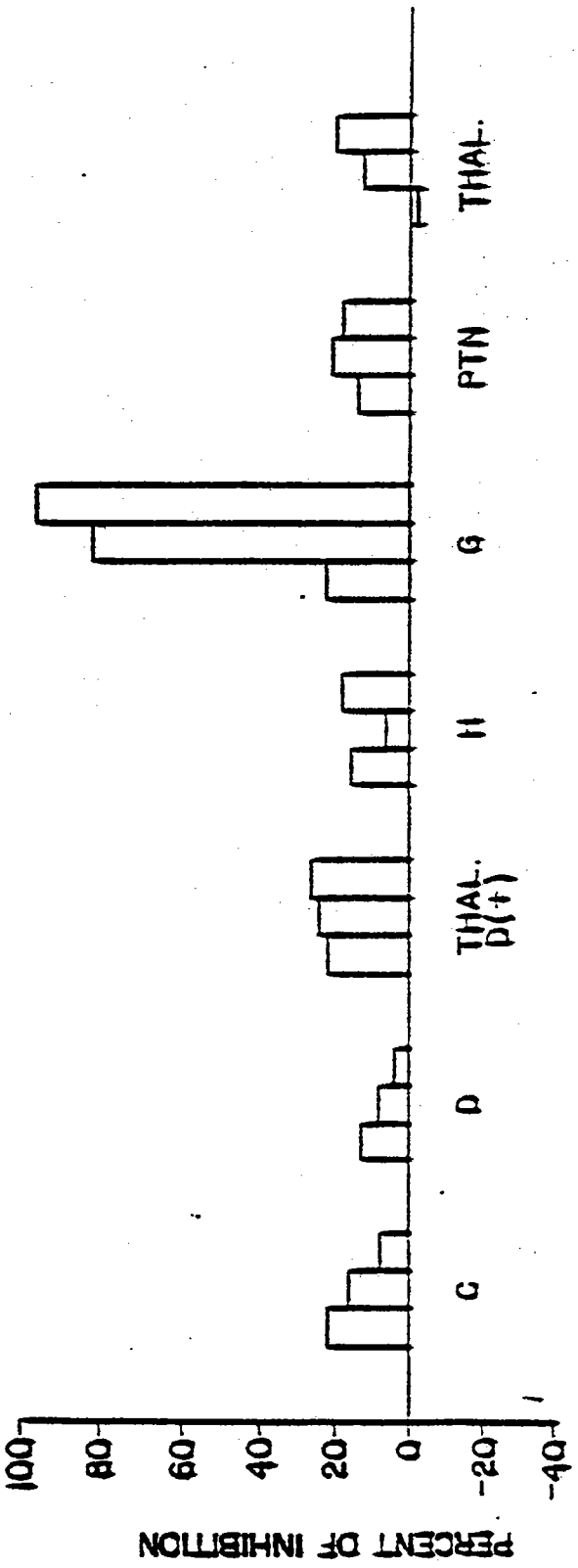
FIG. 6


PERCENT OF INHIBITION
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D
THAL. D(+)
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THAL.

FIG. 7

METHOD OF TREATING ABNORMAL CONCENTRATIONS OF TNF α

This invention was made with Government support under AI 22616-05 AI 07012-25 awarded by the Allergy and Infections Institute. The Government has certain rights in the invention.

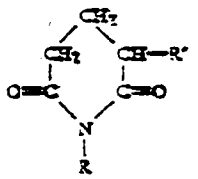
RELATED APPLICATIONS

This is a continuation of Ser. No. 07/834,588 filed Feb. 12, 1992, now abandoned, which in turn is a continuation of Ser. No. 07/655,087 filed Feb. 14, 1991, now abandoned.

BACKGROUND OF THE INVENTION

Debilitation, i.e. loss of weight, strength, vascular weakness, and other symptoms are natural sequelae of many diseases which afflict humans. These may include, for example bacterial infections such as tuberculosis; viral infections, particularly retroviral infections including HIV infections such as AIDS; various forms of arthritis particularly rheumatoid and degenerative; ulcerative colitis; regional enteritis; and the like. Human patients with these symptoms may present with an acute condition such as septic shock or with a chronic condition such as cachexia.

U.S. Pat. No. 2,330,991 describes a class of therapeutic agents of the general formula I



I

wherein R is selected from the group consisting of hydrogen, alkyl radicals containing 1–6 carbon atoms, the phenyl radical, and the benzyl radical; and wherein R' is selected from the group consisting of the phthalimido radical and the succinimido radical.

The subject matter of this patent and of any other patents or publications identified in this disclosure are incorporated herein by reference.

Preferred compounds within the scope of the above formula I, for use in this invention are:

3-phthalimido-2,6-dioxo-1-ethyl piperidine
3-phthalimido-2,6-dioxo-1-phenyl piperidine
3-phthalimido-2,6-dioxo-1-benzyl piperidine
3-phthalimido-2,6-dioxo-1-allyl piperidine
3-phthalimido-2,6-dioxo-piperidine

As described in the patent, the compounds are produced by reacting an aliphatic dicarboxylic acid, which contains five carbon atoms in a straight chain, the methylene groups of which are substituted by the substituents in accordance with the appropriate general formula, with urea or substitution products thereof or with a primary amine or an acid amide in such manner that water is split off and the ring is closed. If an amino group is present in the aliphatic chain, this group must not exist in free form in this stage of the process, since otherwise there is the danger of this amino group participating in an undesirable manner in the reaction. Instead of using the dicarboxylic acid, it is also possible to employ functional derivatives thereof, such as acid halides, acid esters and acid amides.

Compounds of the glutaminic acid series may be used as starting materials for the present invention. In this case also, the acid halides, esters and amides of glutaminic acid may be employed instead of the acid itself. It is known that glutaminic acids tends to form 5-membered rings with a free amino group. This reaction is undesirable for the purposes of the present invention. The amino group must therefore be substituted or protected prior to the ring-closing reaction. The protection of the amino group may be carried out, when using products of the glutaminic acid series, by introducing the phthalyl, succinyl or like radical in a manner known per se. The proportions of the components used for the ring formation must be such that at least 1 mol of the compound yielding the imide nitrogen is used to one mol of the glutaminic acid component.

The first compound listed above is prepared by reacting 27.7 g. of N-phthalyl glutaminic acid with 60 g. of a 33% solution of ethyl amine in water and slowly heating in an oil bath 160°–180° C., the mixture being maintained at this temperature for 15 to 20 minutes. The reaction product is recrystallised from alcohol by fractionation. It melts at 209° C.

The last compound listed above prepared by reacting 13 g. of phthalyl glutaminic acid anhydride and 6 g. of urea in 75 cc. of absolute xylene for 4 hours at the boiling point of the mixture. Formation of a sublimate takes place with evolution of ammonia and carbon dioxide. The xylene is then distilled off in vacuo and the residue recrystallized from 95% alcohol by fractionation. In addition to some phthalimide and phthalyl glutamine, the required N2-phthalyl glutamine acid imide is obtained, having a melting point of 269°–271° C.

In the patent, the compounds are disclosed as having low toxicity and as useful for certain spasmolytic and antihistaminic effects. The compound 3-phthalimido-2,6-dioxopiperidine is disclosed as being particularly useful as a sedative. This compound was marketed as a sedative under the generic name thalidomide. It was subsequently discovered to be teratogenic and was withdrawn from the market.

Despite its teratogenicity, thalidomide has long been employed for the treatment of erythema nodosum leprosum (ENL) an acute inflammatory state occurring in lepromatous leprosy. See, for example Meilin, G. W., and M. Kartzenstein. *N. Engl. J. Med.* 267:1174 (1962). More recently, it has been shown to be useful in the treatment of graft-versus-host disease by Vogelsany, G. B., S. Taylor, G. Gordon and A. D. Hess. *Transplant Proc.* 21:904 (1986); for treatment of rheumatoid arthritis by O. Gutierrez-Rodriguez, P. Starnsa-Bazzi and O. Gutierrez-Montes. *The Journal of Rheumatology* 16:1 158 (1989); and for treatment of aphthous ulceration in patients positive for HIV antibody. *Brit. Med. J.* 298:432 (1989).

The tumor necrosis factor (TNF-α) is one of several cytokines released mainly by mononuclear phagocytes together with several other cytokines in response to stimuli to the immune system. It is required for a cell mediated immune response to overcome infections. As its name suggests, it is associated with the destruction of tumor cells. It is not present in measurable amounts in normal sera, but appears, often very rapidly, in response to immunostimulators such as bacterial and viral infections, particularly HIV infections. In the case of chronic infection it may be found in the sera at relatively high or low levels for extended periods of time. It may also appear suddenly in high concentrations in response to

release of a toxin by an invading bacteria. It is markedly elevated in ENL.

TNF-α has been recognized as manifesting a dose dependent toxicity. If present at low levels for too long a period it results in cachexia. At high levels even for a short time it results in septic shock.

Cachexia is a general weight loss and wasting occurring in the course of a chronic disease. More specifically, it is a weight loss not accounted for by decreased caloric intake. It is associated with cancer, the opportunistic infections of AIDS, inflammatory diseases, parasitic diseases, tuberculosis, high dose IL-2 therapy and the like. It is a chronic condition related to chronic diseases.

Septic shock is an acute condition usually, but not always attributed to infection or to toxic substances in the tissue. It is characterized by hypotension due to loss of vascular tone. It may result in patient collapse, or even death if not treated promptly and efficiently.

The retroviruses are a broad group of RNA viruses which, during their replication, employ the reverse transcription enzyme (RT) to convert a RNA message to DNA. The retroviridae family of viruses includes lentiviruses (visna, maedi, progressive pneumonia virus -"slow viruses"), spumaviruses (foamy viruses) and oncornaviruses (types A, B, C, D, RNA tumor viruses). The retroviruses have been shown to infect murine, avian, feline, primate, and human species.

The human immunodeficiency virus (HIV-1) or human T-Cell lymphotropic viruse (HTLV-III) which causes Acquired Immune Deficiency Syndrome (AIDS), AIDS related complex (ARC) and other AIDS related diseases is a retrovirus. TNF-α functions in an autocrine manner in the induction of HIV-1 expression (G. Poli et al, PNAs Vol 87 p 782, 1990).

It is apparent, therefore, that it is necessary to control the concentration of TNF-α in the sera to avoid the debilitating effects of abnormal concentrations of this cytokine including, for example, cachexia and septic shock.

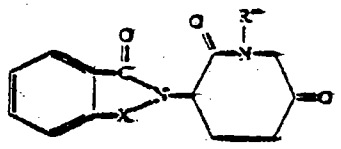
Other cytokines which are necessary for a proper immune response are also produced by mononuclear phagocytes. These include, for example, various interleukins such as IL-1, IL-6, IL-8 and the granulocyte macrophage colony stimulating factor, GM-CSF. Still other cytokines are produced by the T-cells. It is desirable to control the concentration of TNF without appreciably affecting the concentration and activity of other cytokines.

Heretofore, antiinflammatory and immunosuppresive steroids such as prednisolone and dexamethasone have been employed to treat the debilitating effects of TNF-α. Unfortunately, these therapeutic agents also block the production of other cytokines so that the patients become susceptible to life threatening infections.

BRIEF SUMMARY OF THE INVENTION

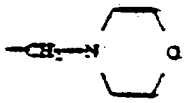
It has now been discovered that the debilitating effects of toxic concentrations of TNF-α, whether acute or chronic, can be controlled in humans by treating a human patient in need of such treatment with an anti-debilitating amount of a compound within the scope of the above description. Typically the treatment may be either oral or parenteral, for example intravenously or subcutaneously.

It has further been discovered that certain compounds within the scope of the above formula as well as other closely related compounds are especially useful for the practice of this invention. These compounds are presently preferred for the therapeutic purposes of the inventions. These preferred compounds include those represented by formula II



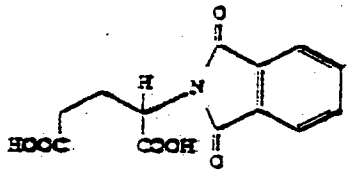
II

wherein X is CH_2 or C=O; R is H, $-CH_2CH_3$, $-C_6H_5$, $-CH_2C_6H_5$, $-CH_2CH=CH_2$, or

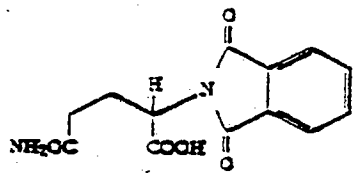


and hydrolysis products of said compounds wherein R is H and the peperidino ring or both the peperidino and the imido ring are hydrolyzed.

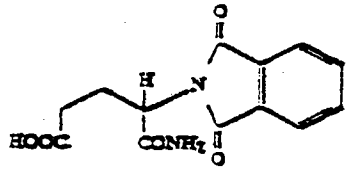
Especially preferred compounds within the ambit of the above definition are represented by the formulas:



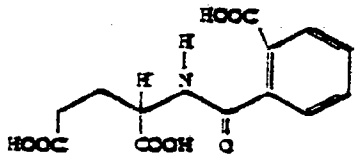
N-phthalyl-D,L-glutamic acid
A



N-phthalyl-D,L-glutamine
B

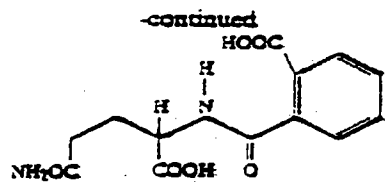


N-phthalyl-D,L-isoglutamine
C



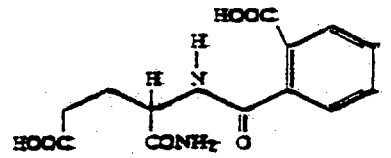
N-[carbethoxyacetyl]-D,L-glutamic acid
D

-continued



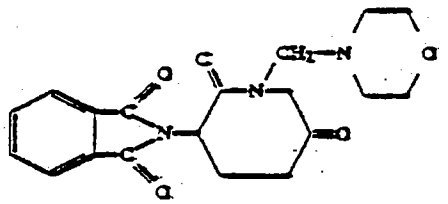
N-[o-carboxybenzoyl]-D,L-glutamine

E



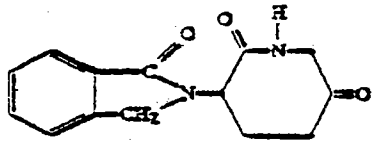
N-[o-carboxybenzoyl]-D,L-isoglutamine

F



G

1-Morpholino methyl-3-phthalimido-2,6-dioxo piperidine



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3-phthalimidino-2,6-dioxo piperidine

Most of the non-hydrolyzed compounds whose formulas are given above can be prepared by the processes described in the aforesaid U.S. Pat. No. 2,830,991. The preparation of the phthalimidine compounds is described in U.S. Pat. No. 3,705,162. U.S. Pat. No. 3,563,986 describes the preparation of the morpholino substituted compounds. The hydrolytic compounds are prepared by standard hydrolysis procedures several of which will be known to the skilled artisan.

The compounds used in the invention can exist as racemic mixtures. The racemic mixtures and separate isomers are included within the scope of the invention.

The compounds may be administered alone, but will normally be employed in a composition containing a pharmaceutically acceptable carrier. It may be advantageous, as will be discussed more fully below to administer the selected compound or compounds together with an effective amount of a therapeutic agent appropriate for treating the cause of the abnormal concentration of TNF-$_\alpha$, for example with an antibacterial agent if the condition under treatment is shock caused by the sudden release of large amounts of a toxin because of bacterial infection.

THE DRAWINGS

FIGS. 1*a*, 1*b*, 1*c* 2, 3, show the effects of thalidomide on TNF-$_\alpha$ production in the presence of various reagents.

FIGS. 4 through 7 show the results of studies conducted to establish the utility of the compounds of this invention to inhibit HIV-1 RT activity.

The drawings and the balance of this disclosure will be better understood by recognizing the meanings of certain abbreviations. CWP-ML means cell wall protein of *Mycobacterium leprae*. ENL means erythema nodosum leprosum. GM-CSF means granulocyte macrophage colony-stimulating factor. PPD means purified protein derivative of tuberculin. PBMC means peripheral blood mononuclear cells.

The studies described hereinafter will be recognized by those skilled in the art as establishing that the compounds of this invention selectively inhibit the production of human TNF-$_\alpha$ without substantially affecting the production of other proteins or of total serum protein. Therefore, although the compounds of the invention will not cure diseases, they will significantly improve the quality of life of the patients. An important consequence of the study is the finding that TNF-$_\alpha$ secretion is not totally inhibited. This is important since, as indicated above, TNF-$_\alpha$ appears to be an essential mediator in the immune response.

There follows a complete description of one procedure for establishing the ability of the compounds of this invention to inhibit the production of TNF-$_\alpha$ without inhibiting the production of other cytokines.

Monocyte Isolation

PBMC obtained by Ficoll-Hypaque (Pharmacia Fine Chemicals, Piscataway, N.J.) density centrifugation were rosetted with neuraminidase-treated (Vibrio cholerae neuraminidase: Calbiochem-Behring Corp. La Jolla, Calif.) sheep erythrocytes (Scott Laboratories, Fiskville, R.I.) (SRBC rosetting), and the nonrosetted cells were counted (E$^-$ population monocytes enriched). 10^6 cells were cultured at 37° C. in 24-well plates (Corning Glass Works, Corning, N.Y.) in 1 ml of RPMI 1640 (Gibco Laboratories, Grand Island, N.Y.) supplemented with 10% AB$^-$ serum, 100 U/ml penicillin, 100 μg/ml streptomycin, and 2 mM l-glutamine. Adherent E$^-$ cells were used for the studies.

Cytokine Agonist

LPS of *Salmonella minnesota* R595 (List Biological Laboratories, Campbell, Calif.) was diluted in PBS, pH 7.4, and used at 1 g/ml. Purified protein derivative of tuberculin (PPD) was purchased from Statens Seruminstitut, Copenhagen, Denmark. CWP-ML was prepared using known and published methods. The concentrations of the stimulating agents were those known to induce optimal TNF-$_\alpha$ protein production by cultured monocytes. The endotoxin content of solutions and mycobacterial preparations was estimated by the Limulus amebocyte lysate assay (LAL: Whittaker M. A. Bioproducts, Walkersville, Md.). All solutions used contained less than 10 pg/ml of endotoxin.

Cytokine Induction

Adherent E$^-$ cells were stimulated with 1 μg/ml of LPS, 10 μg/ml of PPD, or 10 μg/ml of CWP-ML for up to 18–20 h. At various times, supernatants were harvested, centrifuged to remove cells and debris, and kept frozen until use (−20° C.).

TNF-$_\alpha$ Assay

TNF-$_\alpha$ concentration in the supernatants was determined with a TNF-$_\alpha$ specific ELISA, specific for the

biologically active molecule. Assays were performed in 96-well plates (Nunc Immunoplates, Roskilde, Denmark) coated with the affinity-purified rabbit anti-TNF-α antibody (0.5 μg/ml; 12–16 h; 4° C.) and blocked for 2 h at room temperature with PBS/0.05% Tween 20 (Sigma Chemical Co., St. Louis, Mo.) containing 5 mg/ml BSA. After washing, 100 μl of TNF-α standards, samples, and controls were applied to the wells, and the plates were incubated for 12–24 h at 4° C. After the incubation, plates were washed and a second antibody, horseradish peroxidase (HRP)-conjugated mouse monoclonal anti-TNF-α, diluted 1:2,000 in PBS/BSA/-Tween, was applied to the wells and incubated for 2 h at room temperature. The color reaction was developed with the OPD substrate (0.4 mg/ml o-phenylenediamine [Sigma Chemical Co.] in 24 mM citric acid, 51 mM sodium phosphate, pH 5.0 [phosphate-citrate buffer: Sigma Chemical Co.] containing 0.012% hydrogen peroxide [H_2O_2; Fisher Scientific Co., Pittsburgh, Pa.]) and absorbance read at 492 nm in an automated ELISA reader (Dynatech Laboratories, Inc., Alexandria, Va.).

IL-1 Assays

IL-1 levels were determined using a commercial ELISA kit (Cistron Biotechnology, Pine Brook, N.J.) according to the manufacturer's specifications. IL-1 levels are expressed as pico-grams per milliliter of protein.

IL-6 Assay

IL-6 levels were determined using a biological assay as described by Finkelman et al. Proc. Natl. Acad. Sci. USA, 83:9675 (1986). Proliferation of 7TD1 hybridoma cell line specifically sensitive to IL-6 was measured by colorimetric determination of hexosaminidase levels. Landegren et al J. Immunol. Methods, 67:379 (1984), and values for IL-6 in the samples were obtained by interpolation from a standard curve. 1 U/ml of IL-6 corresponds to the concentration that yields half-maximal growth.

Granulocyte/Macrophage CSF GM-CSF Assay

GM-CSF levels were determined using a commercial ELISA kit (Genzyme, Boston, Mass.) according to the manufacturer's specifications, and were expressed as picograms per milliliter of protein.

Thalidomide Inhibition

The thalidomide used in this study was the purified drug (racemic mixture: D[+] and L [−] forms) (lot No. JB-I-114; Andrulis Research Corporation, Bettsville, Md.). The compound was shown to be at least 99% pure, as analyzed by Fourier Transform Infrared Spectrum. It was then diluted in DMSO (Sigma Chemical Co.); further dilutions were done in sterile PBS.

Percentage inhibition of TNF-α secretion was calculated as: $100 \times [1-(\text{TNF-}\alpha \text{ experimental}/\text{TNF-}\alpha \text{ control})]$; where TNF-$\alpha$ experimental represents TNF-secretion by stimulated monocytes that were cultured in the presence of thalidomide, and TNF-α control represents TNF-α secretion by stimulated monocytes that were cultured in the absence of the drug. Monocytes cultured in medium containing equivalent amounts of DMSO in the presence or absence of the stimulating agent were used as controls for thalidomide-treated cells. Neither thalidomide nor DMSO had any effect on cell viability or function at the concentrations used.

Protein Synthesis

Human monocytes were cultured in Teflon beakers in methionine-free RPMI with 10% AB$^-$ serum at 37° C. for 1 h, when 200 μCi/ml ^{35}S-methionine (1,153 μCi/mmol; ICN Biomedicals Inc., Calif.) was added to the cultures for the next 3 h with or without the stimulating and the suppressive agent. At the end of the labeling period, ^{35}S-labeled cells were washed twice in ice-cold PBS and lysed directly in 500 μl lysis solution (10 mM Tris-HCl buffer, pH 7.4 150 NaCl, 1 mM EDTA, and 1% SDS). Resolving 8% SDS-PAGE was performed overnight. The gel was washed, dried, and analyzed by autoradiography at −70° C. using XAR-5 radiographic film (Kodak, Rochester, N.Y.) with an intensifying screen.

RESULTS OF THIS STUDY

Monocytes were enriched from PBMC of normal donors and stimulated in vitro for 18–20 h with bacterial LPS and mycobacterial products, known agonist of monocyte TNF-α synthesis and secretion. Thalidomide suppressed LPS-stimulated TNF-α production (FIG. 1A) with a 50% inhibitory concentration (IC_{50}) of 1–4 μg/ml, and 90% inhibition observed at 10 μg/ml (18–20-h assay). Similar results were obtained when PPD and CWP-ML were used as stimulants (FIG. 1, B and C, respectively).

FIG. 1 shows the effect of thalidomide on (A) bacterial endotoxin (LPS, 1 μg/ml), (B) PPD, (10 μg/ml), and (C) CWP-ML (10 μg/ml)- induced TNF-α production. Monocytes were simultaneously incubated with 2 ng/ml to 10 μg/ml of thalidomide in the culture medium. Control cells were cultured in medium alone. A dose-dependent inhibition of TNF-α secretion by thalidomide is apparent. No detectable production of TNF-α protein was observed in supernatants of unstimulated monocytes. Data represent mean ± SD of 15(A), two (B), and one (C) different experiments, respectively.

The inhibition of TNF-α secretion by thalidomide was dependent upon the state of monocyte stimulation as shown in Table 1. Preincubation of unstimulated monocytes with thalidomide, followed by removal of the drug before LPS stimulation, did not lead to suppression. By comparison, when LPS and thalidomide were added simultaneously to the cultures, irreversible suppression occurred, even when the drug was removed after a few hours (Table 1). Therefore, the thalidomide sensitive reaction(s) occurs only after the LPS induction of TNF-α production.

TABLE 1

	[illegible]			[illegible]			
A	0–4	0	0	4–20	0	+	100
B	0–4	−	0	4–20	0	+	90 ± 4.6
C	None	0	0	0–4	+	+	48 ± 15
D	0–4	−	+	4–20	0	+	56 ± 0.5
E	None	0	0	0–20	+	+	52 ± 9.3

Human monocytes cultured in 24-well plates were preincubated with the inhibitory drug with or without the stimulating agent. After 4 h, the cultures were washed, medium was replaced, and LPS was added again for the next 16 h. Culture supernatants were recovered at the different periods and TNF-α levels determined as described. LPS-induced release of TNF-α by monocytes cultured for 20 h in the absence of thalidomide (A). No inhibitory action of thalidomide was de-

tected when the drug was washed away before the addition of the stimulating agent (B). Thalidomide-induced inhibition of TNF- production in the present of LPS after 4 h of stimulation (C), which persisted even after the drug was washed away (D). Control experiment in which thalidomide was kept in the cultures with the stimulating agent during the whole assay (E). Data represent mean ± SD of two different experiments.

The inhibition of LPS-stimulated TNF-α secretion by thalidomide occurs in a setting in which many other proteins are being synthesized by both constitutive and induced mechanisms. Thus, a simple explanation for the effect of the drug on TNF-α production could be a suppression of overall protein synthesis.

FIG. 2 illustrates the effect of thalidomide on the pattern and quantity of proteins synthesized after a 3-h pulse of ^{35}S-methionine. The total incorporation of isotope into TCA-precipitable proteins as well as the intensity of most of the individual bands on SDS-PAGE of LPS-triggered monocytes remained unchanged after thalidomide treatment.

In FIG. 2 can be seen the effect of thalidomide on protein synthesis by human peripheral blood monocytes. Electrophoretic analysis of lysates from monocytes incubated with ^{35}S-methionine was performed. Cells were stimulated in vitro with and without LPS in the presence or absence of thalidomide at 1 and 4 μg/ml. TCA-precipitable radioactivity (10% TCA precipitation) was measured by liquid scintillation counting. The amount of radioactivity in the pellets expressed as cpm × 10^{-3} and represents the mean of three precipitates with a SD of 10%. Neither total radioactivity nor the pattern of most of the protein bands in the gel was affected by thalidomide (lane 1) unstimulated cells, 3.3 × 10^{-2} cpm in TCA precipitates; (lane 2) cells stimulated with 1 μg/ml LPS, 4.2 × 10^{-2} cpm in TCA precipitate; (lane 3) cells stimulated with LPS in the presence of 1 μg/ml thalidomide, 4.2 × 10^{-2} cmp in TCA precipitate; (lane 4) cells stimulated with LPS in the presence of μg/ml thalidomide, 4.1 × 10^{-2} cpm in TCA precipitate; (lanes 5 and 6) cells incubated only with thalidomide at 1 or 4 μg/ml, respectively, 3.2 × 10^{-2} and 2.8 × 10^{-2} cpm in TCA precipitates, respectively.

Several cytokines are produced by monocytes in response to LPS in addition to TNF-α, including IL-1 and IL-6. FIG. 3 shows that thalidomide exerts a selective effect by suppressing only TNF-α secretion LPS-stimulated monocytes. Whereas 4 μg/ml thalidomide suppressed TNF-α production (41.9% inhibition) (FIG. 3A), neither IL-1 (FIG. 3B), IL-6 (FIG. 3 C), nor GM-CSF production (FIG. 3 D) was influenced by the drug. Similar but more extensive selective suppression was observed with much higher (up to 20 μg/ml) concentrations of thalidomide. It was also observed that the D (+) enantiomer appeared to be more active than the L(−) enantiomer.

FIG. 3 shows the levels of different cytokines tested in culture supernatants of human monocytes stimulated with LPS for 6 h (A-C) or 20 h (D) in the presence or absence of 4 or 10 μg/ml of thalidomide. Data represent mean ± SD of six different experiments for TNF-α and IL-1 determinations and three experiments for IL-6 and GM-CSF measurements. About 41.9±14.6% and 52.8±14.7% inhibition of TNF-α secretion was found in the presence of 4 and 10 μg/ml of thalidomide, respectively. "Cont" illustrates unstimulated cells cultured in medium. No effect on IL-1, IL-6, or GM-CSF secretion was detected in these cultures.

The following study establishes the utility of compounds of the invention for reducing TNF-α concentration in HIV infections. TNF-α is known to induce HIV replication. Similarly, it is known that peripheral blood monocytes from HIV infected patients secrete higher amounts of TNF-α than do monocytes from uninfected individuals. TNF-α is a cytokine capable of inducing viral expression in cells chronically infected with HIV. The art, therefore, has long been concerned with discovering products capable of inhibiting TNF-α production in HIV infected patients. The compounds of this invention are capable of so doing. This fact was established in studies using the known and commercially available chronically infected cell lines U1 and ACH-2, a promonocytic cell line and a T-lymphocytic cell line. The procedure employed is described by Poli et al. (1990) Proc. Nat'l. Acad. sci. U.S.A. Vol. 87, pp 782–785.

Briefly, the expression of HIV was upregulated by the addition of 10^{-7} m of phorbol 12-myristate 13-acetate (PMA) or 1 μg/ml of TNF$_\alpha$ to ACH-2 and U1 cells. The cells were suspended at 4 × 10^5 per ml in RMPI 1640 medium (M.A. Bioproducts) supplemented with 10% (vol/vol) fetal calf serum in the presence of the selected amount of stimulator at 37° C. in 5% CO_2/95% air for 48 hours, the supernatants collected and tested for the presence of Mg^{++}-dependent reverse transcriptase activity using the procedure of Willy et al (1988) J. Virol. 62, 139–147.

For the test, 10 μl of supernatants were added to 50 μl of a mixture containing 5 μg per ml of poly(rA) p(dT) 12–18, (Pharmacia), 5 mM $MgCl_2$ and 10 μci/μl of ^{32}P-labeled deoxythymidine 5'- triphosphate (dTTP-Amersham), and the mixture was incubated for 1½ hours at 37° C. Eight microliters of the mixture were spotted onto DE31 paper (Wharman), air-dried and washed 5 times in 2× standard saline citrate buffer, and two additional times with 95% ethanol. The paper was dried, cut and radioactivity assayed. The results are shown in the figures.

FIG. 4 shows the results of tests in which 5, 10 and 50 μg/ml of thalidomide (THAL) and the known TNF$_\alpha$ inhibitor pentoxyvilline (PTN) were used to inhibit reverse transcriptase production with the cell line U1. For the comparison, reverse transcriptase activity in the absence of the inhibitor was taken as 100%. It will be seen that at a concentration of 50 μg/ml, thalidomide was as effective as PTN.

FIG. 5 shows the results of a similar test with a U1 cell line stimulated with PMA comparing thalidomide and PTN with other compounds of the invention including the D isomer of thalidomide. The other compounds of the invention are identified in this and the following figures by the letters used under their formulas hereinabove.

FIG. 6 shows a similar study in which the same compounds were tested with ACH-2 stimulated with TNF-α.

FIG. 7 records the results of a test using the ACH-2 cell line stimulated with PMA.

The compounds of the invention or their pharmaceutically acceptable salts may be administered perorally in a pharmaceutical carrier in standard form such as tablets, pills, lozenges, dragees and similar shaped and/or compressed preparations. It is also possible to produce emulsions or suspensions of the compounds in water or aqueous media such as unsweetened fruit juices and by means of suitable emulsifying or dispersing agents.

They may also be employed in the form of powders filled into gelatin capsules or the like.

Such powders and mixtures for use in the preparation of tablets and other shaped and/or compressed preparations may be diluted by mixing and milling with a solid pulverulent extending agent to the desired degree or firmness or by impregnating the already milled, finely powdered, solid carrier with a suspension of the compounds in water or with a solution thereof in an organic solvent and then removing the water or solvent.

When preparing tablets, pills, dragees, and the like shaped and/or compressed preparations, the commonly used diluting, binding, and disintegrating agents, lubricants, and other tableting adjuvants are employed, provided they are compatible with agent to be administered. Such diluting agents and other excipients are, for instance, sugar, lactose, levulose, starch, bolus alba; as disintegrating and binding agents, gelatin, gum arabic, yeast extract, agar, tragacanth, methyl cellulose, pectin; and as lubricants stearic acid, talc, magnesium stearate, and others.

They may be administered in the form of suppositories, typically utilizing such commonly used suppository vehicles, as cocoa butter.

The compounds may also be administered parenterally employing aqueous solutions or suspensions of watersoluble compounds or suspensions. The compositions may be made isotonic e.g. with salt or other solute and may contain a buffer, for example a phosphate buffer.

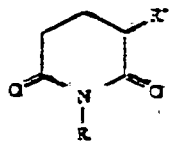
As indicated above, the compound employed in the invention may be the only active ingredient administered or it may be coadministered with another therapeutic agent in an amount which is effective to treat the condition associated with the debilitating effect. For example, if the cause of the condition is a toxin released by an infectious bacteria, an antibiotic such as tetracycline, penicillin, streptomycin and the like may be coadministered. If there is hypotension associated with lack of vascular tone, a vasopressive agent such as epinephrine or dopamine may be coadministered. If the patient is under treatment with a chemotherapeutic agent such as adriamycin, the compound of the invention and the chemotherapeutic agent may be coadministered.

The term "coadministered" does not mean that the compound of the invention and the additional therapeutic agent are administered in the same dosage unit, although they may be so administered. It means that they are administered within the same time span.

An "effective amount" of the compound or additional therapeutic agent will vary with the condition being treated, the age, weight and general physical condition of the patient under treatment and other factors readily evaluated by the physician in attendance.

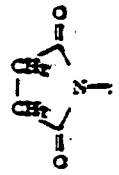
What is claimed is:

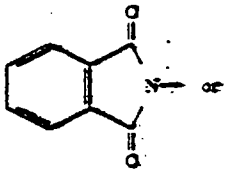
1. The method of treating the toxic symptoms of high concentrations of TNF_α manifested in septic shock, cachexia, and HIV infection by inhibiting the production of TNF_α which comprises administering to a human susceptible to or exhibiting such symptoms an effective amount of a compound of the formula:

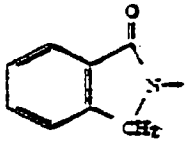


in which R is hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, or benzyl, and

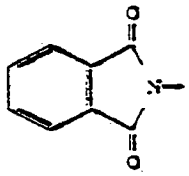
R' is







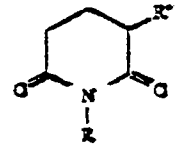
2. The method of claim 1 wherein R' is



3. The method of claim 2 wherein said compound is 3-phthalimido-2,6-dioxopiperidine.

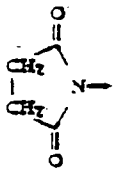
4. The method of claim 2 wherein said effective amount is sufficient to produce a blood level of said compound of at least 0.1 μg/ml.

5. The method of treating the debilitating effects of septic shock caused by high concentrations of TNF_α by inhibiting production of TNF_α which comprises administering to a human susceptible to or exhibiting such effects an effective amount of a compound of the formula:

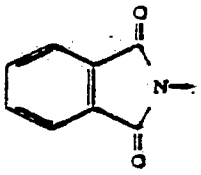


in which R is hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, or benzyl, and

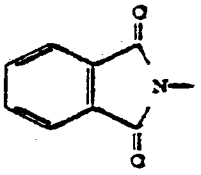
R' is



or



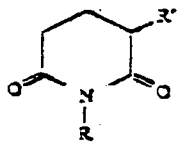
6. The method of claim 5 wherein R' is



7. The method of claim 6 wherein said compound is 3-phthalimido-2,6-dioxopiperidine.

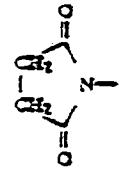
8. The method of claim 6 wherein said effective amount is sufficient to produce a blood level of said compound of at least 0.1 μg/mL.

9. The method of treating the debilitating effects of cachexia caused by high concentrations of TNF_α by inhibiting production of TNF_α which comprises administering to a human susceptible to or exhibiting such effects an amount of a compound of the formula:

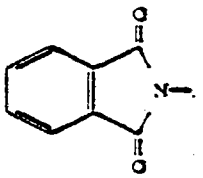


in which R is hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, or benzyl, and

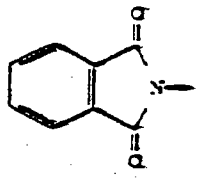
R' is



or



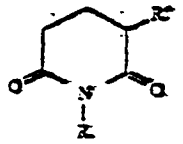
10. The method of claim 9 wherein R' is



11. The method of claim 10 wherein said compound is 3-phthalimido-2,6-dioxopiperidine.

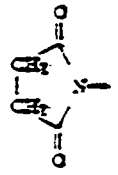
12. The method of claim 10 wherein said effective amount is sufficient to produce a blood level of said compound of at least 0.1 μg/mL.

13. The method of treating the debilitating effects of an HIV infection caused by high concentrations of TNF_α by inhibiting production of TNF_α which comprises administering to a human susceptible to or exhibiting such effects an amount of a compound of the formula:

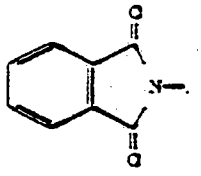


in which R is hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, or benzyl, and

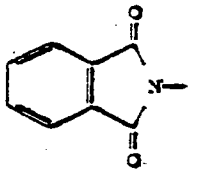
R' is



or



14. The method of claim 13 wherein R' is

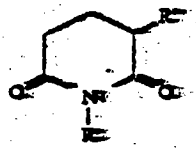


15. The method of claim 14 wherein said compound is 3-phthalimido-2,6-dioxopiperidine.

16. The method of claim 14 wherein said effective amount is sufficient to produce a blood level of said compound of at least 0.1 μg/mL.

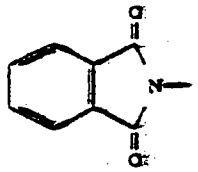
17. The method of treating the toxic symptoms of high concentrations of TNF_α manifested in septic shock, cachexia, and HIV infection by inhibiting the production of TNF_α which comprises administering to

a human susceptible to or exhibiting such symptoms an effective amount of a compound of the formula:

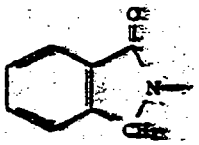


in which R is allyl or morpholinomethyl, and

R' is:



or



18. The method of claim 17 wherein said effective amount is sufficient to produce a blood level of at least 0.1 μg/ml.

US005463063A

United States Patent [19]

Muller

[11] Patent Number: 5,463,063

[45] Date of Patent: Oct. 31, 1995

[54] **RING CLOSURE OF N-PHTHALOYLGLUTAMINES**

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[21] Appl. No.: 140,237

[22] Filed: Oct. 20, 1993

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 87,510, Jul. 2, 1993, abandoned.

[51] Int. Cl.[6] C07D 401/04

[52] U.S. Cl. 546/201; 528/331; 528/317

[58] Field of Search 546/201; 528/331, 528/317

OTHER PUBLICATIONS

Fieser, Louis F., *Experiments in Organic Chemistry*, 3rd edition, p. 75, 1955.

J. C. Craig, "Absolute Configuration . . .", *J Org Chem*, vol. 53, pp. 1167–1170, 1988.

Primary Examiner—C. Warren Ivy

Assistant Examiner—D. Margaret M. Mach

Attorney, Agent, or Firm—Mathews, Woodbridge & Collins

[57] **ABSTRACT**

Cyclic imides are inhibitors of tumor necrosis factor α and can be used to combat cachexia, endotoxic shock, and retrovirus replication. A typical embodiment is 2-(2,6-dioxo-3-piperidinyl)-4-azaisoindoline-1,3-dione.

1 Claim, No Drawings

RING CLOSURE OF N-PHTHALOYLGLUTAMINES

CROSS REFERENCE TO RELATED APPLICATION

This is a continuation-in-part of Ser. No. 08/087,510 filed Jul. 2, 1993 now abandoned, the disclosure of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

The present invention relates a method of reducing levels of TNF_α in a mammal and to compounds and compositions useful therein.

TNF_α, or tumor necrosis factor α, is a cytokine which is released primarily by mononuclear phagocytes in response to various immunostimulators. Excessive or unregulated TNF_α production has been implicated in a number of disease conditions. These include endotoxemia and/or toxic shock syndrome (Tracey et al., *Nature* 330, 662–664 (1987) and Hinshaw et al., *Circ. Shock* 30, 279–292 (1990)); cachexia (Dezube et al., *Lancet*, 335 (8690), 662 (1990)); and Adult Respiratory Distress Syndrome where TNF_α concentration in excess of 12.00 pg/ml have been detected in pulmonary aspirates from ARDS patients {Millar et al., *Lancet* 2(8665), 712–714 (1989)}. Systemic infusion of recombinant TNF_α also resulted in changes typically seen in ARDS {Ferrai-Baliviera et al., *Arch. Surg.* 124(12), 1400–1405 (1989)}.

TNF_α appears to be involved in bone resorption diseases, including arthritis where it has been determined that when activated leukocytes will produce a bone-resorbing activity, and data suggest that TNF_α contributes to this activity. {Bertolini et al., *Nature* 319, 516–518 (1986) and Johnson et al., *Endocrinology* 124(3), 1424–1427 (1989).} It has been determined that TNF_α stimulates bone resorption and inhibits bone formation in vitro and in vivo through stimulation of osteoclast formation and activation combined with inhibition of osteoblast function. Although TNF_α may be involved in many bone resorption diseases, including arthritis, the most compelling link with disease is the association between production of TNF_α by tumor or host tissues and malignancy associated hypercalcemia {*Calci. Tissue Int.* (US) 46(Suppl.), S3–10 (1990)}. In Graft versus Host Reaction, increased serum TNF_α levels have been associated with major complication following acute allogenic bone marrow transplants {Holler et al., *Blood*, 75(4), 1011–1016 (1990)}.

Cerebral malaria is a lethal hyperacute neurological syndrome associated with high blood levels of TNF_α and the most severe complication occurring in malaria patients. Levels of serum TNF_α correlated directly with the severity of disease and the prognosis in patients with acute malaria attacks {Grau et al., *N. Engl. J. Med.* 320(24), 1586–1591 (1989)}.

TNF_α also plays a role is the area of chronic pulmonary inflammatory diseases. The deposition of silica particles leads to silicosis, a disease of progressive respiratory failure caused by a fibrotic reaction. Antibody to TNF_α completely blocked the silica-induced lung fibrosis in mice {Pignet et al., *Nature*, 344:245–247 (1990)}. High levels of TNF_α production (in the serum and in isolated macrophages) have been demonstrated in animal models of silica and asbestos induced fibrosis {Bissonnette et al., *Inflammation* 13(3), 329–339 (1989)}. Alveolar macrophages from pulmonary sarcoidosis patients have also been found to spontaneously release massive quantities of TNF_α as compared with macrophages from normal donors {Baughman et al., *J. Lab. Clin. Med.* 115(1), 36–42 (1990)}. TNF_α is also implicated

in the inflammatory response which follows reperfusion, called reperfusion injury, and is a major cause of tissue damage after loss of blood flow {Vedder et al., *PNAS* 87, 2643–2646 (1990)). TNF_α also alters the properties of endothelial cells and has various pro-coagulant activities, such as producing an increase in tissue factor pro-coagulant activity and suppression of the anticoagulant protein C pathway as well as down-regulating the expression of thrombomodulin {Sherry et al., *J. Cell Biol.* 107, 1269–1277 (1988)}. TNF_α has pro-inflammatory activities which together with its early production (during the initial stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to, myocardial infarction, stroke and circulatory shock. Of specific importance may be TNF_α-induced expression of adhesion molecules, such as intercellular adhesion molecule (ICAM) or endothelial leukocyte adhesion molecule (ELAM) on endothelial cells {Munro et al., *Am. J. Path.* 135(1), 121–132 (1989)}.

Moreover, it now is known that TNF_α is a potent activator of retrovirus replication including activation of HIV-1. {Duh et al., *Proc. Nat. Acad. Sci.* 86, 5974–5978 (1989); Poll et al., *Proc. Nat. Acad. Sci.* 87, 782–785 (1990); Monto et al., *Blood* 79, 2670 (1990); Clouse et al., *J. Immunol.* 142, 431–438 (1989); Poll et al., *AIDS Res. Hum. Retrovirus*, 191–197 (1992)}. At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by this T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Monokines, specifically TNF_α, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Monokines, specifically TNF_α, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with monokine activity such as by inhibition of monokine production, notably TNF_α, in an HIV-infected individual aids in limiting the maintenance of T lymphocyte caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. (Rosenberg et al., *The Immunopathogenesis of*

Infection. Advances in Immunology, 57 (1989)). Monokines, such as TNF_α, have been shown to activate HIV replication in monocytes and/or macrophages {Poli et al. *Proc. Natl. Acad. Sci.* 87, 782–784 (1990)}, therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T cells. Additional studies have identified TNF_α as a common factor in the activation of HIV in vitro and has provided a clear mechanism of action via a nuclear regulatory protein found in the cytoplasm of cells (Osborn, et al., *PNAS* 86 2336–2340). This evidence suggests that a reduction of TNF_α synthesis may have an antiviral effect in HIV infections, by reducing the transcription and thus virus production.

AIDS viral replication of latent HIV in T cell and macrophage lines can be induced by TNF_α {Folks et al., *PNAS* 86, 2365–2368 (1989)). A molecular mechanism for the virus inducing activity is suggested by TNF_α's ability to activate a gene regulatory protein (NFkB) found in the cytoplasm of cells, which promotes HIV replication through binding to a viral regulatory gene sequence (LTR) {Osborn et al., *PNAS* 86, 2336–2340 (1989)). TNF_α in AIDS associated cacheria is suggested by elevated serum TNF_α and high levels of spontaneous TNF_α production in peripheral blood monocytes from patients {Wright et al. *J. Immunol.* 141(1), 99–104 (1988)}.

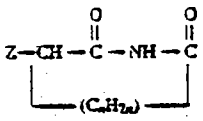
TNF_α has been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, adenovirus, and the herpes family of viruses for similar reasons as those noted.

Efforts directed to the suppression of the effects of TNF_α have ranged from the utilization of steroids such as dexamethasone and predmisolone to the use of both polyclonal and monoclonal antibodies {Beutler et al., Science 234, 470–474 (1985); WO 92/11383 }.

DETAILED DESCRIPTION

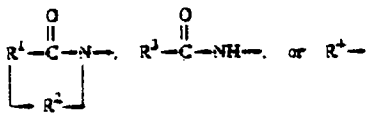
The present invention is based on the discovery that a class of non-polypeptide imides more fully described herein appear to inhibit the action of TNF_α.

A first aspect of the present invention pertains to compounds of the formula:



I.

in which Z is



in which

R^1 is the divalent residue of (i) pyridine, (ii) pyrrolidine, (iii) imidizole, (iv) naphthalene, (v) thiophene, or (vi) a straight or branched alkane of 2 to 6 carbon atoms, unsubstituted or substituted with phenyl or phenyl substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, wherein the divalent bonds of said residue are on vicinal ring carbon atoms;

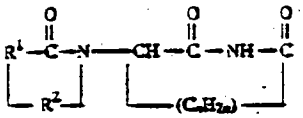
R^2 is —CO— or —SO_2—;

R^3 is (i) phenyl substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, (ii) pyridyl, (iii) pyrrolyl, (iv) imidazolyl, (v) napthyl, (vi) thienyl, (vii) quinolyl, (viii) furyl, or (ix) indolyl;

R^4 is alanyl, arginyl, glycyl, phenylglycyl, histidyl, leucyl, isoleucyl, lysyl, methionyl, prolyl, sarcosyl, seryl, homoseryl, threonyl, thyronyl, tyrosyl, valyl, benzimidol-2-yl, benzoxazol-2-yl, phenylsulfonyl, methylphenylsulfonyl, or phenylcarbamoyl; and

n has a value of 1, 2, or 3.

More particularly, a first preferred subclass pertains to compounds of the formula:

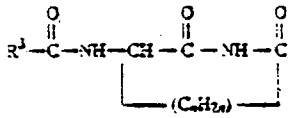


IA.

in which R^1 is the divalent residue of (i) pyridine, (ii) pyrrolidine, (iii) imidizole, (iv) naphthalene, (v) thiophene, or (vi) a straight or branched alkane of 2 to 6 carbon atoms, unsubstituted or substituted with phenyl or phenyl substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, wherein the divalent bonds of said residue are on vicinal ring carbon atoms; R^2 is —CO— or —SO2—; and n has a value of 1, 2, or 3.

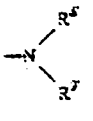
Preferred compounds of Formula IA include those in which R^1 is a divalent residue of pyridine, naphthalene or imidazole, R^2 is —CO—, and n is 2.

A second preferred subclass pertains to compounds of the formula:



IB.

in which R^3 is (i) phenyl substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, (ii) pyridyl, (iii) pyrrolyl, (iv) imidazolyl, (v) naphthyl, (vi) thienyl, (vii) quinolyl, (viii) furyl, (ix) indolyl, or (x)

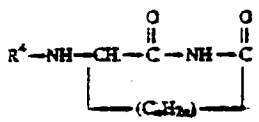


in which R^9 is hydrogen or alkyl of 1 to 4 carbon atoms, and R^9 is hydrogen, alkyl of 1 to 4 carbon atoms, COR^{10} or $—SO_2R^{10}$ in which R^{10} is hydrogen alkyl of 1 to 4 carbon atoms, or phenyl; and

n has a value of 1, 2, or 3.

Preferred compounds of Formula IB are those wherein R^3 is trifluoromethylphenyl, cyanophenyl, methoxyphenyl, fluorophenyl, or furyl, and n is 2.

A third preferred subclass pertains to compounds of the formula:

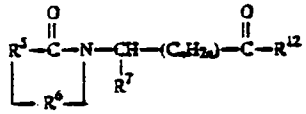


IC.

in which R^4 is alanyl, arginyl, glycyl, phenylglycyl, histidyl, leucyl, isoleucyl, lysyl, methionyl, prolyl, sarcosyl, seryl, homoseryl, threonyl, thyronyl, tyrosyl, valyl, benzimidol-2-yl, benzoxazol-2-yl, phenylsulfonyl, methylphenylsulfonyl, or phenylcarbamoyl, and n has a value of 1, 2, or 3.

Preferred compounds of Formula IC are those wherein R^4 is phenylsulfonyl or 2-amino-3-phenylpropanoyl and n is 2.

A second aspect of the present invention pertains to compounds of the formula:



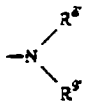
II.

in which R^5 is (i) o-phenylene, unsubstituted or substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, or (ii) the divalent residue of pyridine, pyrrolidine, imidizole, naphthalene, or thiophene, wherein the divalent bonds are on vicinal ring carbon atoms;

R^6 is —CO—, $—CH_2—$, or $—SO_2—$;

R^7 is (i) hydrogen, (ii) straight or branched alkyl of 1 to 6 carbon atoms, (iii) pyridyl, (iv) phenyl or phenyl substituted with one or two substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, (v) alkyl of 1 to 4 carbon atoms, (vi) benzyl unsubstituted or substituted with one or two substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, and (vi) $—(C_mH_{2m})—CO—R^{11}$.

each of R^{11} and R^{12}, independently of the other, is —OH or

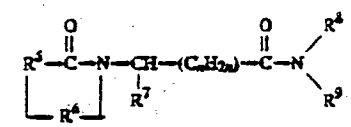


each of n and m, independently of the other, has a value of 0, 1, 2, or 3;

R^8 is hydrogen or alkyl of 1 to 4 carbon atoms; and

R^9 is hydrogen, alkyl of 1 to 4 carbon atoms, $—COR^{10}$, or $—SO_2R^{10}$ in which is hydrogen, alkyl of 1 to 4 carbon atoms, or phenyl.

A first preferred subclass of Formula II pertains to compounds of the formula:

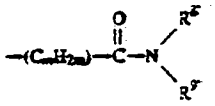


IIA.

in which R^5 is (i) o-phenylene, unsubstituted or substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, or (ii) the divalent residue of pyridine, pyrrolidine, imidizole, naphthalene, or thiophene, wherein the divalent bonds are on vicinal ring carbon atoms;

R^6 is —CO—, $—CH_2—$, or $—SO_2—$;

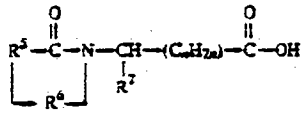
R^7 is (i) hydrogen, (ii) straight or branched alkyl of 1 to 6 carbon atoms, (iii) pyridyl, (iv) phenyl or phenyl substituted with one or two substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, (v) imidazol-4-yl-methyl, and (vi)



each of n and m, independently of the other, has a value of 0, 1, 2, or 3; each of R^8 and $R^{8'}$, independently of the other, is hydrogen or alkyl of 1 to 4 carbon atoms; and each of R^9 and $R^{9'}$, independently of the other, is hydrogen, alkyl of 1 to 4 carbon atoms, $—COR^{10}$ or $—SO_2R^{10}$ in which R^{10} is hydrogen, alkyl of 1 to 4 carbon atoms, or phenyl.

Preferred compounds of Formula IIA are those in which R^5 is o-phenylene, R^6 is —CO—; R^7 is phenyl, substituted phenyl or pyridyl; n is 0 or 1, and each of R^8 and R^9 is hydrogen.

A second preferred subclass of Formula II pertains to compounds of the formula:



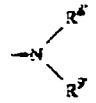
IIB.

in which R^5 is (i) o-phenylene, unsubstituted or substituted with nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, or (ii) the divalent residue of pyridine, pyrrolidine, imidizole, naphthalene, or thiophene, wherein the divalent bonds are on vicinal ring carbon atoms;

R^6 is —CO—, $—CH_2—$, or $—SO_2—$;

R^7 is (i) hydrogen, (ii) straight or branched alkyl of 1 to 6 carbon atoms, (iii) pyridyl, (iv) phenyl or phenyl substituted with one or two substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, (v) alkyl of 1 to 4 carbon atoms, (vi) benzyl unsubstituted or substituted with one or two substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbo-

propoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, and (vi) —(C_nH_{2n})—CO-R^{11} in which R^{11} is —OH or



each of n and m, independently of the other, has a value of 0, 1, 2, or 3;

$R^{8'}$ is hydrogen or alkyl of 1 to 4 carbon atoms; and

$R^{9'}$ is hydrogen, alkyl of 1 to 4 carbon atoms, —COR^{10}, or —SO_2R^{10} in which R^{10} is hydrogen, alkyl of 1 to 4 carbon atoms, or phenyl.

Preferred compounds of Formula IIB are those in which R^5 is o-phenylene, R^6 is —CO—; R^7 is phenyl, substituted phenyl or pyridyl; and n is 0 or 1.

Typical compounds of this invention include 2-(2,6-dioxo- 3-piperidinyl)-4-azaisoindoline-1,3-dione, 2-(2,6-dioxo-3-piperidinyl)-benzo[e]isoindoline-1,3-dione, 5-(2,6-dioxo-3-piperidinyl)-pyrrolo[3,4-d]imidazole-4,6-dione, 3-(trifluoromethylphenylcarboxamido)piperidine- 2,6-dione,3-(cyanophenylcarboxamido) piperidine-2,6-dione, 3-(methoxyphenylcarboxamido) piperidine-2,6-dione, 3-(3-pyridylcarboxamido)-piperidine- 2,6-dione, 3- (2-furylcarboxamido) piperidine-2,6-dione, 3-phenylsulfonamidopiperidine-2,6-dione, 3-(2-amino- 3-phenylpropaneamido)-piperidine-2,6-dione, 2-phthalimido-2-phenylacetamide, 3-phthalimido-3-phenylpropanamide, 2-phthalimido-3-phenylpropanamide, 2-phthalimido-3-(4hydroxy)phenylpropanamide, 3-phthalimido-3-phenylpropionic acid, 2-phthalimido-2-(4-hydroxyphenyl)acetic acid, 2-phthalimido-2-phenylacetic acid, 2-phthalimido-2-(4-fluorophenyl)acetic acid, 2-phthalimido-2-(2-fluorophenyl)acetic acid, 2-phthalimido-2-(4-fluorophenyl)acetamide, 2-phthalimido- 3-phenylpropionic acid, 2-phthalimido-4-methylpentanoic acid, 3-phenylcarboxamidopiperidine-2,6-dione, 2-phthalimidoacetamide, 3-phthalimidopropanamide, 3-phthalimidoimidazoline- 2,5-dione, 3-phenylcarboxamidopropanamide, 2-phthalimido- 3-carbamoylpropionic acid, 2-(1,3-dioxo-4-azaisoindolinyl)- 3-carbamoylpropionic acid, 3-(1,3-dioxo-4-azaisoindolinyl)piperidine- 2,6-dione, 2 -(1,3-dioxo-4-azaisoindolinyl)-acetamide, 3-phthalimido-3-carbamoylpropionic acid, 4-phthalimidobutyramide, and 4 -phthalimidobutyric acid.

The term alkyl as used herein denotes a univalent saturated branched or straight hydrocarbon chain. Unless otherwise stated, such chains can contain from 1 to 18 carbon atoms. Representative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tertbutyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, isohexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, and the like. When qualified by "lower", the alkyl group will contain fro 1 to 6 carbon atoms. The same carbon content applies to the parent term "alkane" and to derivative terms such as "alkoxy".

The compounds can be used, under the supervision of qualified professionals, to inhibit the undesirable effects of TNF_α. The compounds can be administered orally, rectally, or parenterally, alone or in combination with other therapeutic agents including antibiotics, steroids, etc., to a mammal in need of treatment. Oral dosage forms include tablets, capsules, dragees, and similar shaped, compressed pharmaceutical forms. Isotonic saline solutions containing 20–100 mg/ml can be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intraarterial routes of administration. Rectal administration can be effected through the use of suppositories formulated from conventional carriers such as cocoa butter.

Dosage regimens must be titrated to the particular indication, the age, weight, and general physical condition of the patient, and the response desired but generally doses will be from about 10 to about 500 mg/day as needed in single or multiple daily administration. In general, an initial treatment regimen can be copied from that known to be effective in interfering with TNF_α activity for other TNF_α mediated disease states by the compounds of the present invention. Treated individuals will be regularly checked for T cell numbers and T4/T8 ratios and/or measures of viremia such as levels of reverse transcriptase or viral proteins, and/or for progression of monokine-mediated disease associated problems such as cachexia or muscle degeneration. If no effect is soon following the normal treatment regimen, then the amount of monokine activity interfering agent administered is increased, e.g., by fifty percent a week.

The compounds of the present invention also can be used topically in the treatment or prophylaxis of topical disease states mediated or exacerbated by excessive TNF_α production, respectively, such as viral infections, such as those caused by the herpes viruses, or viral conjunctivitis, etc.

The compounds also can be used in the veterinary treatment of mammals other than in humans in need of inhibition of TNF_α production. TNF_α mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples include feline immunodeficiency virus, equine infectious anaemia virus, caprine arthritis virus, visna virus, and maedi virus, as well as other lentiviruses.

Certain of these compounds possess centers of chirality and can exist as optical isomers. Both the racemates of these isomers and the individual isomers themselves, as well as diastereomers when then are two chiral centers, are within the scope of the present invention. The racemates can be used as such or can be separated into their individual isomers mechanically as by chromatography using a chiral absorbant. Alternatively, the individual isomers can be prepared in chiral form or separated chemically from a mixture by forming salts with a chiral acid, such as the individual enantiomers of 10-camphorsulfonic acid, camphoric acid, alpha-bromocamphoric acid, methoxyacetic acid, tartaric acid, diacetyltartaric acid, malic acid, pyrrolidone- 5-carboxylic acid, and the like, and then freeing one or both of the resolved bases, optionally repeating the process, so as obtain either or both substantially free of the other; i.e., in a form having an optical purity of >95%.

The compounds can be prepared using methods which are known in general for the preparation of imides. However, the present invention also pertains to an improvement in the formation of the final compounds, as discussed below in greater detail.

An N-alkoxycarbonylimide and an amine thus are allowed to react in the presence of a base such as sodium carbonate or sodium bicarbonate substantially as described by Shealy et al., *Chem. & Ind.*, (1965) 1030–1031) and Shealy et al., *J. Pharm. Sci.* 57, 757–764 (1968) to yield the N-substituted imide. Alternatively, a cyclic acid anhydride can be reacted with an appropriate amine to form an imide. Formation of a cyclic imide also can be accomplished by refluxing a solution of an appropriately substituted dicarboxylic acid monoamide in anhydrous tetrahydrofuran with

N,N'-carbonyldiimidazole. In contrast to prior art methods which produced a yield of less than 50%, this reaction produces yields in excess of 60%, in some cases greater than 90%. This reaction also has broader applicability, being useful not only in the preparation of compounds of the present invention but also in the preparation of known compounds such as thalidomide.

Inhibition of TNF_α by these compounds can be conveniently assayed using anti-TNF_α antibodies. For example, plates (Nunc Immunoplates, Roskilde, DK) are treated with 5 μg/mL of purified rabbit anti-TNF_α antibodies at 4° C. for 12 to 14 hours. The plates then are blocked for 2 hours at 25° C. with PBS/0.05% Tween containing 5 mg/mL BSA. After washing, 100 μL of unknowns as well as controls are applied and the plates incubated at 4° C. for 12 to 14 hours. The plates are washed and assayed with a conjugate of peroxidase (horseradish) and mouse anti-TNF_α monoclonal antibodies, and the color developed with o-phenylenediamine in phosphatecitrate buffer containing 0.012% hydrogen peroxide and read at 492 nm.

The following examples will serve to further typify the nature of this invention but should not be construed as a limitation in the scope thereof, which scope is defined solely by the appended claims.

EXAMPLE 1

A stirred suspension of (S)-glutamine (14.6 g, 100 mmol) and 2,3-pyridinedicarboxylic anhydride (14.9 g, 100 mmol) in 100 mL of acetic acid is heated and refluxed for 1 hour. The reaction solution is cooled to form a solid. The solid is removed by filtration and washed with acetic acid to yield 7.11 g (26%) of 2-(1,3-dioxo-4-azaisoindolin-2yl)glutaramic acid. The product can be further purified by slurring in 700 mL of refluxing ethanol, cooling, filtering, and drying to produce a white powder with a melting point of 222°–226° C.; ^1H NMR (DMSO-d_6) δ 13.25 (br s, 1 H, COOH), 9.04 (dd, 1 H, J=1.2, 4.9 Hz, pyr), 8.37 (dd, 1 H, J = 1.2, 7.8 Hz, pyr), 7.85 (dd, 1 H, J=4.9, 7.8 Hz, pyr), 7.20 (s, 1 H, $CONH_2$), 6.73 (s, 1 H, $CONH_2$), 4.83 (dd, 1 H, J=10.2, 4.8 Hz, CHN), 2.55–1.90 (m, 4 H, CH_2CH_2); ^{13}C NMR (DMSO-d_6) δ1173.22, 170.21, 165.8, 165.7, 155.4, 150.9, 131.7, 128.3, 126.9, 51.5, 31.4, 24.0.

Utilization of asparagine in place of glutamine produces 2-(1,3-dioxo-4-azaisoindolin-2-yl)-malonamic acid.

By substituting equivalent amounts of 2,3-napithalenedicarboxylic anhydride and 4,5-imidazoledicarboxylic anhydride for 2,3-pyridinedicarboxylic anhydride in the foregoing procedure, there are respectively obtained 2-(1,3-dioxobenzo[e]isoindolin-2-yl)glutaramic acid and 2-(4,6-dioxopyrrolo[3,4-d]imidazol-5-yl)glutaramic acid.

EXAMPLE 2

A stirred suspension of 1.39 g, 5.01 mmol, of 2-(1,3-dioxo- 4-azaisoindolin-2-yl)glutaramic acid (see Example 1), N,N'-carbonyldiimidazole (0.890 g, 5.49 mmoL) and N,N-dimethylaminopyridine (0.005 g, 0.04 mmoL) in 20 mL of tetrahydrofuran is refluxed for 15 hours. The reaction slurry is cooled and the solid removed by filtration and washed with minimal tetrahydrofuran. 2-(2,6-Dioxo-3-piperidinyl)- 4-azaisoindoline-1,3-dione (0.859 g, 66%) is recovered as a white powder. ^1H NMR (DMSO-d6) 6 11.18 (s, 1 H, NHCO), 9.04 (d, 1 H, J=5.0 Hz, pyr), 8.39 (d, 1 H, J= 7.7 Hz, pyr), 7.86 (dd, 1 H, J=5.0, 7.7 Hz, pyr), 5.25 (dd, 1 H, J=15.3, 13 Hz, 1 H, CHCO) , 3.05–2.75 (m, 1 H, CH_2CO), 2.75 (m, 2 H, CH_2CO, CH_2), 2.20–2.00 (m, 1 H, CH_2CO, CH_2); ^{13}C NMR (DMSO-d6) 6 172.6, 169.6, 165.4, 155.3, 150.8, 131.7, 128.2, 126.9, 49.0, 30.8, 21.8. Anal. Calcd for $Cl_2H_9N_3O_4$. Theory 55.60, 3.50, 16.21. Found 55.50, 3.53, 16.11.

Substitution of 2-(1,3-dioxo-4-azaisoindolin-2-yl)malonamic acid in the foregoing procedure yields 2-(2,5-dioxo-3-pyrrolidinyl)-4-azaisoindoline-1,3-dione.

By substituting equivalent amounts of 2-(1,3-dioxobenzo[e]isoindolin-2-yl)glutaramic acid and 2-(4,6-dioxopyrrolo[3,4-d]imidazol-5-yl)glutaramic acid in the foregoing procedure, there are respectively obtained 2-(2,6-dioxo- 3-piperidinyl)-benzo[e]isoindoline-1,3-dione and 5-(2,6-dioxo-3-piperidinyl)-pyrrolo[3,4-d]imidazole-4,6-dione.

EXAMPLE 3

A solution of L-glutamine (2.92 g, 20.0 mmoL) and sodium hydroxide (20 mmoL) in water is added to a stirred solution of phenylisocyanate (2.4 g, 2.2 mL, 20 mmoL) in acetonitrile (40 mL). The reaction mixture is stirred for 45 hours and is partially concentrated to remove acetonitrile. The reaction mixture is washed with ethyl acetate (2 x 25 mL each). The pH of the reaction mixture is adjusted to 1–2 with 4N hydrochloric acid. The slurry of the reaction mixture is filtered and the solid washed and dried to yield 4.70 g of N-phenyl-N'-(4-carboxybutyramide)urea (89%) as a white powder.

By substituting 4-trifluoromethylphenylisocyanate, 3-cyanophenylisocyanate, 2-methoxyphenylisocyanate, fur-2-yl-isocyanate, and pyrid-3-ylisocyanate for phenylisocyanate in the foregoing procedure, there are respectively obtained N-(4-trifluoromethylphenyl)-N'-(4-carboxybutyramide)urea, N-(3-cyanophenyl)-N'-(4-carboxybutyramide)urea, N-(2-methoxy-phenyl)-N' -(4-carboxybutyramide)urea, N-(fur-2-yl)-N'-(4-carboxybutyramide)urea, and N-(pyrid-3-yl)-N'-(4-carboxybutyramide)urea.

EXAMPLE 4

N-Phenyl-N'-(4-carboxybutyramide)urea (2.00 g, 7.54 mmoL) is mixed with carbonyldiimidazole (1.24 g, 7.95 mmoL) in tetrahydrofuran (30 mL) is heated and refluxed for 16 hours. The reaction mixture is concentrated and the residue slurried in water (25 mL). The resulting slurry is filtered and the solid is washed with water and air dried to yield 0.63 g of 3-phenylcarboxamidopiperidine-2,6-dione which can be alternatively named as N-phenyl-N'-(2-glutarimide)urea as a white flocculent powder. After being allowed to stand, the filtrate is refiltered to yield 0.70 g of additional material. ^1H NMR (DMSO-d_6) 6 8.51 (s, 1H, CONHCO), 7.6–7.2 (m, 6 H, Ar, ArNH), 6.83 (s, 1 H, NHCH), 4.26 (t, 1 H, CHCO), 2.4–1.8 (m, 4 H, CH_2CH_2); ^{13}C NMR (DMSO-d_6) δ 173.2, 155.6, 132.2, 128.7, 127.7, 126.7, 55.7, 29.8, 27.2. Anal. Calcd for $C_{12}H_{13}N_3O_3$. Theoretical: C, 58.29; H, 5.29; N, 16.99. Found: C, 58.12; H, 5.17; N, 17.02.

By substituting N-(4-trifluoromethylphenyl)-N'-(4-carboxybutyramide)urea, N-(3-cyanophenyl)-N'-(4-carboxybutyramide)urea, N-(2-methoxyphenyl)-N'-(4-carboxybutyramide)urea, N-(fur-2-yl)-N'-(4-carboxybutyramide)urea, and N-(pyrid- 3-yl)-N'-(4-carboxybutyramide)urea for N-phenyl-N'-(4-carboxybutyramide)urea in the foregoing procedure, there are respectively obtained 3-(4-trifluoromethylphenylcarboxamido)piperidine- 2,6-dione, 3-(3-cyanophenylcarboxamido)-piperidine- 2,6-dione, 3-(2-methoxyphenylcarboxamido)piperidine- 2,6-dione, 3-(fur-2-ylcarboxamido)piperidine-2,6-dione, and 3-(pyric

ylcarboxamido)piperidine-2,6-dione.

EXAMPLE 5

To a stirred mixture of phenylglycine (3.0 g, 20 mmoL) and sodium carbonate (2.23 g, 21 mmoL) in 450 mL of water is added N-carbethoxyphthalimide (4.38 g, 20 mmoL). After 45 minutes, the reaction slurry is filtered. The filtrate is stirred and the pH adjusted to 1–2 with 4 N hydrochloric acid. After 1 hour, the resulting slurry is filtered and the solid washed with water. The solid is dried in vacuo (60° C., <1 mm) to afford 2.88 g (51%) of 2-phthalimido-2-phenylacetic acid, which can be alternatively named as N-phthaloylphenylglycine, as a white powder.

Use of β-phenyl-β-alanine, β-phenyl-β-alanine, histidine, and tyrosine in place of phenylglycine in the procedure of this example yields respectively 3-phthalimido-3-phenylpropionic acid, 2-phthalimido-3-phenylpropionic acid, 2-phthalimido-3-imidazolylpropionic acid, and 2-phthalimido- 3-(4-hydroxyphenyl)propionic acid.

EXAMPLE 6

To a stirred mixture of 2-phthalimido-2-phenylacetic acid (2.50 g, 8.89 mmoL) in tetrahydrofuran (50 mL) is added carbonyldiimidazole (1.50 g, 9.25 mmoL) and a few crystals of 4-dimethylaminopyridine. The reaction is then heated to 50° C. for 45 minutes. After the reaction mixture cools to room temperature, 1 mL of concentrated ammonium hydroxide is added via syringe. The reaction is stirred for 1 hour, then diluted with 50 mL of water and partially concentrated to remove the majority of the tetrahydrofuran. The resulting slurry is filtered and the solid washed with copious amounts of water. The solid is dried in vacuo (60° C., <1 mm) to afford 1.9 g (76%) of 2-phthalimido-2-phenylacetamide, which may be alternatively named as N-phthaloylphenylglycinamide, as an off-white powder: mp 218°–220½° C.; ^{1}H NMR (DMSO-d_6) δ 9.00–7.75 (m, 4 H, Ar), 7.61 (br s, 1 H, $CONH_2$), 7.55–7.20 (m, 6 H, Ar, $CONH_2$), 5.82 (s, 1 H, $CHCO_2$); ^{13}C NMR (DMSO-d_6) δ 168.2, 167.1, 135.6, 134.5, 131.4, 129.4, 127.9, 127.7, 123.1, 56.3. Anal ($C_{16}H_{12}N_2O_3$), C, H, N.

Use of 3-phthalimido-3-phenylpropionic acid, 2-phthalimido- 3-phenylpropionic acid, 2-phthalimido-3-imidazolylpropionic acid, and 2-phthalimido-3-(4-hydroxyphenyl)propionic acid in place of 2-phthalimido-2-phenylacetic acid in the procedure of this example yields respectively 3-phthalimido- 3-phenylpropanamide, 2-phthalimido-3-phenylpropanamide, 2-phthalimido-3-imidazolylpropanamide, and 2-phthalimido- 3-(4-hydroxy)phenylpropanamide.

EXAMPLE 7

To a stirred mixture of β-alanine (4.45 g, 50.0 mmoL) and sodium carbonate (5.35 g, 50.5 mmoL) in 100 mL of water is added N-carbethoxyphthalimide (10.95 g, 50.0 mmoL). After 1.5 hour, the reaction slurry is filtered. The filtrate is stirred and the pH adjusted to 1–2 with 4N hydrochloric acid. After 15 minutes, the resulting slurry is filtered and the solid washed with water. The solid is dried in vacuo (60° C., <1 mm) to afford 6.96 g (64%) of N-phthaloyl-β -alanine, which can be alternatively named as 3-phthalimidopropionic acid, as a white powder.

EXAMPLE 8

To a stirred solution of N-phthaloyl-β-alanine (2.19 g, 10.0 mmoL) in tetrahydrofuran (25 mL) is added carbonyldiimidazole (1.62 g, 10.0 mmoL) and a few crystals of 4-N,N-dimethylaminopyridine followed by 15 mL of tetrahydrofuran. The reaction is then heated to 40°–45° C. for 1 hour. After the reaction mixture cools to room temperature, 1 mL of concentrated ammonium hydroxide is added via syringe. The reaction is stirred for 20 minutes and the resulting slurry filtered and the solid washed with tetrahydrofuran. The solid is dried in vacuo (60° C., <1 mm) to afford 1.72 g (79%) of N-phthaloyl-β-alanine amide, which can be alternatively named as 3-phthalimidopropanamide, as a white powder: mp 252°–253° C.; ^{1}H NMR (DMSO-d6) δ 8.00–7.70 (m, 4 H, Ar), 7.45 (br s, 1 H, $CONH_2$), 6.89 (br s, 1 H, $CONH_2$), 3.78 (t, 2 H, J=7 Hz, CH_2CO), 2.43 (t, 2 H, CH_2); ^{13}C NMR (DMSO-d_6) δ 171.5, 167.6, 134.2, 131.6, 122.9, 34.1, 33.5. Anal. Calcd for $C_{11}H_{10}N_2O_3$. Theoretical: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.49; H, 4.59; N, 12.82.

EXAMPLE 9

To a stirred solution of glycinamide hydrochloride (2.20 g, 20.0 mmoL) and sodium carbonate (2.54 g, 24 mmoL) in 25 mL of water is added N-carbethoxyphthalimide (4.38 g, 20.0 mmoL). The resulting suspension is stirred for 1.5 hour and then filtered to afford 3.22 g (79%) of the crude product as a white powder. The crude product is slurried in 200 mL of refluxing ethanol. The resulting suspension after cooling to room temperature is filtered and the solid dried in vacuo (60° C., <1 mm) to afford 2.65 g (65%) of N-phthaloylglycinamide as a white powder: mp 199°–201° C.; ^{1}H NMR (DMSO-d_6) δ 8.00–7.8 (m, 4 H, Ar), 7.70 (br s, 1 H, $CONH_2$), 7.26 (br s, 1 H, $CONH_2$), 4.16 (s, 2 H, CH_2); ^{13}C NMR (DMSO-d_6) δ 167.8, 167.5, 134.4, 131.7, 123.1, 39.9. Anal. Calcd for $C_{11}H10N_2O_3$. Theoretical: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.49; H, 4.59; N, 12.82.

EXAMPLE 10

To a stirred solution of L-glutamine (43.8 g, 300 mmoL) and sodium carbonate (33.4 g, 315 mmoL) in 750 mL of water is rapidly added N-carbethoxyphthalimide [65.8 (97% pure, 67.8 g), 300 mmoL] as a solid. After 1 hour, the reaction mixture is filtered to remove unreacted N-carbethoxyphthalimide. The pH of the stirred filtrate is adjusted to 3–4 with 4N hydrochloric acid. The mixture is then seeded with N-phthaloyl-L-glutamine and the pH adjusted to 1–2 with 4N hydrochloric acid. The resulting slurry is stirred for 1 hour. The slurry is filtered and the solid washed with copious amounts of water. The solid is air-dried and then dried in vacuo (60° C., <1 mm) overnight to afford 49.07 g (59%) of N-phthaloyl-L-glutamine, which can be alternatively named as 2-phthalimidoglutaramic acid, as a white powder.

EXAMPLE 11

A stirred mixture of N-phthaloyl-L-glutamine (48.0 g, 174 mmoL), carbonyldiimidazole (30.43 g, 188 mmoL), and 4-dimethylaminopyridine (0.105 g, 0.861 mmoL) in anhydrous tetrahydrofuran (300 mL) is heated to reflux for 16 hours. The reaction slurry is filtered and the solid washed with methylene chloride (200 mL). The solid is air-dried and then dried in vacuo (60° C., <1 mm) to afford 40.40 g (90%) of thalidomide as a white powder. ^{1}H NMR (DMSO-d_6) δ

11.16 (s, 1 H, NH), 8.05–7.80 (br s, 4 H, Ar), 5.18 (dd, 1 H, J=12.5 Hz, CHCO), 3.05–2.85 (m, 1 H, CH_2CO), 2.70–2.45 (m, 2 H, CH_2CH_2), 2.15–2.00 (M, 1 H, CH_2). ^{13}C NMR (DMSO-d_6) δ 172.8, 169.8, 167.1, 134.9, 131.2, 123.4, 49.0, 30.9, 22.0.

EXAMPLE 12

A stirred suspension of (S)-glutamine (14.6 g, 100 mL) and pyridine-2,3-dicarboxylic anhydride (14.9 g, 100 mmol) in 100 mL of acetic acid is heated at reflux for 1 hour. The resulting solution is allowed to cool. The solid which forms upon cooling is filtered and the solid washed with acetic acid and dried to afford 7.11 g (26%) of crude product. The crude product is slurried in 700 mL of refluxing ethanol, the suspension cooled, and the slurry collected by filtration and dried to afford 6.10 g (23%) of N-quinolinylglutamine, which can be alternatively named as 2-(1,3-dioxo-4-azaisoindol- 2-yl)-3-carbamoylpropionic acid, as a white powder: mp 222°–226° C.; ^1H NMR (dmso-d_6) δ 13.25 (br s, 1 H, COOH), 9.04 (dd, 1 H, J=1.2, 4.9 Hz, pyr), 8.37 (dd, 1 H, J=1.2, 7.8 Hz, pyr), 7.85 (dd, 1 H, J=4.9, 7.8 Hz, pyr), 7.20 (s, 1 H, $CONH_2$), 6.73 (s, 1 H, $CONH_2$), 4.83 (dd, 1 H, J=10.2, 4.8 HZ, CHN), 2.55–1.90 (m, 4 H, CH_2CH_2); ^{13}C NMR (dmso-d_6) δ 1173.22, 170.21, 165.8, 165.7, 155.4, 150.9, 31.7, 128.3, 126.9, 51.5, 31.4, 24.0.

EXAMPLE 13

A stirred suspension of N-quinolinylglutamine (1.39 g, 5.01 mmol), carbonyldiimidazole (0.890 g, 5.49 mmol), and N,N-dimethylpyridine (0.005 g, 0.04 mmol) in 20 mL of tetrahydrofuran is heated at reflux for 15 hours. After cooling, the reaction slurry is filtered and the solid washed with minimal tetrahydrofuran to afford, after drying 0.859 g (66%) of N-quinolinylglutarimide, which can be, alternatively named as 3-(1,3-dioxo-4-azaisoindol-2-yl)-2,6-dioxopiperidine, as a white powder: ^1H NMR (dmso-d_6) δ 11.18 (s, 1 H, NHCO), 9.04 (d, 1 H, J=5.0 Hz, pyr), 8.39 (d, 1 H, J=7.7 Hz, pyr), 7.86 (dd, 1 H, J=5.0, 7.7 Hz, pyr), 5.25 (dd, 1 H, J=15.3 , 13 Hz, 1 H, CHCO), 3.05–2.75 (m, 1 H, CH_2CO), 2.75 (m, 2 H, CH_2CO, CH_2), 2.20–2.00 (m, 1 H, CH_2CO, CH_2); ^{13}C NMR (dmso-d_6) δ 172.6, 169.6, 165.4, 155.3, 150.8, 131.7, 128.2, 126.9, 49.0, 30.8, 21.8. Anal. Calculated for $C_{12}H_9N_3O_4$. Theory 55.60, 3.50, 16.21. Found 55.50, 3.53, 16.11.

EXAMPLE 14

To a stirred mixture of phenylglycine (3.0 g, 20 mmol) and sodium carbonate (2.23 g, 21 mmol) in 450 mL of water is added N-carbethoxyphthalimide (4.38 g, 20 mmol). After 45 minutes, the reaction slurry is filtered. The filtrate is stirred and the pH adjusted to 1–2 with 4N hydrochloric acid. After 1 hour, the resulting slurry is filtered and the solid washed with water. The solid is dried in vacuo (60° C., <1 mm) to afford 2.88 g (51%) of 2-phthalimidophenylacetic acid as a white powder.

By employing (R)-phenylglycine, there is obtained (R) 2-phthalimido-phenylacetic acid, as a white powder: mp 175°– 177° C.; ^1H NMR (dmso-d_6, 250 M Hz) δ 12.50 (br s, 1H), 7.95– 7.85 (m, 4H), 7.55–7.28 (m, 5H), 6.04 (s, 1H); ^{13}C NMR (dmso-d_6) δ 168.9, 166.9, 135.0, 134.9, 131.0, 129.1, 128.1, 127.9, 123.5, 56.1. Anal. Calculated for $C_{16}H_{11}NO_4$. Theoretical: C, 68.32; H, 3.94; N, 4.98. Found: C, 68.32; H, 3.85; N, 4.95.

Likewise from (S)-phenylglycine, there is obtained (S)-2-phthalimido-phenylacetic acid as a white powder: mp 180°– 184° C.; ^1H NMR (dmso-d_6, 250 M Hz) δ 12.5 (br s, 1H), 7.95 7.85 (m, 4H) , 7.55–7.28 (m, 5H) , 6.04 (s, 1H); ^{13}C NMR (dmso-d_6) δ 168.9, 166.9, 135.0, 134.9, 130.9, 129.1, 128.1, 127.9, 123.5, 55.1. Anal. Calculated for $C_{16}H_{11}NO_4$. Theoretical: C, 68.32; H, 3.94; N, 4.98. Found: C, 68.14; H, 3.87; N, 4.96.

EXAMPLE 15

To a stirred solution of N-phthaloylglycine (2.50 g, 8.89 mmol) in tetrahydrofuran (50 mL) is added carbonyldiimidazole (1.50 g, 9.25 mmol) and a few crystals of 4-N,N-dimethylaminopyridine. The reaction is then heated to 50° C. for 45 minutes. After the reaction mixture had cooled to room temperature, 1 mL of concentrated ammonium hydroxide is added via syringe. The reaction is stirred for 1 hour, then diluted with 50 mL of water and partially concentrated to remove the majority of the tetrahydrofuran. The resulting slurry was filtered and the solid washed with copious amounts of water. The solid was dried in vacuo (60° C., 1 mm) to afford 1.9 g (76%), of 2-phthalimido-2-phenylacetamide as an off-white powder: mp 218°–220° C.; ^1H NMR (dmso-d_6) δ 9.00–7.75 (m, 4 H, Ar), 7.61 (br s, 1 H, $CONH_2$), 7.55–7.20 (m, 6 H, Ar, $CONH_2$), 5.82 (s, 1 H, $CHCO_2$); ^{13}C NMR (dmso-d_6) 6 168.2, 167.1, 135.6, 134.5, 131.4, 129.4, 127.9, 127.7, 123.1, 56.3.

EXAMPLE 16

To a stirred mixture of β-alanine (4.45 g, 50.0 mmol) and sodium carbonate (5.35 g, 50.5 mmol) in 100 mL of water is added N-carbethoxyphthalimide (10.95 g, 50.0 mmol). After 1.5 hour, the reaction slurry is filtered. The filtrate is stirred and the pH adjusted to 1–2 with 4N hydrochloric acid. After 15 minutes, the resulting slurry is filtered and the solid washed with water. The solid is dried in vacuo (60° C., <1 mm) to afford 6.96 g (64%) of N-phthaloyl-β -alanine, which can be alternatively named as 3-phthalimido- 3-phenylpropionic acid, as a white powder.

EXAMPLE 17

To a stirred solution of N-phthaloyl-β-alanine (2.19 g, 10.0 mmol) in tetrahydrofuran (25 mL) is added carbonyldiimidazole (1.62 g, 10.0 mmol) and a few crystals of 4-N,N-dimethylaminopyridine, followed by 15 mL of tetrahydrofuran. The mixture is heated at 40°–45° C. for 1 hour. After the reaction mixture is cooled to room temperature, 1 mL of concentrated ammonium hydroxide is added via syringe. The reaction is stirred for 20 minutes and the resulting slurry is filtered and the solid washed with tetrahydrofuran. The solid is dried in vacuo (60° C., < 1 mm) to afford 1.72 g (79%) of N-phthaloyl-β-alanine amide, which can be alternatively named as 3-phthalimidopropionic acid, as a white powder: mp 252°–253° C.; ^1H NMR (dmso-d_6) δ 8.00–7.70 (m, 4 H, Ar), 7.45 (br s, 1 H, $CONH_2$), 6.89 (br s, 1 H, $CONH_2$), 3.78 (t, 2 H, J=7 Hz, CH_2CO), 2.43 (t, 2 H, CH_2); ^{13}C NMR (dmso-d_6) δ 171.5, 167.6, 134.2, 131.6, 122.9, 34.1, 33.5. Anal. Calculated for $C_{11}H_{10}N_2O_3$. Theoretical: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.49; H, 4.59; N, 12.82.

EXAMPLE 18

To a stirred solution of glycinamide hydrochloride (2.20 g, 20.0 mmol) and sodium carbonate (2.54 g, 24 mmol) in 25 mL of water is added N-carbethoxyphthalimide (4.38 g, 20.0 mmol). The resulting suspension is stirred for 1.5 hour and then filtered to afford 3.22 g (79%) of crude product as a white powder. The crude product is slurried in 200 mL

refluxing ethanol and, after cooling to room temperature, the resulting suspension is filtered and the solid dried in vacuo (60° C., <1 mm) to afford 2.65 g (65%) of N-phthaloylglycinamide, which can be alternatively named as phthalimidoacetamide, as a white powder: mp 199°–201° C.; 1H NMR (dmso-d_6) δ 8.00–7.8 (m, 4 H, Ar), 7.70 (br s, 1 H, $CONH_2$), 7.26 (br s, 1 H, $CONH_2$), 4.16 (s, 2 H, CH_2); ^{13}C NMR (dmso-d_6) δ 167.8, 167.5, 134.4, 131.7, 123.1, 39.9. Anal. Calculated for $C_{11}H_{10}N_2O_3$. Theoretical: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.49; H, 4.59; N, 12.82.

EXAMPLE 19

By following the procedure of Example 17 but utilizing an equivalent amount of 4-aminobutyric acid, there is obtained a 67% yield of 4-phthalimidobutyric acid as a white powder: mp 108°–111° C.; ^1H NMR (dmso-d_6) δ 12.10 (s, 1 H), 7.92°–7.75 (m, 4 H, Ar), 3.62 (t, J=6.8 Hz, 2 H), 2.29 (t, J=7.2 Hz, 2 H), 1.90–1.76 (m, 2 H); ^{13}C NMR (dmso-d_6) δ 173.8, 167.9, 134.2, 131.6, 122.9, 36.8, 30.9, 23.3.

EXAMPLE 20

By following the procedure of Example 15 but utilizing an equivalent amount of 4-phthalimidobutyric acid, there is obtained 4-phthalimidobutyramide as a white powder in a 23% yield: mp 159.5°–161.5° C.; ^1H NMR (dmso-d_6) δ 8.0–7.7 (m, 4 H, Ar), 3.58 (t, J=6.9 Hz, 2 H), 2.09 (t, 2 H), 1.92–1.70 (m, 2 H); ^{13}C NMR (dmso-d_6) δ 173.3, 167.9, 134.2, 131.6, 122.9, 37.1, 32.3, 23.9.

Example 21

By following the procedure of Example 18 but employing N-carbethoxyphthalimide and (S)-phenylalaninamide hydrochloride, there is obtained (S)-2-phthalimido-3-phenylpropionamide which can be recrystallized from ethanol to afford white crystals: mp 211°–215° C.; ^1H NMR (dmso-d_6) δ 7.92 (s, 5 H, Ph), 7.72, 7.33 (2 s, 2 H), 7.2–7.0 (m, 4 H, Ar), 4.92 (dd, 1 H, J=12, 4.5 Hz), 3.52 (dd, 1 H, J=4.3, 13.9), 3.35 (dd, 1 H, J=12, 13.9); ^{13}C NMR (dmso-d_6) δ 169.6, 167.4, 137.7, 134.3, 131.2, 128.5, 128.1, 126.3, 122.9, 54.2, 33.7.

EXAMPLE 22

To a stirred solution of dl-phenylalanine (4.17 g, 25.0 mmol) and sodium carbonate (2.78 g, 26.25 mmol) in 50 mL of water is added N-carboethoxyphthalimide (5.65 g, 25.0 mmol). The resulting slurry is stirred for 1.5 hour and filtered. The pH of the filtrate is adjusted to 1–2 with 4 N hydrochloric acid with stirring. After 20 minutes, the slurry is refiltered and the solid washed with water. The solid is dried in vacuo (60° C., <1 mm) to afford 5.44 g (74%) of 2-phthalimido-3-phenylpropionic acid as a white powder: mp 165°–169° C.; ^1H NMR (dmso-d_6, 250 M Hz) δ 12.5(br s, 1H), 7.84(s, 4H), 7.23–7.06 (m, 5H), 5.13 (dd, 1H, J=5.0), 3.26–3.05 (m, 2H); ^{13}C NMR (250 MHz, dmso-d_6) δ 170.0, 167.0, 137.2, 134.8, 130.6, 128.6, 128.2, 126.5, 123.3, 52.8, 33.8. Anal. Calculated for $C_{17}H_{13}NO_4$. Theoretical: C, 69.15; H, 4.44; N, 4.74. Found: C, 69.07; H, 4.34; N, 4.78.

EXAMPLE 23

To a stirred solution of 2-phthalimido-3-phenylpropionic acid (2.95 g, 10.0 mmol) in tetrahydrofuran (25 mL) are added carbonyldiimidazole (1.62 g, 10.0 mmol) and a few crystals of 4-N,N-dimethylaminopyridine, followed by 15 mL of tetrahydrofuran. The reaction mixture is stirred at room temperature for 45 minutes and 1 mL of concentrated ammonium hydroxide then is added. After 10 minutes, the reaction mixture is diluted with 50 mL water and the resulting slurry is partially concentrated to remove the tetrahydrofuran and filtered. The solid is washed with water and dried in vacuo (60° C., <1 mm) to afford 2.46 g (84%) of 2-phthalimido-3-phenylpropionamide as a white powder: mp 224°–226° C.; ^1H NMR (dmso-d_6, 250 MHz) δ 7.79 (s, 4 H, Ar), 7.71 (br s, 1 H, $CONH_2$), 7.32 (br s, 1 H, $CONH_2$), 7.20–7.02 (m, 5H, Ar), 5.06–4.98 (m, 1H), 3.56–3.25 (m, 2H); ^{13}C NMR (dmso-d_6, 250 MHz) δ: 169.6, 168.0, 137.1, 134.3, 131.2, 129.5, 128.1, 126.3, 122.9, 54.2, 33.7. Anal. Calculated for $C_{17}H_{14}N_2O_3$. Theoretical: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.37; H, 4.73; N, 9.43.

EXAMPLE 24

To a stirred solution of 4-fluorophenylglycine (3.38 g, 20.0 mmol) and sodium carbonate in 450 mL of 2:1 water:acetonitrile is added N-carbethoxyphthalimide (4.38 g, 20 mmol). After 1 hour, the reaction mixture is partially concentrated to remove the acetonitrile. The resulting slurry is filtered and the pH of the stirred filtrate is adjusted to 1–2 with 4 N hydrochloric acid and then stirred for an additional 30 minutes and filtered. The solid is air-dried and then dried in vacuo (60° C., < 1 mm) to afford 4.55 g (76%) of 2-phthalimido-2-(4-fluorophenyl)acetic acid as a white powder: mp 180°–183° C.; ^1H NMR (dmso-d_6, 250 MHz) δ 8.10–7.80 (m, 4 H), 7.65–7.45 (m, 4 H), 7.3–7.10 (t, 2 H), 6.10 (s, 1 H); ^{13}C NMR (dmso-d_6, 250 MHz) δ168.9, 166.9, 163.6, 159.7, 135.0, 131.4, 131.3 (m), 130.9, 123.5, 115.0, 114.7, 54.4. Anal. Calculated for $C_{16}H_{10}NO_4F$. Theoretical: C, 64.22; H, 3.37; N, 4.68. Found: C, 64.13; H, 3.33; N, 4.63.

Similarly prepared from 2-fluorophenylglycine is 2-phthalimido-2-(2-fluorophenyl)acetic acid as a white solid: mp 174.5°–180.5° C.; ^1H NMR (dmso-d_6) δ 13.8 (br s, 1 H), 7.65–7.15 (m, 4H), 6.18 (s, 1 H); ^{13}C NMR (dmso-d_6) δ 168.1, 166.8, 162.1, 158.2, 135.0, 130.9, 130.8, 130.5, 130.4, 124.1, 123.6, 121.8, 121.6, 115.3, 114.9, 48.9. Anal. Calculated for $C_{16}H_{10}NO_4F$. Theoretical: C, 64.22; H, 3.37; N, 4.68. Found: C, 63.93; H, 3.27; N, 4.68.

EXAMPLE 25

Similarly prepared according to the procedure of Example 23 from 2-phthalimido-2-(4-fluorophenyl)acetic acid, carbonyldiimidazole, 4-N,N-dimethylaminopyridine and concentrated ammonium hydroxide is 2-phthalimido-2-(4-fluorophenyl)acetamide which can be recrystallized from tetrahydrofuran to afford 0.76 g (51%) of the product as white crystals: mp 180°–183° C.; ^1H NMR (dmso-d_6) δ 8.00–7.55 (m, 4 H), 7.64 (s, 1 H), 7.60–7.40 (m, 3 H), 7.25–7.05 (m, 2 H), 5.83 (s, 1 H). Anal. Calculated for $C_{16}H_{11}N_2O_3F$. Theoretical: C, 64.43; H, 3.72; N, 9.39. Found: C, 64.16; H, 3.62; N, 9.18.

Likewise from 2-phthalimido-2-(2-fluorophenyl)acetic acid there is obtained 2-phthalimido-2-(2-fluorophenyl)acetamide as small white crystals: mp 197°–201° C.; 1H NMR (dmso-d_6) δ 8.05–7.75 (m, 5 H), 7.65–7.05 (m, 5 H), 6.06 (s, 1 H), ^{13}C NMR (dmso-d_6) δ 167.4, 166.9, 162.2, 158.3, 134.6, 131.3, 131.2, 131.1, 130.2, 130.0, 123.9, 123.8, 123.2, 122.4, 115.1, 114.8, 49.9.

EXAMPLE 26

To a stirred solution of dl-leucine (3.31 g, 25.0 mmol) and sodium carbonate (2.78 g, 26.25 mmol) in 50 mL of water is added N-carboethoxyphthalimide (5.65 g, 25.0 mmol). After 1 hour at room temperature, the reaction slurry

is filtered, the filtrate stirred, and the pH adjusted to 1–2 with 4N hydrochloric acid. The mixture is stirred overnight, the resulting slurry is filtered, and the solid washed with water and dried in vacuo (60° C., <1 mm) to afford 5.32 g (81%) of the 2-phthalimido-4-methylpentanoic acid as a white powder: mp 134°–137° C.; ^{1}H NMR (dmso-d_6, 250 M Hz) δ 12.50 (br s, 1H), 8.00–7.80 (m, 4H), 4.79 (dd, 1H, J=4.3), 2.28–2.10 (m, 1H), 1.94–1.77 (m, 1H), 1.51–1.34 (m, 1H), 0.89 (d, 3H, J=4.4), 0.86 (d, 3H, J=4.5); ^{13}C NMR (dmso-d_6) δ 170.8, 167.4, 134.8, 131.1, 123.3, 50.2, 36.7, 24.6, 23.0, 20.8. Anal. Calculated for $C_{14}H_{15}NO_4$. Theoretical: C, 64.36; H, 5.74; N, 5.36. Found: C, 64.18; H, 5.73; N, 5.98.

EXAMPLE 27

To a stirred solution of 2-phthalimido-4-methylpentanoic acid (1.32 g, 5.0 mmol) in tetrahydrofuran (25 mL) are added carbonyldiimidazole (0.81 g, 5.0 mmol) and a few crystals of 4-N,N-dimethylaminopyridine followed by 15 mL of tetrahydrofuran. The reaction mixture is stirred at room temperature for 1 hour, then 1 mL of concentrated ammonium hydroxide is added. After 10 minutes, the reaction mixture is diluted with 50 mL water. The resulting slurry is partially concentrated to remove the tetrahydrofuran and filtered. The solid is washed with water and dried in vacuo (60° C., <1 mm) to afford 1.16 g (89%) of 2-phthalimido-4-methylpentanamide as a white powder: mp 173°–176° C.; ^{1}H NMR (dmso-d_6, 250 MHz) δ 7.95–7.79 (m, 4 H, Ar), 7.61 (br s, 1 H, $CONH_2$), 7.22 (br s, 1 H, $CONH_2$), 4.73–4.60 (m, 1 H), 2.30–2.10 (m, 1 H), 1.95–1.80 (m, 1H), 1.45–1.25 (m, 1H); ^{13}C NMR (dmso-d_6) δ: 170.4, 167.7, 134.4, 131.5, 123.1, 51.3, 36.4, 24.7, 23.2, 20.6. Anal. Calculated for $C_{14}H_{16}N_2O_3$. Theoretical: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.63; H, 6.11; N, 10.70.

EXAMPLE 28

To a stirred solution of histidine (3.17 g, 20.0 mmol) and sodium carbonate (2.23 g, 21 mmol) in 50 mL of water is added N-carboethoxyphthalimide (4.52 g, 20.0 mmol). After 1.5 hour, the reaction slurry is filtered. The filtrate is stirred and the pH adjusted to 1–2 with 4N hydrochloric acid. The resulting slurry is filtered and the solid washed with water and dried in vacuo (60 C, <1 mm) to afford 3.65 g (64%) of 2-phthalimido-3-(imidazol-4-yl)propionic acid as a white powder: mp 280°–285° C.; ^{1}H NMR (dmso-d_6, 250 M Hz) δ 12.5 (br s, 1H), 7.90–7.60 (m, 6H), 6.80(s, 1H), 4.94 (t, 1H, J=7.8), 3.36 (d, 2H, J=7.8); ^{13}C NMR (dmso-d_6) δ 170.1, 167.1, 134.8, 134.6, 133.2, 131.1, 123.2, 116.3, 52.4, 25.8; Anal. Calculated for $C_{14}H_{11}N_3O_4$. Theoretical: C, 58.95; H, 3.89; N, 14.73. Found: C, 58.80; H, 3.88; N, 14.66.

EXAMPLE 29

To a stirred mixture of 3-amino-3-(4-methoxyphenyl)propionic acid (1.95 g, 10.0 mmol) and sodium carbonate (1.11 g, 10.5 mmol) in 200 mL of acetonitrile-water 1:1 is added N-carboethoxyphthalimide (2.26 g, 10.0 mmol). After 1 hour, the reaction slurry is filtered. The filtrate is concentrated to remove the acetonitrile and the pH adjusted to 1–2 with 4 N hydrochloric acid and stirred over night. The resulting slurry is filtered and the solid washed with water. The solid is dried in vacuo (60 C, <1 mm) to afford 2.82 g (87%) of the 3-phthalimido-3-(4-methoxyphenyl)propionic acid as a white powder: mp 160°–164° C.; ^{1}H NMR (dmso-d_6, 250 MHz) δ 12.5 (br s, 1H), 7.95–7.80 (m, 4 H), 7.36 (d, 2 H, J=8.7), 6.92 (d, 2 H, J=8.4 Hz), 5.18–5.10 (m, 1 H), 3.70–3.15 (m, 2 H); ^{13}C NMR (dmso-d_6) δ 171.7, 167.6, 158.6, 134.6, 131.0, 130.8, 128.3, 123.1, 113.9, 55.0, 49.6, 35.9. Anal. Calculated for $C_{18}H_{15}NO_5$. Theoretical: C, 66.46; H, 4.63; N, 4.31. Found: C, 66.25; H, 4.65; N, 4.28.

Similarly from 3-amino-3-(3-methoxyphenyl)propionic acid there is obtained 3-phthalimido-3-(3-methoxyphenyl-)propionic acid as white crystals: mp 111°–115° C.; ^{1}H NMR (dmsod$_6$, 250 MHz) δ 12.5 (br s, 1H), 7.94–7.81 (m, 4 H), 7.32–7.23 (m, 1H), 7.02–6.85 (m, 3 H), 5.70–5.60 (m, 1 H), 3.77–3.67 (s, 3H), 3.56–3.15 (m, 2 H); ^{13}C NMR (dmso-d_6) δ 171.6, 167.6, 159.2, 140.4, 134.7, 131.0, 129.7, 123.2, 119.0, 112.9, 112.7, 54.9, 50.0, 35.8.

Likewise from 3-amino-3-(2-methoxyphenyl)propionic acid there is obtained 3-phthalimido-3-(2-methoxyphenyl-)propionic acid as a white powder: mp 163°–168 ° C.; ^{1}H NMR (dmso-d_6, 250 MHz) δ 12.5 (br s, 1H), 7.95–7.80 (m, 4 H), 7.45–6.90 (m, 4H), 6.05–5.92 (m, H), 3.78 (s, 3H) 3.55–3.05 (m, 2 H); ^{13}C NMR (dmso-d_6) 171.7, 167.5, 156.1, 134.5, 131.0, 128.9, 127.3, 126.1, 123.0, 120.1, 111.0, 55.5, 45.3, 35.1.

EXAMPLE 30

By following the procedure of Example 27 utilizing 3-phthalimido-3-(4-methoxyphenyl)propionic acid, there is obtained 3-phthalimido-3-(4-methoxyphenyl)propionamide as a white powder: mp 183°–188° C.; ^{1}H NMR (dmso-d_6, 250 MHz) δ 7.90–7.75 (m, 4 H, Ar), 7.58 (br s, 1 H, $CONH_2$), 7.38 (d, 2H, J=8.6), 6.91 (d, 3H, J=8.6), 5.73 (t, 1H, J=7.8), 3.23(d, 2H, J=7.9); ^{13}C NMR (dmso-d_6) δ: 171.2, 167.6, 158.5, 134.5, 131.3, 131.2, 128.4, 123.0, 113.7, 55.0, 49.9, 36.8.. Anal. Calculated for $C_{18}H_{16}N_2O_4$. Theoretical: C, 66.66; H,4.97; N, 8.64. Found: C, 66.27; H, 5.04; N, 8.40.

EXAMPLE 31

To a stirred mixture of 3-amino-3-(4-cyanophenyl)propionic acid (3.80 g, 20.0 mmol) and sodium carbonate (2.23 g, 21 mmol) in 100 mL of water is added N-carboethoxyphthalimide (4.52 g, 20.0 mmol). After 2 hour, the reaction slurry is filtered and the pH of the stirred filtrate adjusted to 1–2 with 4 N hydrochloric acid. The resulting gel is extracted with ethyl acetate (3×30 mL). The extract is dried over magnesium sulfate and concentrated in vacuo. The crude product is recrystallized from 10% aqueous acetonitrile and then recrystallized from 20% aqueous methanol. The product is dried in vacuo (60° C., <1 mm) to afford 1.5 g (23%) of 3-phthalimido-3-(4-cyanophenyl)propionic acid as a white powder: mp 134°–137° C.; ^{1}H NMR (dmso-d_6, 250 MHz) δ 12.5 (br s, 1H), 7.95–7.56 (m, 8 H), 5.76 (t, 1 H, J=7.7), 3.57–3.15 (m, 2 H); ^{13}C NMR (dmso-d_6) δ 171.5, 167.6, 144.2, 134.8, 132.6, 131.1, 128.1, 123.3, 118.5, 49.7, 35.5.

Likewise from 3-amino-3-(3-cyanophenyl)propionic acid there is obtained 3-phthalimido-3-(3-cyanophenyl)propionic acid as a white powder: mp 172°–175° C.; ^{1}H NMR (dmso-d_6, 250 MHz) δ 12.5 (br s, 1H), 8.05–7.51 (m, 8 H), 5.82–5.70 (m, 1 H), 3.63–3.20(m, 2 H); ^{13}C NMR (dmso-d_6) δ 171.5, 167.6, 140.3, 134.6 132.0, 131.5, 131.2, 130.7, 129.8, 123.22, 118.5, 111.6, 49.3, 35.6.

EXAMPLE 32

By following the procedure of Example 27 utilizing 3-phthalimido-3-(4-cyanophenyl)propionic acid, there is obtained 3-phthalimido-3-(4-cyanophenyl)propionamide as a white powder: ^{1}H NMR (dmso-d_6, 250 MHz) δ 8.05–7.50 (m, 9 H), 6.97 (s, 1 H), 5.87–5.72 (m, 1 H), 3.44–3.12 (m, 2 H); ^{13}C NMR (dmso-d_6) δ 170.8, 167.6, 144.6, 134

132.4, 131.1, 127.9, 123.2, 118.5, 110.3, 49.8, 36.4.

Similarly from 3-phthalimido-3-(3-cyanophenyl) propionic acid (1.60 g, 5.0 mmol), there is obtained 3-phthalimido-3-(3-cyanophenyl)propionamide as a white powder: mp 217°–220° C.; ^{1}H NMR (dmso-d_6, 250 MHz) δ 8.05–7.40 (m, 9 H), 6.99 (br s, 1 H), 5.90–5.75 (m, 1H), 3.50–3.10 (m, 2H); ^{13}C NMR (dmso-d_6) δ: 171.0, 167.7, 140.8, 134.6, 132.2, 131.5, 131.4, 130.8, 129.9, 123.2, 118.7,111.5, 49.7, 36.7.

EXAMPLE 33

To a stirred solution of phenyl isocyanate (2.2 mL, 2.4 g, 20 mmol) in acetonitrile (40 mL) is added a solution of L-glutamine (2.92 g, 20.0 mmol) and sodium hydroxide (20 mmol) in water (20 mL). The reaction mixture is stirred for 45 hours, partially concentrated to remove the acetonitrile, and washed with ethyl acetate (2×25 mL). The pH of the aqueous layer is adjusted to 1–2 with 4N hydrochloric acid, the resulting thick slurry filtered, and the solid washed with water and air-dried to afford 4.70 g (89%) yield of 2-(N-phenyluriedo)-4-carbamoylbutyric acid as a white powder.

2-(N-phenyluriedo)-4-carbamoylbutyric acid (2.00 g, 7.54 mmol) and carbonyldiimidazole (1.24 g, 7.95 mmol) in tetrahydrofuran (30 mL) are heated at reflux for 16 hours. The reaction mixture is concentrated and the residue slurried in water (25 mL), the slurry filtered, and the solid washed with water and air-dried to afford 0.63 g of N-phenyl-N'-(1,6-dioxopiperidin-2-yl)urea. After sitting, filtration of the filtrate afforded 0.70 g (38%) of the product as a white flocculent powder: ^{1}H NMR (dmso-d_6) δ 8.51 (s, 1 H, CONHCO), 7.6–7.2 (m, 6 H, Ar, ArNH), 6.83 (s, 1 H, NHCH), 4.26 (t, 1 H, CHCO), 2.4–1.8 (m, 4 H, CH_2CH_2); ^{13}C NMR (dmso-d_6) δ 173.2, 155.6, 132.2, 128.7, 127.7, 126.7, 55.7, 29.8, 27.2. Anal. Calculated for $C_{12}H_{13}N_3O_3$. Theoretical: C, 58.29; H, 5.29; N, 16.99. Found: C, 58.12; H, 5.17; N, 17.02.

EXAMPLE 34

Tablets, each containing 50 mg of active imide ingredient, can be prepared in the following manner:

Constituents (for 1000 tablets)	
active imide ingredient	50.0 g
lactose	50.7 g
wheat starch	7.5 g
polyethylene glycol 6000	5.0 g
talc	5.0 g
magnesium stearate	1.8 g
demineralised water	q.s.

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active imide ingredient, the lactose, the talc, the magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 ml of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 ml of water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35° C., forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

EXAMPLE 35

Tablets, each containing 100 mg of active imide ingredient, can be prepared in the following manner:

Constituents (for 1000 tablets)	
active imide ingredient	100.0 g
lactose	100.0 g
wheat starch	47.0 g
magnesium stearate	3.0 g

All the solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active imide ingredient, the lactose, the magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 ml of water and this suspension is added to 100 ml of boiling water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35° C., forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

EXAMPLE 36

Tablets for chewing, each containing 75 mg of active imide ingredient, can be prepared in the following manner:

Composition (for 1000 tablets)	
active imide ingredient	75.0 g
mannitol	230.0 g
lactose	150.0 g
talc	21.0 g
glycine	12.5 g
stearic acid	10.0 g
saccharin	1.5 g
5% gelatin solution	q.s.

All the solid ingredients are first forced through a sieve of 0.25 mm mesh width. The mannitol and the lactose are mixed, granulated with the addition of gelatin solution, forced through a sieve of 2 mm mesh width, dried at 50° C. and again forced through a sieve of 1.7 mm mesh width. The active imide ingredient, the glycine and the saccharin are carefully mixed, the mannitol, the lactose granulate, the stearic acid and the talc are added and the whole is mixed thoroughly and compressed to form tablets of approximately mm diameter which are concave on both sides and have a breaking groove on the upper side.

EXAMPLE 37

Tablets, each containing 10 mg of active imide ingredient, can be prepared in the following manner:

Composition (for 1000 tablets)	
active imide ingredient	10.0 g
lactose	328.5 g
corn starch	17.5 g
polyethylene glycol 6000	5.0 g
talc	25.0 g
magnesium stearate	4.0 g
demineralised water	q.s.

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. Then the active imide ingredient, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 ml of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 ml of water. The resulting paste is added to the pulverulent substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35° C., forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking notch on the upper side.

EXAMPLE 38

Gelatin dry-filled capsules, each containing 100 mg of active imide ingredient, can be prepared in the following manner:

Composition (for 1000 capsules)	
active imide ingredient	100.0 g
microcrystalline cellulose	30.0 g
sodium lauryl sulphate	2.0 g
magnesium stearate	8.0 g

The sodium lauryl sulphate is sieved into the active imide ingredient through a sieve of 0.2 mm mesh width and the two components are intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a sieve of 0.9 mm mesh width and the whole is again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a sieve of 0.8 mm width and, after mixing for a further 3 minutes, the mixture is introduced in portions of 140 mg each into size 0 (elongated) gelatin dry-fill capsules.

EXAMPLE 39

A 0.2% injection or infusion solution can be prepared, for example, in the following manner:

active imide ingredient	5.0 g
sodium chloride	22.5 g
phosphate buffer pH 7.4	300.0 g
demineralised water	to 2500.0 ml

The active imide ingredient is dissolved in 1000 ml of water and filtered through a microfilter. The buffer solution is added and the whole is made up to 2500 ml with water. To prepare dosage unit forms, portions of 1.0 or 2.5 ml each are introduced into glass ampoules (each containing respectively 2.0 or 5.0 mg of imide).

What is claimed is:

1. In the process of preparing thalidomide in which N-phthaloylisoglutamine or N-phthaloylglutamine is cyclized with N-N'-carbonyldiimidazole, the improvement which comprises cyclizing said N-phthaloylisoglutamine or N-phthaloylglutamine by refluxing a mixture of N-phthaloylisoglutamine or N-phthaloylglutamine, N-N'-carbonyldiimidazole and anhydrous tetrahydrofuran.

* * * * *

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

(NDA)/PLA # 20-785 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 540 Trade (generic) name/dosage form: (TRADE NAME) (Thalidomide capsules) Action: AP (AE) NA

Applicant Celgene, Inc. Therapeutic Class immunomodulator

Indication(s) previously approved none

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___ NA

✓ Indication in this application THE TREATMENT OF ERYTHEMA NODOSUM LEPROSUM

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

✓ M Wenkert Dr Ops 9/19/97

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig (NDA)/PLA # 20785
HFD 540 /Div File
(NDA)/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

25 April 1997

Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-785
Thalidomide Capsules
(Synovir™)
Debarment Certification
and Patent Information

Dear Dr. Wilkin:

Please find enclosed a statement from Celgene that the company has not used in any capacity the services of a person debarred under Section 306 (a) or (b) of the Federal, Food, Drug and Cosmetic Act. Also, please find enclosed information on and copies of patent number 5,385,901 Method of Treating Abnormal Concentrations of TNF α and patent number 5, 463,063 Ring Closure of N-phthaloylglutamines as submitted in NDA 20-785 on 20 December 1996.

Please do not hesitate to contact me with any questions or additional comments.

Sincerely,

Steve Thomas -KSC

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development

Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Tel 908-271-1001
Fax 908-271-4184

New Drug Application (NDA) 20-785

Debarment Certification

The undersigned hereby certifies that Celgene Corporation did not and will not use in any capacity the services of any person debarred under Section 306(a) or (b) of the Federal, Food, Drug and Cosmetic Act, in connection with New Drug Application (NDA) 20-785.

Steve Thomas, Ph.D.
Vice President, Pharmaceutical Development
Celgene Corporation

NDA 20-785

These items relate to the review of Celgene's responses to the toxicology concerns raised in the approvable letter for NDA 20-785 dated September 19, 1997. We expect complete resolution of the issues to be post-approval, i.e., Phase 4.

1) The submitted reproductive toxicity dose range finding studies in male and female rabbits appear to be adequate.

2) The Segment I reproductive toxicity study protocol appears to be adequate, but the dose selection for this study will need to be evaluated after completion of the two reproductive toxicity dose range finding studies.

3) It is unclear how the effect of the test article on the functional development will be measured in the submitted Segment III reproductive toxicity study protocol. It is recommended that Celgene clearly outline at the beginning of the protocol what will be examined for effects of the test article on functional development. This can be accomplished when the study is resubmitted after completion of the dose range studies. It is recommended that, at a minimum, the following tests be included in the protocol: a) spontaneous locomotor activity (in an open field), b) righting reflex and tilting plane, c) acoustic startle, d) passive avoidance, and e) schedule controlled behavior (operant learning tasks). Aside from this issue, the protocol outlined for the Segment III study appears adequate.

cc: NDA 20-785
Hill, HFD-540
Weintraub, HFD-105

PREP:WALLING 12/12/98
c:\wpfiles\toxfax.wpd

MEMORANDUM OF TELECON

DATE: July 7, 1998

APPLICATION NUMBER: NDA 20-785; Thalomid (thalidomide) Capsules, 50 mg

BETWEEN:

Name: Drs. Steve Thomas and David Stirling and Ms. Tricia Brooks
Representing: Celgene

AND

Name: Wilson H. DeCamp, Ph.D. (HFD-540), Dr. Chi-Wan Chen (HFD-830)
Ms. M. J. Walling (HFD-500)

SUBJECT: NDA 20-785/Celgene's Thalidomide

The call was placed by FDA at the request of the chemistry reviewer to discuss release specifications, stability data and assurance that the validated manufacturing process was not changed.

The following specific Phase 4 commitments were discussed and a request was made to provide in writing the following assurances.

1.. Please develop and propose a component qualification test/specification for the packaged drug product that will verify the integrity of the blister pack with respect to moisture vapor transmission. This should not be considered to be a regulatory specification. This commitment should be completed in six months.

2. Please commit to submission of the results of release testing results for lots 0091N, 0092N and 0149N, along with updated stability data for lots DEV 2775, 2800 and 2811, as well as release data for lots 0091N, 0092N and 0149N. These results will be used to evaluate the bulk drug and finished product specifications.

3. Please develop and propose a component qualification test/specification for the packaged drug product that will verify the integrity of the blister pack with respect to moisture vapor transmission. [

] This should not be considered to be a regulatory specification. This commitment should be completed in one year.

4. Please confirm, in writing, that the validated manufacturing procedures used to produce the market lots have not changed.

The following points were clarified:

1. Lots DEV 2775, 2811, and 2800 were produced prior to the validation, but were produced by the validated method. These particular lots are not the ones to be considered for extended expiration dating, nor are they the lots intended for marketing.

MEMORANDUM OF TELECON
July 7, 1998
NDA 20-785; Thalomid (thalidomide) Capsules, 50 mg

2. The lots intended for market are N0091, N0092 and N0149, all manufactured between May and June, 1997.

3. The granting of [ ] (extension to) expiry will be contingent upon submission and review of data from the lots, submitted subsequent to approval.

4.. The outstanding phase 4 commitments 5(a) (accumulation in fatty tissue) and 5(e) (solubility information) from the Approvable letter of Sept.19, 1997 were brought to the attention of the applicant.

5. The applicant was reminded of our request to submit typical COA's for the blister package components.

6. The applicant was reminded of our request for testing of the existing packaging component inventory (or the next batch obtained) to verify the claimed moisture vapor transmission rate for the components.

7. These Phase 4 commitments are not the only ones that will be in the letter, but the applicant already knows about the others.

8. A fax of the commitments and the language for the agreement will be sent to the applicant in order that Celgene can respond in writing prior to approval.

9. The issue for [ ] to monitor the Q.A. for the S.T.E.P.S. was agreed to.

Mary Jane Walling.

Mary Jane Walling
Project Manager

cc: NDA 20-785
IND 48,177
HFD-590/Div. Files
HFD-540/Div. Files
HFD-105/CSO/Walling
HFD-540/Chem/DeCamp MJW 7/9/98
HFD-830/DNDC3/Chen

TELECON

July 7, 1998

NDA 20-785

Please confirm, in writing, that the validated manufacturing procedures used to produce the market lots have not changed.

In addition, please commit, in writing, to conducting the following Phase 4 studies in the prescribed time lines. A facsimile of the commitment letter followed by a signed copy is preferable. A copy of this letter should be provided to Mary Jane Walling, fax 301-827-2317, as soon as is convenient.

1. Ongoing Study E003/P for efficacy should be continued and efforts should be made to expand the population in order to accrue the full compliment of subjects, as stated in our letter to you dated May 12, 1998.

2. Studies to demonstrate the absence or presence of thalidomide in sperm and/or semen.

3. Rat and mouse carcinogenicity studies.

4. Segment I reproductive toxicity study in rabbits.

5. Segment III reproductive toxicity study in rabbits.

6. Please develop and propose a component qualification test/specification for the packaged drug product that will verify the integrity of the blister pack with respect to moisture vapor transmission. This should not be considered to be a regulatory specification. This commitment should be completed in six months.

7. Please commit to submission of the results of release testing results for lots 0091N, 0092N and 0149N, along with updated stability data for lots DEV 2775, 2800 and 2811, as well as release data for lots 0091N, 0092N and 0149N. These results will be used to evaluate the bulk drug and finished product specifications.

8. Please develop and propose a component qualification test/specification for the packaged drug product that will verify the integrity of the blister pack with respect to moisture vapor transmission. This should not be considered to be a regulatory specification. This commitment should be completed in one year.

cc:
NDA 20-785
IND 48,177
HFD-590/Div. Files
HFD-105/CSO/Walling
HFD-540/Chem/DeCamp
HFD-540/Tox/Hill
HFD-550/Biopharm/Bashaw
HFD-830/ONDC/DD

20-785
INFORMATION REQUEST

RECORD OF MEETING

DATE: May 29, 1998/9:00am

PLACE: Corporate Blvd/200A

ATTENDEES: Drs. Birnkrant, LePay, ElHage, Vega, Rodriguez, MJ Walling

SUBJECT: NDA 20-785/Celgene's thalidomide: post approval inspection of registry sites

A paragraph will be added to the Approval letter delineating the inspection plan frequency and intent to hold subsequent meeting(s) with the sponsor to discuss the results of the inspection(s).

A checklist for inspectors will be developed based on the responsibilities (using the contracts in the STEPS) of each of the Celgene contractors, i.e., [ ]

We will request a list of the registered prescribers.

The data entry forms for [ ] will be requested from the sponsor.

Portions of the label will be added to the inspectors checklists for the purposes of training.

Two more meetings with this group will be scheduled.

[ ] SOPs will be requested.

PREP:MJWALLING/0529/98
inspmins/wpd

Dr. Friedman will alert the department about the meetings.

PREPBY:MJWALLING:08/25/97
REVBY:MWEINTRAUB:08/26/97
thalmins.wpd

ADDENDUM

Ms. Pendergast's's office, HRSA, NIH and the FDA Press Office have been contacted. Orphan Drug contact (Mike Dreif) indicated that Celgene has applied for the Orphan designations as stated above and been granted designation for ENL. In addition,
[

3

May 22, 1998

IND: 48,177
Serial Number 055

NDA: 20-785

Steve Thomas, Ph.D.
Celgene Corp
7 Powder Horn Drive
Warren NJ 07059
Fax 732-271-4184

The revised mouse and rat oncogenicity protocols appear to be adequate.

HFD-105/Walling
HFD-540/Hill
NDA 20-785
IND 48,177

NDA 20-785, Serial Numbers 047 and 048

Record of telecon

Date: May 13, 1998/2:30-4:00p

FDA Participants: M. Weintraub, MJ Walling

Sponosr: Celgene Corp- K. Kook, S. Thomas, B. Williams< D. Stirling

Subject: Celgene's NDA 20-785/thalidomide for ENL/the review of NDA 20-785, Serial Numbers 047 and 048.

The language for the label, particularly the neuropathy, was discussed.

The reviewers' comments on the Patient Education Video were relayed.

The sponsor will resubmit revised labeling and the video when available.

See attached faxed to sponsor on May 13.

Attachments

cc; NDA 20-785
HFD-105/Walling
HFD 530/Birnkrant

RECORD OF TELECON

DATE: May 24, 1996/11:45am

FDA REPS: D. Bashaw, M. Weintraub, M.J. Walling

SPONSOR: S. Thomas, K. Kook, Wayne Coburn/ Celgene

SUBJECT: IN 48,177/Celgene's Thalidomide for ENL/PK requirements

The call was placed by FDA to respond to concerns voiced by representatives of Celgene in a fax dated May 10, 1996 (attachment 1).

The sponsor specifically had concerns about a metabolism study in leprosy patients employing radiolabel, mentioned to them in a May 6 teleconference. That teleconference was followed by a fax (May 15)outlining the requested studies (attachment 2). Today's call was meant to clarify the May 15 memo, specifically, the overall objectives of the study requested.

The sponsor had sent in 14 reprints which Drs. Weintraub and Bashaw had reviewed.

Dr. Bashaw stated that we had deferred much of what would be ordinarily requested preapproval but that we needed metabolism data in a definitive population (leprosy). He stated that the articles were helpful and suggested that Celgene and the consultants distill the published data into a summary report and based on the information presented in the literature, design a study that would allow the appropriate primary and secondary metabolites to be quantified (unlabeled) in plasma from 3-5 patients.

Dr. Coburn stated that ordinarily metabolism studies would be done in normal volunteers. Dr. Bashaw stated that in this case, due to rarity of the patient population, we would accept dose escalation in normals and do the metabolism study in patients.

Dr. Coburn asked about p 450 human metabolism studies done in vitro. Dr. Bashaw said that would be fine for studying drug-drug interactions.

The Celgene representatives agreed to have the draft study protocol done by the June 12 meeting. FDA indicated that they

should call if we could provide any guidance or answer questions.

Cordial

attachments

cc: file
Blay
Wilkin
Weintraub

3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

22 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

RECORD OF A MEETING

TIME/PLACE: April 1, 1998/10:00am/MPN 1 room 120

PARTICIPANTS: Walling, Hartman, Blumenshein, Birnkrant, Woollen, Miracco, Vega, Lepay

SUBJECT: NDA 20-785/Celgene's application for thalidomide: post market audits/inspections of the S.T.E.P.S.

DISCUSSION: Members of OC, OEB, ODE IV and ODE V met today to discuss the post market audits/inspections to be conducted starting in the first quarter after launch (TBD but in no case later than July 27) of the drug and continuing on an ad hoc basis as needed throughout the distribution of this drug.

1- DMPQ in the Office of Compliance will coordinate the inspections with the field.

2- The sites are in Dallas for [ ](the pharmacy registry), New Jersey (the sponsor), and Boston (the physician and patient registry).

3- Members of OEB, ODE IV and ODE V will generate a list(s) of what information needs to be reviewed and validated by the inspectors. The list is due to me by April 13. This list will be given to OC to design the inspection request.

4- OC believes we have the authority to issue notices of inspection and inspectional findings under the regulations since this drug will be approved under 21 CFR 314.500 Subpart H. They will check about the authority for inspecting pharmacies.

5- We will meet again as necessary.

6- A similar initiative is ongoing for clozapine. The efforts should be harmonized as to process and possibly objectives. OC will arrange if appropriate.

CC: attendees
Woodcock
Weintraub
Famulare
NDA 20-785

ocsteps.wpd

NDA 20-785

PHARM TOX COMMENTS to be relayed to sponsor.

March 27, 1998

1- Please submit the final study report for the 52 week toxicity study conducted in dogs to the IND (IND 48,177) for proper tracking purposes.

2- Please submit any additional nonclinical studies fort thalidomide to both the NDA (NDA 20-785) and the IND (IND 48,177) for proper tracking purposes

cc: IND 48,177
NDA 20-785
HFD-540/HILL
HFD-105/WALLING

3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

SEP 19 1997

NDA 20-785

Office Director's Review Memorandum of NDA 20-785

NDA 20-785

Sponsor:	Celgene Corporation 7 Powder Horn Drive Warren, NJ 07059 (908) 271-1001
Drug:	Thalidomide: Synovir™
Pharmacologic Category:	Immunomodulator
Proposed Indication:	Erythema Nodosum Leprosum (ENL)
Dosage Form:	Thalidomide 50 mg Capsules
Route of Administration:	Oral
NDA Drug Classification:	1P
Related Drugs:	None
Related IND/NDA(s):	IND 48,177,IND 11,359

Documents Reviewed:
Medical Officer's Review of NDA 20-785, dated Aug 13, 1997; Secondary Medical Officer's Review, dated Aug 13, 1997, Addendum to Major Amendment Review, dated Sep 3, 1997, Addendum Review of Draft Data Listings for Study E-003/P, dated Sep 3, 1997; Division Director's Review Memorandum, dated Aug 15, 1997, Addendum to Division Director's Review Memorandum, dated Sep 9, 1997; and Clinical Pharmacology/Biopharmaceutics Review Addendum, dated Aug 15, 1997.

FOREWORD

There are five points that I would like to make in overriding the memorandum and reviews that came out of the Division of Dermatologic and Dental Drugs. They are: 1) Efficacy, 2) Safety, 3) Bioavailability, 4) Historical Data, 5) Distribution System proposed by Celgene and its impact on the status of thalidomide.

COMMENTS

Thalidomide Efficacy in Erythema Nodosum Leprosum

The kind of evidence that one requires for an orphan drug, such as thalidomide, is somewhat different from the randomized controlled clinical trials that make up part of the usual NDA. I viewed the efficacy of thalidomide on a concurrence of evidence standard rather than on a standard involving randomized controlled clinical trials. Of course, if those trials were available, it would be wonderful. Unfortunately, in this case we don't have controlled clinical trials that were submitted for our review. One of these purportedly was Dr. Hastings' study. On its face the study as published seemed to be quite good. However, there were some patients missing and other problems with the study, such as naming the medications by the period that they were used in rather than the fact whether they were placebo or active thalidomide. There were just too many problems to make that study acceptable to us even in the concurrence of evidence model. Much more impressive is the study by Iyer and colleagues but even so, this study does have certain problems with the entry criteria and the data. Nonetheless, it is a double blind clinical trial, perhaps not against the most effective comparator but against ASA used in a reasonable, although low, dose. The skin lesions in this study cleared at eight days in about a 75% to 26% percent rate (thalidomide vs. acetyl salicylic acid).

In seeking the weight or concurrence of evidence, one would like to have consistency between the data submitted for this application and the world's literature and experience. It is like putting together a jigsaw puzzle by fitting various pieces together. We have a great deal of material from the world's literature, from Dr. Yoder and his experience, and from Dr. Rae and his experience as well as others. We also have the nonrandomized studies, reports, and patient care material in the literature. In general, Dr. Rae and Yoder, have established a standard of care with criteria that have seemed to work for them for many years. However, it is very difficult to interpret, particularly Dr. Yoder's data, in the way we would like to have it gathered together and analyzed and then placed in the context of the established methodology for treating leprosy patients with thalidomide.

That brings us to Dr. Rae's data which I feel help tip the balance towards thalidomide's efficacy. These data are not perfect but represent a way of assessing his clinical information and seeing that it is consistent with the world's literature and therefore with the type of results that we could use to approve a drug for the cutaneous manifestations of ENL. Of course, we had to go out to Los Angeles and collect the data, bring them back to Rockville and analyze them. We found that some important aspects of the data, including systemic and toxicity information were not collected. But even more important, the data themselves were handled in a way that may have led to errors in some cases. Dr. Rae's data were of the challenge, dechallenge, rechallenge type. They weren't even an "N of 1" type of study because they did not have placebo controls. To analyze these data I looked at the cleanest of all of the patients, the subset (46) of patients who had not received prednisone, clofazamine or high dose aspirin. There certainly is a possibility that these patients were on aspirin, were on ibuprofen, were on acetaminophen but they were the cleanest available patients. In examining them, it seemed to me that there were twenty-four patients who clearly had a least one challenge and dechallenge experiment that was

positive. Often they had as many as seven. In addition, there were fifteen who I called negative and there were seven who clearly had so little data that it was practically impossible to say anything about them. The twenty-four patients represented a 52% response rate. I required that no new lesions appear. I could not and did not pay attention to the other symptoms of ENL or even of the systemic manifestations of the ENL. What is also quite clear is that the dose of the drug was standardized and handled very much as if good clinicians were aware of and involved in the patient care. Certainly the subjective analysis that I carried out is open to critique by others who may interpret the information differently. However, I believe the data are clear and show that ENL can be treated with thalidomide as the major medication.

In the 102 patients there were forty-six on thalidomide alone and fifty-six on thalidomide with prednisone and/or clofazamine. There were also some patients who were on clofazamine alone for some or all of the episodes. It became clear to me that thalidomide could be used as adjunctive therapy for these patients as well as sole therapy for the lesions for ENL. There are a number of patients who received prednisone as well as thalidomide and had the prednisone tapered although thalidomide was continued. Thalidomide was then also tapered. At some later time when the patient was off both drugs, the lesions of ENL recurred. The patients were put on either a higher dose of thalidomide or a lower dose of thalidomide and prednisone. In looking at just at the occasions when thalidomide and prednisone were used, the prednisone was tapered down, usually very slowly over a year period and then was stopped. Thalidomide was continued for several months or years after that and then it too was stopped. When the lesions recurred, the thalidomide was reinstituted. These examples led me to conclude that thalidomide had spared the patients from prednisone. In addition, thalidomide can be used as adjunctive therapy with prednisone.

From Dr. Rae's studies, we have some idea about the dose of thalidomide. Generally, the dose of 100 mg. a day was used as the starting dose. This could be increased to 200 or 300 mg. per day. However, if doses of 300 mg. per day seemed necessary, the tendency would be to start prednisone to get better control of the ENL and to avoid the sedative properties of thalidomide.

Because of the type of data that we collected from Dr. Rae's clinic, I believe we should be rewriting the indication for thalidomide to be for the treatment and prevention of the appearance of new lesions of erythema nodosum leprosum.

Another aspect of the understanding of thalidomide and its actions is the current trial in the Phillippines comparing 100 and 300 mg. per day. It is too early to really assess the full import of this trial it provides another sort of evidence. While all of the patients are receiving thalidomide, the fact that it's a dose response study may make it more valuable. Just looking at the crude levels that were shared with us, we see that the response rate was again around 50%.

Unfortunately, we don't have much data on the time to response. I believe, however, what information we do have indicates that it should be approximately two weeks. We may be able to begin thalidomide dosing with Celgene's product in a way which allows for the collection

of data, on dose adverse effects, duration of therapy, and how long before one can expect to see a clinical response. We can accomplish this by instituting therapy in ENL patients, for example, at Dr. Rae's clinic site, under the IND. We would ask him just to treat his patients using the usual standard of care conditions but, see them perhaps somewhat more frequently. Again, we will not have data in a randomized controlled clinical trials sense. What we have is a confirmation of long use by reasonable clinicians who are expert in their field. This confirmation, of course, may be flawed because it comes from historically controlled information.

The Safety of Thalidomide:

I believe that the main toxicities of thalidomide, neuritis and the fetal toxicity, are both known and well described in their manifestations. Questions remain, however. What isn't known, is that it may or may not be dose related, the incidence in ENL, the possible confusion with the neuritis of leprosy, how one would monitor the presence for neuropathy either by physical examination or by some sort of testing. I believe that the simple physical examination using monofilament testing may be good enough to establish the presence of the syndrome. However, I also believe that the use of a vibration sensation measuring device would be an earlier warning and allow for better definition of the start of the syndrome.

Sedation, which may be thought to be an adverse effect for the use in ENL, can be dealt with by dosing the drug before the patient goes to sleep.

More important are the skin rashes, temperature spikes, edema, and particularly the bradycardia and hypotension which have occurred in HIV patients and to a lesser extent in leprosy patients. The occurrence of skin rash is usually greater in HIV patients and it has not been seen to any extent in the leprosy patients. The edema more likely is associated with the response to ENL but the mechanism is unknown. I think we can take care of the fever, bradycardia and hypotension by dosing the patients during the day and testing their response in the Phillippines. This would mean changing the protocol, however, that could be done without putting too much of a burden on the company or the physician's taking care of the patients. The incidence of neutropenia which occurred in the aphthous ulcer study of thalidomide in HIV patients, is confounded to a certain extent by the fact that patients with white counts of 500 could be entered into that trial. Therefore, while I am convinced that we have to pay some attention to the problem, I don't see it as a safety deterrent in either ENL or other patients with a higher white count. The increase of the HIV load as measured in that study is also of concern. However, there are several points to consider while at the same time paying attention to the possibility that it was a real finding. The authors of that study mentioned that the increased virus number may be within the measurement error of the assay. In addition, the patients were studied at a time when protease inhibitors had not become widely used. If protease inhibitors are included in the regimen of the patients, there may not be an increase in viral loads. The only way to find out, of course, would be to do a clinical trial.

By the concurrence of evidence and the long history of thalidomide use the safety profile has been well described and laid out. Unfortunately, we never do know enough about drugs which have been on the market even for twenty or thirty years. When the drugs have been sold

for a long time but hardly used, newly discovered toxicity can become manifest when they are presented more widely. There may have been changes in the population receiving the medication or newer medications or aspects of the diet which didn't exist at the time when the drugs were first used, for example. However, in this case, I believe we have a reasonable picture of the toxicity so that the label can be written. Once again we must remember that thalidomide has an orphan indication.

Pharmacokinetics:

Certainly the Celgene capsule of thalidomide is not bioequivalent to the Tortuga tablets that it was tested against. It may or may not be equivalent to other lots of that particular tablet or other tablets either. However, those tablets were neither standardized nor reference products of thalidomide. It, thus, would really be difficult and not meaningful to achieve a bridging study showing equivalence between those tablets and Celgene's product. What we do know is that the Celgene material will be a well-made capsule of standard manufacturing (GMP), raw material, and bioavailability with its other characteristics well characterized. In fact, it may be better than many of the tablets currently being sold as unlabeled material.

There are some other pharmacokinetic issues. We do need more information about thalidomide's distribution and its steady state levels. We should have peak and tough levels in 1- 2 months, however.

We have to remember that there is really no drug against which to check Celgene's thalidomide. What we have to do is give the doctors a starting point and an ending point and let them manipulate the dose as they see fit, raising it initially and then lowering it as the patient improves. Later, after the desired efficacy is achieved, the medication can be stopped. This is actually standard for dermatologists and many other physicians. Unfortunately, while taught in medical school, dose adjustment, is not a universal practice. However, it can be made part of the educational process for the use of thalidomide.

Historical Data:

While historical data is the least desirable and the most often misleading type of data, it is listed in the regulations. Historical data is the final type of evidence named as a control of an acceptable study. Not only is historical data part of the evidence by which safety and effectiveness can be tested and established but, in addition, the FDA can make a judgment on whether or not the historical data are valid. In this case, I made a judgment that, given the totality of the information that we have on thalidomide, the historical data are acceptable in this drug approval.

We may be at the fourth of the seven stages that Dr. McKinaly described, or not. I believe that several randomized clinical trials have not been done. Denunciation has started but the erosion and loss of credibility hasn't yet begun. However, the advisory committee voiced its support in word and in votes. In my judgment, the data we have are sufficient to approve thalidomide for ENL.

The Value of the Distribution System:

The system seems to be a well-written program for the education and testing of physicians and pharmacists. It will be a mandatory rather than a voluntary system and it will cover the critical elements of the program. It will discuss toxicities, particularly the fetal toxicity, neuropathy, sedative effects and the other importance adverse effects. Celgene will be able to make the program work well, certainly with the patients knowing what test the physician is supposed to do and what responsibility the patient has in the entire system. There is a continual feedback mechanism with pregnancy testing and pharmacists check of the program's integrity. In supplying thalidomide to the pharmacy in just the appropriate doses we'll have another balance to the system. Pharmacists and physicians will be working together to validate that the system is working. In addition the company has built in a method for evaluating both the pharmacists and the physicians. They can withdraw permission to send any more drug or have the physician write for any more medication by canceling his or her registration. Of course, the program is not perfect. Lou Morris, Ph.D., (Drug Marketing, Advertising and Communications/HFD-40) has made a number of suggestions to improve the program and to make it even better. However, as he said at the advisory committee meeting, he felt that the system could work very well.

Some physicians are concerned about thalidomide finding its way to the street for use and abuse as a sedative agent. I don't think it is likely. Even if it does appear on the street, the control of giving small amounts ≤(28 days) of drug makes it less likely that the medication could be diverted into sales as a drug of abuse.

The other improvement on the system for controlling thalidomide will be a phased-in distribution system. There is a possibility of limiting the company to twenty or thirty physicians in the country to test and assure the FDA that the system will work and that the materials are good and understood by the patients and physicians. This puts another layer of certainty on the distribution system and also another general picture of safety and checking of the materials for instructions of both the physician and the pharmacist. This is one of the tasks that will take place during the time from the approvable letter and the final approval and then in the early periods of the drug availability.

If thalidomide is a subpart H drug we will have very direct and expedited ability to remove the drug from sale if we have evidence that the system is not working.

SUMMARY

The approvable letter will be signed out with the indication for the treatment of new lesions in moderate and severe cutaneous ENL. I believe that the efficacy information supports that indication. The FDA invoked its judgment on the historical data. In this case, with the addition of Dr. Rae's challenge, dechallenge, rechallenge information, I believe that we have sufficient evidence for proof of efficacy. I believe that the safety profile has been well defined and that the special kinds of safety problems that were pointed out in the reviews and also in the advisory committee discussion will be handled in the labeling. I believe that the

pharmacokinetic data are quite clear. There is no reference formulation. Therefore, this formulation does not have to be bridged back to any other. I also believe that the distribution scheme will be valid and function well. It represents the best way to get the thalidomide to the patients while insuring a safe prescribing and distribution of the medication.

Unfortunately, there will be a tragedy at some time or other. It is guaranteed because of the way the drug will be used and because of the way patients take medications, share medications and don't understand or misunderstand what they have been taught. Also physicians can prescribe poorly, not teach appropriately and not prescribe to the right people or for the right indication. Pharmacists also don't perform their dispensing job and an information checking job perfectly. The patient may not see the appropriate pharmacist at the pharmacy. All of these factors create the climate for a tragedy. The tragedy may not only be fetal toxicity problem but a sensory neuropathy problem or some other serious adverse effect. However, all medications which work carry some risks. We have appropriately judged the risk/benefit relationship for the use of this medication. We, and Celgene, will create a good program for the distribution and control of the medication. Finally, in establishing this carefully enforced distribution system will allow us to control, more closely, unlabeled thalidomide then we are now able to do.

/MWeintraub 9/19/97

Michael Weintraub, M.D.
Director
Office of Drug Evaluation V

cc:
Orig NDA 20-785
HFD-001/Woodcock
HFD-002/Lumpkin
HFD-540/Div File
HFD-540/DIV DIR/Wilkin
HFD-540/MO/Vaughan
HFD-540/MO/O'Connell
HFD-540/CHEM/DeCamp
HFD-540/PHARM/Hill
HFD-540/PHARM TL/Jacobs
HFD-725/BIOSTAT/Gao
HFD-725/BIOSTAT TL/Srinivasan
HFD-880/BIOPHARM/Bashaw
HFD-540/PROJ MGR/White
HFD-105/Walling

NDA 20-785

Addendum to Division Director's Review Memorandum of NDA 20-785

NDA 20-785

Sponsor:	Celgene Corporation 7 Powder Horn Drive Warren, NJ 07059 (908) 271-1001
Drug:	Thalidomide; Synovir™
Pharmacologic Category:	Immunomodulator
Proposed Indication:	Erythema Nodosum Leprosum (ENL)
Dosage Form:	Thalidomide 50 mg Capsules
Route of Administration:	Oral
NDA Drug Classification:	1P
Related Drugs:	None
Related IND/NDA(s):	IND 48,177 and IND 11,359
Documents Reviewed:	Clinical Pharmacology/Biopharmaceutics Review Addendum, dated Aug 15, 1997 Secondary Medical Officer's Review of NDA 20-785, Addendum to Major Amendment Review, dated Sep 3, 1997 Addendum Review of Draft Data Listings for Study E-003/P, dated Sep 3, 1997

SEP 9 1997

FOREWORD

After discussing and reviewing the cited addenda to the secondary medical officer's reviews of NDA 20-785, I concur with the secondary medical officer, and I have supplemented selected medical review discussion points under COMMENTS (vide infra).

I concur with the Addendum to the Clinical Pharmacology/Biopharmaceutics Review which "clarifies the Division of Pharmaceutical Evaluation - III's position regarding the approvability of Celgene's thalidomide product." The new Conclusion section states:

"Based on the information provided by the applicant it is clear that Celgene's thalidomide product is markedly different and bioinequivalent to the Tortuga product. Any attempt to 'bridge' the Tortuga clinical experience to the Celgene experience is unsupportable based on this finding of bioinequivalency. This leads to a two-fold biopharmaceutic recommendation:

1. Provided that the Celgene NDA can stand on its own clinical data and that they honor the commitments they have made to the Agency, then the application would be acceptable to the Division of Pharmaceutical Evaluation-III under the provisions of 21 CFR 320.21.

2. Should approval of the Celgene NDA require use of the Tortuga database, the applicant would have to demonstrate bioequivalency between the products. Bioequivalency is the only way in which the Agency has accepted cross-product/cross-formulation data to be used. As they have already demonstrated the bioinequivalency of their product to Tortuga's the use of this data to support either clinical efficacy or safety would not be possible due to the observed statistically significant differences in the plasma level profiles. The net result of this would be to render the clinical data portion of the NDA unacceptable."

Since less than 30 patients with ENL are known to have been exposed to Celgene's thalidomide formulation for more than one dose, there are insufficient data to conclude that "the Celgene NDA can stand on its own clinical data..." Although not all of the data in the NDA are based on the Tortuga formulation, it was the only formulation compared with Celgene product AND it was "markedly different and bioinequivalent".

SIGNIFICANT FINDINGS IN THE MEDICAL REVIEW ADDENDA CITED

1. The single isolated record from the LA data set available for review disclosed the use of aspirin and NSAIDS. Since the medical literature describes mild ENL resolving with NSAIDS, and since the data summary sheets do not qualify the severity of the ENL, it is not possible to extract a thalidomide-only effect from the data summary sheets.

2. The efficacy parameters in E-003/P are fever and cutaneous lesions. The Sponsor's analysis of both endpoints is flawed. Fever was assessed by the Sponsor based on axillary temperatures. The original protocol stated that oral temperatures would be obtained, and the endpoint was based on an oral temperature at or below 98.7°F. Since the Sponsor obtained axillary temperatures which are approximately one degree less than the corresponding oral temperature, the oral temperature endpoint of 99.7°F must be adjusted to 98.7°F for an analysis of axillary temperatures. Thus, instead of 9 complete responses out of 20, there were only 4 out of 20.

The skin lesions are enumerable. However, the Sponsor has chosen a post-hoc algorithm to "convert" estimated lesion counts, e.g.,

few = 2
some = 4

more = 5
most = 7
5-10 = 7
< 10 = 7
> 5 = 7
< 5 = 3
3-5 = 4

Although the presence of new lesions as a primary outcome is quantal, the apparent inability of the sponsor to precisely count less than 10 lesions degrades the information content to be gained from this trial.

COMMENTS

1. The Chemistry Team Leader indicated to me in a personal communication that there is a substantial stockpile of thalidomide at Carville. Dr. Cynthia Moore of the CDC describes the stockpile as sufficient to last to the end of the millenium.

2. Mandatory restriction of distribution is discussed in 21 CFR 314.520, "Approval with restrictions to assure safe use." This section occurs within "Subpart H - Accelerated Approval of New Drugs for Serious or Life - Threatening Illnesses." The first section in Subpart H is 314.500, "Scope." My interpretation is that 314.520 is subsumed by 314.500, since "Scope" refers to the entire Subpart and not 314.510 alone.

21 CFR 314.500:

"This Subpart applies to certain new drug and antibiotic products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy)."

21 CFR 314.520:

"If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product such as:
(1) Distribution restricted to certain facilities or physicians with special training or experience; or
(2) Distribution conditioned on the performance of specified medical procedures..."

Thus, my interpretation is that for restricted distribution under 314.520 the drug product must be consistent with the subpart under which it is subsumed, viz., Subpart H (New Drugs for Serious or Life-Threatening Illnesses).

CONCLUSIONS

1. I reaffirm my previous conclusion that "there is no compelling evidence that thalidomide is effective for life-threatening or severely debilitating forms of the ENL syndrome..."

2. If Celgene's thalidomide is not effective for life-threatening or severely debilitating forms of the ENL syndrome, then it may not be eligible for consideration for mandatory restriction of distribution under Subpart H. Since there are no drugs with restricted distribution under Subpart H, there is no case law to further interpret this Subpart and its Scope that would suggest an alternative interpretation.

3. If a restricted distribution of thalidomide cannot be mandated, then this would further deteriorate the risk-benefit relationship of thalidomide to prevent new lesions of cutaneous ENL.

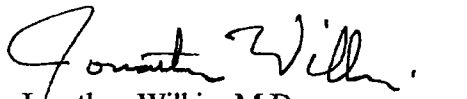
4. Patients with ENL in the United States will be able to obtain thalidomide for several years, so an acute shortage of thalidomide for ENL cannot be the basis for an Approval action at this time.

5. Since an acute shortage in supplies of thalidomide is not likely to occur within a year or two, there is sufficient time available before Approval in which thalidomide can be compared against an active control in the treatment of ENL and the serious question of whether thalidomide promotes the increase of HIV RNA can be addressed rigorously.

RECOMMENDATION

I recommend that this application be NOT APPROVABLE. However, the Sponsor should be informed that a well-designed randomized clinical study of thalidomide that incorporates an arm with an anti-inflammatory drug and a sedative (both at appropriate doses) may provide sufficient evidence of safety and efficacy to permit a more favorable regulatory decision. Such a study would be in addition to the ongoing clinical trial, E-003/P, with modifications such as more sensitive neurologic testing.

In addition, the Sponsor should look at the issue of increased HIV RNA in thalidomide treated subjects, if it is anticipated that off-label use will NOT be prevented by a successful, regulatory mechanism.



Jonathan Wilkin, M.D.
Director, Division of Dermatologic
and Dental Drug Products

cc: NDA 20-785
HFD-540
HFD-540/CSO/White
CH/DeCamp
PH/Hill/Jacobs
DivDir/Wilkin/smc/9/9/97
HFD-725/STATS/Gao/Thomson/Srinivasan
HFD-880/BIOPH/Bashaw

DATE: August 25, 1997
TIME: 9:00-10:30am
LOCATION: Conference Room 14-68, Parklawn

ATTENDEES: Dr. Michael Friedman, Dr. Randolph Wykoff, Dr. Janet Woodcock, Dr. Michael Weintraub, Dr. Jonathan Wilkin, Dr. Debra Birnkrant, Ms. Dianne Maloney (by telephone), Ms. Mary Jean Kozma-Fornaro, Ms. Mary Jane Walling

MEETING PURPOSE: This meeting was held to discuss possible distribution scenarios for thalidomide manufactured by Celgene for the intended purpose of treating erythema nodosum leprosum, should the drug be approved for that indication.

BACKGROUND: The Center for Drug Evaluation and Research has under review a New Drug Application (NDA 20-785) for thalidomide. The sponsor of the application is Celgene Corporation. The proposed indication is for the treatment of erythema nodosum leprosum, a syndrome observed in a small number of patients with treated Hansen's disease. The sponsor has applied for and been granted Orphan designation for this indication and three others, i.e., HIV associated wasting, aphthous stomatitis in immunocompromised patients, and atypical TB. The United States Public Health Service, under an IND, has been dispensing the drug to Hansen's disease patients through the Gillis W. Long Hansen's Disease Center in Carville, Louisiana either on an inpatient or out patient basis through PHS facilities for almost 30 years. Thalidomide is the drug of choice as recommended by the World health Organization. The drug has been supplied by various manufacturers over the years. The quality of the drug, i.e., dissolution specifications and bioavailability, has been variable as determined by FDA labs. The drug (Brazilian source) has been available through unregulated buyers' clubs.

In addition to the NDA, the Center is reviewing a number of Investigational New Drug Applications held by this sponsor and others for the indications of HIV associated wasting, aphthous stomatitis in immunocompromised patients, [

On the 4th and 5th of September, there will be an FDA Advisory Committee meeting to discuss safety, efficacy, labeling, and distribution of this drug for this indication. On September 9th and 10th there will be an interagency sponsored (FDA and NIH) meeting to discuss the development of this drug for other indications.

HIGHLIGHTS: Dr. Friedman asked if there was enough evidence for approval of the application. Dr. Woodcock responded that there was some disagreement in the Center, but that based on what she has seen so far she believes it is effective but she would review the data and that there was voluminous anecdotal data that the drug was effective. Dr. Weintraub believes there is evidence for efficacy. Dr. Wilkin allowed as how the Division believed there was some evidence for efficacy. There are issues of safety, i.e. neuropathy and teratogenicity, and dosing.

Distribution scenarios were discussed, the most restrictive being [redacted] The second scenario provides for either Subpart H or voluntary (by the sponsor) agreement to label the drug in order to partner the physician and pharmacist to assure that the patient has met certain criteria (in this case a negative pregnancy test) before a prescription is dispensed, as in the Sandoz experience with clozapine. The idea of [redacted] was discussed and considered not be an option that we would contemplate. A good model as a starting point is the Accutane experience which is voluntary on the part of Roche and includes patient and physician education packets and labeling which contraindicates the use of the drug without adequate birth control and evidence of a negative pregnancy test. The last scenario was one under which the physician would obtain signed informed consent and provide (by the physician and/or the pharmacist) the patient package insert as in the proposed Medication Guide.

The CDER consensus was to include the pharmacist as with clozapine. Dr. Friedman indicated that we would ask for (1) a physician certification program, (2) mandatory Medication Guide, (3) signed informed consent, (4) physician and pharmacist education program, (5) limit dispensing to a 28 day supply, (6) black box warning, (7) review of production records, and (8) maintenance of both a pregnancy registry and an ADE registry. Dr. Weintraub added a negative pregnancy test to be obtained every month initially and then less frequently.

ACTION ITEMS: Mary Jane Walling will contact HRSA, NIH Office of Women's Health, NICHHD, FDA Media (Mr. McClearn), and Ms. Pendergast's secretary to make sure that they know about this meeting She will verify the status of Orphan designation for ENL and other indications.

Dr. Woodcock will speak with Dr. Cynthia Moore of the CDC about their presence at the AC meeting.

Division Director's Review Memorandum of NDA 20-785

NDA 20-785

AUG 15 1997

Sponsor: Celgene Corporation
7 Powder Horn Drive
Warren, NJ 07059
(908) 271-1001

Drug: Thalidomide; Synovir™

Pharmacologic Category: Immunomodulator

Proposed Indication: Erythema Nodosum Leprosum (ENL)

Dosage Form: Thalidomide 50 mg Capsules

Route of Administration: Oral

NDA Drug Classification: 1P

Related Drugs: None

Related IND/NDA(s): IND 48,177 and IND 11,359

Documents Reviewed: Medical Officer's Review of NDA 20-785, dated July 28, 1997
Secondary Medical Officer's Review of NDA 20-785, dated Aug 13, 1997
Statistical Review and Evaluation of NDA 20-785, dated Aug 7, 1997
Clinical Pharmacology/Biopharmaceutics Review dated Aug 13, 1997

FOREWORD

After discussing and reviewing the cited reviews of NDA 20-785, I concur with the two medical reviewers, and I have supplemented selected medical review discussion points under COMMENTS (vide infra).

The cited Statistical Review and Evaluation does not directly comment on approvability. Thus, it is difficult to state that I concur with their recommendation, since it remains unstated. However, I do concur with the following statements in their Summary and Conclusions:

1. This data set is not from an adequate and well-controlled clinical trial.
2. There was no control group for comparison, which seriously impacts the efficacy evaluation and risk associated with use of thalidomide.
3. There was not only a serious problem due to missing data, especially in recording the severity of the disease such as lesion size, erythema status, tenderness and number of lesions, but also in recording advent (sic: adverse) events and safety associated with drug use.
4. Virtually no adverse event data was collected. The percentage of missing data in these categories ranged from 86% to 94%.
5. ...it was decided that summary statistics using patient as an observational unit could not be meaningfully performed.
6. Great caution should be exercised in the interpretation of these summary statistics.
7. It is not known how much of these differences are due to concurrent medications such as prednisone and clofazimine, the waxing and waning of the disease, or to the massive amount of missing data.
8. It should be noted that this analysis is very likely to mask the fact that ENL could be present or active during the on-thalidomide episodes even though it may not be present at the last visit.
9. The sample size for the truncated off-thalidomide episodes was too small to provide a meaningful comparison with the truncated on-thalidomide episodes.
10. Due to the total absence of any safety and adverse event data, no benefit to risk evaluation can be made.

I do not concur with the final sentence in the Conclusions section of the cited Clinical Pharmacology/Biopharmaceutics Review: "Given that this drug is being approved for an orphan indication and given that the applicant has done pharmacokinetic studies with their clinical and to-be-marketed dosage forms, the amount of information submitted in support of this NDA is sufficient for approval provided that the applicant makes a firm commitment to supply the other information outlined in this review in a timely manner."

The principal issue is in the interpretation of the reviewer's finding that "Neither version of Celgene's thalidomide is bioequivalent to the 'Tortuga' formulation" (p. 16 of cited review). The Tortuga formulation was "included in this study as it was commonly used from time to time in the Hansen's program and there were questions as to the validity of extrapolating the results from subjects treated with the Tortuga formulation to the Celgene material" (p. 5 of cited review). Here the reviewer recognizes that bioequivalence to the Tortuga formulation would

have provided a "bridge" from the current Celgene formulations to the database from which Celgene obtained the information for this NDA. Although there were other formulations and other lots of Tortuga used in this database, none were tested. The only one which was tested was found to be "markedly different as evidenced by both AUC, Cmax, and half-life. It appears to be very poorly absorbed relative to either of the other two (sic: Celgene) formulations" (p. 6 of cited review). "Clearly the relative bioavailability of thalidomide from the Tortuga formulation is much less than that of either Celgene formulation" (p. 7 of cited review).

Since the Celgene formulations demonstrate a much greater bioavailability, any safety data from the Celgene NDA database emerging from non-Celgene formulations may seriously underestimate dose-dependent toxicities for the subject of this NDA, viz, the Celgene formulations. Virtually all of the data in this submission are derived from non-Celgene formulations. Only 14 patients with ENL are known to have been treated with Celgene formulations, and this limited data set does not support approval.

Although in the body of the Clinical Pharmacology/Biopharmaceutics Review the reviewer identifies "questions as to the validity of extrapolating the results from subjects treated with the Tortuga formulation to the Celgene material", the Conclusions section of that review surprisingly does not refer to this critical "bridging " issue. In my assessment this should have been an important factor supporting non-approvability from a Biopharmaceutics perspective.

SIGNIFICANT FINDINGS IN THE MEDICAL REVIEWS CITED

1. Celgene's thalidomide formulation is much more bioavailable than the formulation (Tortuga) used most recently by the USPHS.
2. Only 14 patients with ENL are known to have been exposed to Celgene's thalidomide formulation for more than one dose. (Six additional leprosy patients received a single dose).
3. The information base submitted by the Sponsor contains multiple methodologic problems which make assessment of efficacy or safety difficult to impossible. These clinical experiences and studies presented by the Sponsor were never intended for the purpose of supporting an NDA and were not conducted or planned in a manner that would readily disclose either efficacy or safety.
4. Thalidomide may have a positive effect on the cutaneous lesions of ENL; however, it is difficult to assess the clinical significance of the effect of thalidomide on cutaneous lesions of ENL, and a risk-benefit assessment is not possible. There is no compelling evidence that thalidomide is effective for the serious systemic manifestations of ENL.

COMMENTS

1. Methodological Problems

There is compelling evidence that many improperly implemented randomized controlled trials (RCTs) are biased with exaggerated estimates of treatment effects (Schulz KF. Lancet 1996; 348:596-598). The prevention of selection biases and confounding biases depends on randomization, which consists of two elements: the generation of an unpredictable assignment sequence and the concealment of that sequence until allocation occurs. None of the studies in

this NDA, reported to have been blinded, contain adequate methodological details to ensure that proper randomization was even part of their design.

Double-blinding and avoidance of exclusions after trial entry are the most important other methods for reducing bias (Schulz RF. ibid.). Blinding seeks to prevent ascertainment bias and protects the sequence after allocation. It is likely that the sedation accompanying thalidomide would lead to unblinding, unless a sedative were added to the placebo or active control arm. Sedative blinding was not employed in any of the studies reported in this NDA.

2. Need for Adequate RCTs

The tenacity and sincerity with which a belief is held is no guide to its factual reliability. Reynold Spector (The Scientific Basis of Clinical Pharmacology, 1986, pp. 3-6) provides examples of two universally used and accepted treatments, insulin coma therapy for schizophrenia and internal mammary artery ligation for angina pectoris, that were ultimately shown to be NOT effective in controlled trials (Appendix A).

The "sulfisoxazole lesson" described by W.A. Silverman and D. G. Altman (Lancet 1996; 347:171-174) may be more closely analogous to thalidomide for ENL, since penicillin plus sulfisoxazole did have a positive effect, viz, reduction of the number of fatal infections (Appendix B). Although the number of fatal infections was reduced, the mortality was strikingly higher in infants treated with penicillin plus sulfisoxazole (the widely used standard regimen) compared to infants treated with oxytetracycline.

Likewise, thalidomide may have a positive effect in the treatment of ENL, based on the clinical impressions reported in the NDA. However, there is insufficient information to determine the overall long-term risk-benefit relationship for thalidomide for ENL. Adequate studies of the safety of thalidomide for ENL have not been reported in this NDA, and safety cannot be assumed even if thalidomide is the leprologists' treatment of choice for ENL.

3. Compassion and the Use of Unapproved Drugs

The FDA acts as a public health protector by ensuring that all drugs on the market are safe and effective. Authority to do this comes from the 1938 Federal Food, Drug, and Cosmetic Act, a law that has undergone many changes over the years. Although the importance of showing effectiveness through controlled trials had been advocated for years by many experts, the thalidomide tragedy was the trigger for the Kefauver-Harris Amendments of 1962. These amendments required firms to prove in adequate and well-controlled studies not only safety but also effectiveness for the product's intended use.

Under President Reagan the FDA responded with great flexibility to the AIDS epidemic and permitted the use and sale of drugs not yet approved (but in use in ongoing studies) if, inter alia, the drug was intended to treat a serious or immediately life-threatening disease. Also, the FDA has permitted individual patients to import unapproved drugs from other countries for their personal, medical use. George Annas (Villanova Law Rev 1989; 34: 771-797) regards these regulations as almost purely political, without scientific basis, and tending to conflate treatment and research and to undermine the very purpose of clinical trials. He describes the theory used to justify these exceptions to federal drug laws: terminally ill patients have "nothing to lose" and

should not be deprived of the hope (even the false hope) that they might escape death.

As a physician who has cared for dying patients whose final consolation was hope, I find Dr. Annas' criticism excessive. Still, in the setting of non-life-threatening conditions, particularly those conditions like ENL which may be chronic, I find valid his injunction to demonstrate effectiveness before making a drug commercially available. Since there is no compelling evidence that thalidomide is effective in the rare, severe expressions of ENL that might be life-threatening, I conclude that thalidomide should not be approved based on the insufficient evidence of efficacy and safety in the current Celgene NDA.

Since thalidomide has been available in an unapproved manner through buyers' clubs, one proposed advantage of the approval of thalidomide (for any use) is that thalidomide will have labeling to inform the physician, pharmacist, and patient. Also, the physician and pharmacist can reinforce the transfer of appropriate information to the patient. Additionally, the physician will have important information to guide the selection and management of patients taking thalidomide. Such a potential improvement in the flow of information to off-label users that could be realized with the approval of thalidomide is wholly contingent upon an adequate database from which thalidomide labeling can be developed. However, there are insufficient data at this time to craft labeling for any subset of ENL. Even more problematic would be including safety data to inform the possible off-label use. Jacobson et al (N Engl J Med 1997; 336:1487-1493) reported increases in HIV RNA levels, Grade 4 neutropenia in 2 of 28 patients, and intolerance of dosing levels in thalidomide treated patients with oral aphthous ulcers and HIV infection (Appendix C).

4. Requirement for Unique Efficacy

The Agency, with advice from the Dermatologic Drugs Advisory Committee, has approved teratogenic drug products consistent with less conservative standards than a requirement for unique efficacy. Etretinate (Tegison) was approved for women without reproductive potential and for men for severe recalcitrant psoriasis that also responds to other drug products. Acitretin (Soriatane) was approved for women without reproductive potential and for men for severe psoriasis that also responds to other drug products. This would suggest that thalidomide could be approved (if adequate efficacy and safety data were submitted) for women without reproductive potential and for men even if it were not uniquely effective.

5. Labeling Goals For Teratogens

The Secondary Medical Reviewer is correct in pointing out that thalidomide-injured infants will be born if thalidomide is approved. As she has articulated, the risk of teratogenicity must be weighed in the risk-benefit analysis. Systemic retinoids were approved, even though risks of injured infants were known. It must be acknowledged that, for any teratogenic drug product approved, pregnancy or fetal exposure prevention programs and appropriate product labeling cannot guarantee that no human embryopathy will ever occur. A goal of such programs and product labeling cannot be that nobody will use the drug product incorrectly. An achievable objective is to craft an informational context that reinforces the correct use of the drug product and describes what happens when the drug product is used incorrectly.

CONCLUSIONS AND RECOMMENDATIONS

1. There are insufficient safety and efficacy data to create labeling at this time. I recommend that labeling be deferred.
2. Since there is no compelling evidence that thalidomide is effective for life-threatening or severely debilitating forms of the ENL syndrome, and given the paucity of safety data and dose-ranging data along with concerns about teratogenicity and neuropathy, I recommend that this application be NOT APPROVABLE. However, the Sponsor should be informed that a well-designed randomized clinical study of thalidomide that incorporates an arm with an anti-inflammatory drug and a sedative (both at appropriate doses) may provide sufficient evidence of safety and efficacy to permit a more favorable regulatory decision. Such a study would be in addition to the ongoing clinical trial, E-003/P, with modifications such as more sensitive neurologic testing.

Jonathan Wilkin, M.D. 8/15/97
Director, Division of Dermatologic
and Dental Drug Products

cc: NDA 20-785
HFD-540
HFD-540/CSO/White
HFD-540/Chem/DeCamp
HFD-540/Pharm/Hill/Jacobs
HFD-725/Stats/Gao/Thomson/Srinivasan/Harkins
HFD-540/MO/Vaughan/O'Connell/Walker
HFD-880/Biopharm/Bashaw
HFD-540/DivDir/Wilkin

12 PAGE(S) COPYRIGHT MATERIAL - REMOVED FROM THIS SECTION

Appendix A

Reynold Spector, "Introduction to Therapeutics," The Scientific Basis of Clinical Pharmacology, 1986, pp. 3-6.

Appendix B

William A. Silverman and D. G. Altman, Sulfisoxazole, Lancet, 1996, 347, pages 171-174.

Appendix C

Jeffrey M. Jacobson, M.D., et al., "Thalidomide For The Treatment Of Oral Aphthous Ulcers in Patients With Human Immunodeficiency Virus Infections," The New England Journal of Medicine, Vol. 336, No. 21, May 22, 1997, pages 1487-1493.

5 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

4 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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____ § 552(b)(4) Draft Labeling

CELGENE CORP
7 POWDER HORN DRIVE
WARREN, NJ 07059

10:36
Brian Williams

FACSIMILE TRANSMITTAL SHEET

TO:	FROM:
Mr. K.D. White	Sol Barer
COMPANY:	DATE:
FDA	February 18, 1997
FAX NUMBER:	TOTAL NO. OF PAGES INCLUDING COVER:
1-301-827-2075	3
RE:	YOUR REFERENCE NUMBER:
News Release	

X URGENT X FOR REVIEW X PLEASE COMMENT ☐ PLEASE REPLY ☐ PLEASE RECYCLE

NOTES/COMMENTS:

Dear Mr. White

As I mentioned on your voicemail system, Celgene will be issuing a news release regarding the filing of the NDA for ENL. I'm attaching a draft (note handwritten corrections) for your review. Please let me know if you have any comments/changes. We are scheduling the release for 8:00AM tomorrow (Wednesday) morning.

Thanks in advance for your help.

Sincerely,

Sol J. Barer

PS I can be reached at 908-271-4153

Date: 1/13/96

DRAFT

To: Steve Thomas, Ph.D

From: Jonathan Wilkin, M.D.

Subject: NDA 20-785 Synovir

As per our telephone conversation earlier today, the following issues should be amended in the NDA to facilitate filing.

- Clarification of terminology in data sets; specifically
  1. Nomenclature: for example, is PATIENT the same as OBSERV in the data sets? OBS = SEQ. REPORTS ≈ "VISIT"
  2. We want time required to get "excellent", etc., time of diagnosis mm/dd/yy, time of start date to response; can we subtract time of outcome to get this?
  3. Label to variables in SAS data sets.
  4. We need someone thoroughly versed on the database to communicate with us on these issues.

- Revise label and protocols so that thalidomide is intended as adjunctive therapy. Neither L-001 nor L-002 appear to support BOTH monotherapy AND treatment of severely debilitating illness.

- Certain of the end organs affected by the inflammation of ENL, namely the peripheral nerves, testes, the anterior chamber of the eye, and kidneys may also be permanently damaged and may result in serious disability. Primary endpoints of the phase 4 efficacy trials must be arrest or prevention of such major irreversible morbidity.

- Storage and dispensing information for the label.

If you have any questions, please call Kevin Darryl White at (301) 827-2020. Thank you.

Attachment II

Memorandum

To: *Mary-Jane Walling*
From: *E. Dennis Bashaw, Pharm.D.*
Date: *May 15, 1996*
Subject: *Thalidomide-PK Requirements*

From our joint meeting on May 6th between the staff of the Division of Pharmaceutical Evaluation-III and the ODE-V medical staff involved in the review of thalidomide, the following pharmacokinetic trials were classified as those required for the filing of an NDA for ENL:

1. Single dose bioequivalency study (clinically studied vs. to-be-marketed).
2. A dose proportionality study over the clinically studied range (50-400mg as single doses).
3. A definitive metabolism/disposition study (c-14 or tritium or other accepted technique) in patients with leprosy. This data should also be used in conjunction with in vitro metabolism studies to provide preliminary information on the metabolic character of thalidomide and to provide preliminary information on drug-drug interactions.
4. In vitro dissolution method (in conjunction with FDA St. Louis lab).

Ideally these studies should be done with subjects with ENL, however, given the nature of the disease and the number of subjects involved, the use of normal volunteers is unavoidable. One may want to consider the possibility of using subjects with either ENL or leprosy in the definitive metabolism study as this type of study normally includes less than 5 subjects.

Those studies that are being either deferred or made as a phase IV requirement:

1. Multiple dose steady-state (may be added to an ongoing clinical study).
2. Food effect study (modify ongoing clinical protocols to indicate fasted dosing).
3. Special populations (hepatic & renal) will be labeled as not studied (metabolism study data may be useful here). In addition information on the effect of gender, race, and age will need to be developed.
4. Drug interaction studies (e.g., dapsone and rifampin). The results of the definitive in vivo metabolism study may be useful in selecting in vitro screening methods (using P-450 isoenzymes) for drug interactions. In vivo work may be required for confirmatory studies.

As an unstated issue on the table that the sponsor needs to address is a rationale for using a non-specific assay technique for a racemic drug product. Inter-conversion between the two forms may become an issue. Published data in the scientific literature may be useful here.

9 PAGE(S) COPYRIGHT MATERIAL - REMOVED FROM THIS SECTION

Tommy Eriksson, et al., "Stereospecific Determination, Chiral Inversion In Vitro and Pharmacokinetics in Humans of the Enantiomers of Thalidomide," Chirality, Volume 7, Issue 1, 1995, pages 44-52.

SOLUBILITY OF THALIDOMIDE

SOLVENT	SOLUBILITY MG/ML
WATER	
ETHANOL	
PROPYLENE GLYCOL	
PEG 400	
GLYCEROL	
HPCD	

4 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

(5)

THALIDOMIDE

RECORD OF A MEETING

DRAFT

Date: January 22, 1996

Between: Members of Celgene Corporation:
Steve Thomas, Director, Pharmaceutical Development
David Stirling, Senior Vice President of Pharmaceutical R&D
[ ], Consultant to Celgene, [ ]
[ ], Consultant to Celgene, [ ]
[ ], Consultant to Celgene

and Members of the Division of Dermatologic and Opthalmologic Drug Products:
Michael Weintraub, Office Director, ODE V
Mary Jane Walling, Special Assistant to the Director
Jonathan Wilkin, Division Director
Linda Katz, Deputy Director
Brenda Vaughan, Medical Officer
Abby Jacobs, Pharmacology/Toxicology Team Leader
Hilary Sheevers, Pharmacology/Toxicology Reviewer
Wilson DeCamp, Supervisory Chemist
Frank Pelsor, Team Leader of Anti-Infective Drug Products, Biopharmaceutics
Ralph Harkins, Acting Division Director, ODE IV
Joanne Holmes, Project Manager
Matthew Tarosky, Project Manager, Division of Anti-Viral Drug Products

Subject: Clinical and Preclinical requirements for the proposed NDA submission
Accelerated approval of the NDA
Timeline for the proposed NDA submission

Drug: Thalidomide

Proposed Indication: Erythema nodosum leprosum

Sponsor: Celgene Corporation

The following topics were discussed:

1. The meeting opened with a discussion of what information is available in the patient database at the Hansen's Disease Center in Carville, LA. The Division expressed concern that until it is able to see what information is there, particularly regarding safety, it is unable to say whether this data will be acceptable in support of the proposed NDA. Celgene indicated that several years of data on 24 patients are available. Some statistical evaluation has been performed. It was agreed that by the end of three weeks, Celgene will provide full data on one of the 24 patients and a study summary. Any other patient records will be available upon request from Drs.

Hastings & Carville data

DRAFT

Rea and Yoder.

2. Celgene indicated that due to the shortage of the thalidomide supply at Hansen's, they had been encouraged by meetings with other parts of the Agency in November 1995, to apply for accelerated approval using restricted distribution according to 21 CFR 314.520. While they have considered the Accutane model, they have not developed a final proposal for restricted distribution.

Subpart H

Celgene stated that if they failed to comply with any commitments made for the accelerated approval, that the drug would be withdrawn from the market, according to the regulations.

Celgene further stated that they have agreed to supply thalidomide to any single-patient INDs requested.

Dr. Wilkin reminded Celgene that while thalidomide is used in ENL, AIDS, GVH, ocular diseases, and more, the Division must be mindful of the drug's toxicity profile and history. He cited the Sheskin studies on ENL, where the dose chosen was based on that used as a sedative, rather than any exploration of dose-ranging studies, which the Division would like to see. He also expressed concern that dermatologists who have confidently prescribed Accutane without incident of birth defects will readily prescribe thalidomide while disregarding the possibility of neurotoxicity, which seems to be dose-related. He added that by knowing the minimum dose required for treatment, physicians are less likely to overtreat and therefore predispose the patients to neurotoxicity.

Dose-ranging studies

Dr. Thomas stated that because the number of patients in the United States who present the first time with ENL is small, the primary investigators are resistant to any study that is more aggressive than what is now proposed.

US with small "n"

Dr. Wilkin acknowledged this problem, and offered Celgene the opportunity for a teleconference with the Division, Celgene, and Drs. Rea and Yoder to discuss a protocol that will provide the most data possible. Celgene agreed.

US investigators won't do dose-ranging studies

Dr. Katz added that Protocol E001, submitted in the original IND dated June 15, 1995, and revised December 21, 1995, appears convoluted. She proposed that Celgene reconsider a protocol whereby the trial is shorter than the two years proposed, with a more simplified tapering regimen.

Dr. Wilkin concluded that the Division will work with Drs. Rea and Yoder on a protocol, and if Celgene can supply data that indicate promise in the clinical and statistical evaluations, then the Division will consider Subpart H. Dr. Katz added that the Division needs to see what data are currently available before it can say what trials need to be either initiated or completed in order for this application to qualify for Subpart H.

Subparts E & H dependent on data Celgene will supply (Hastings &

DRAFT

3. Dr. Thomas said that the data on the one year chronic toxicity study in beagles will be available by the end of this year. It is unclear, due to the readiness of the clinical data, whether this study will be completed or ongoing at the time of the NDA submission. Dr. Sheevers agreed to look at the interim data, as well as the interim data from the NCTR primate study, before stating whether completion of the beagle study would be required for submission of the NDA.

4. Celgene agreed to provide a copy of the randomization protocol they had drafted, and Drs. Rea and Yoder rejected.

5. Dr. Pelsor informed Celgene that the PK protocol E002, as revised in the December 21, 1995, submission, is acceptable.

Joanne M. Holmes

cc:
IND 48,177
HFD-540 Div Files
HFD-540/PHARM/TOX/Sheevers
HFD-540/TEAM LEADER PHARM/TOX/Jacobs
HFD-540/ SUP CHEM/DeCamp
HFD-880/BIOPHARM/Pelsor
HFD-725/ACTING DIV DIR BIO V/Harkins
HFD-540/MO/Vaughan
HFD-540/Dep Dir/Katz
HFD-540/Div Dir/Wilkin
HFD-540/Proj Mgt Supv/Cook
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HFD-105/Weintraub/OFF DIR, ODE V
HFD-105/Walling/SPEC ASST, ODE V
HFD-530/Tarosky/PROJ MGR