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(71) **Applicant (for all designated States except US): AVEN-TIS PHARMACEUTICALS INC. [US/US]; 300 Somerset Corporate Boulevard, Bridgewater, NJ 08807-2854 (US).**

(72) **Inventors; and**
(75) **Inventors/Applicants (for US only): SCHEYER, Richard, D.** [US/US]; 3415 Round Hill Road, Branchburg, NJ 08876 (US). **STYREN, Scot, D.** [US/US]; 117 Sleepy Hollow Drive, Niantic, CT 06357 (US)

(74) **Agents:** STRUPCZEWSKI, Joseph et al.; Sanofi-Aventis, Route 202-206, P. O. Box 6800, Bridgewater, NJ 08807-0800 (US).

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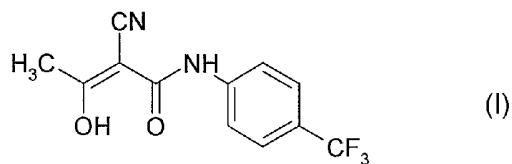
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(54) Title: USE OF (Z)-2-CYANO-3-HYDROXY-BUT-2-ENOIC ACID-(4'-TRIFLUOROMETHYLPHENYL)-AMIDE FOR TREATING INFLAMMATORY BOWEL DISEASE



(57) Abstract: The invention relates to the use of formula (I) in treating patients for the symptoms of inflammatory bowel disease including Crohn's disease and ulcerative colitis.

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10 USE OF (Z)-2-CYANO-3-HYDROXY-BUT-2-ENOIC ACID-(4'-TRIFLUOROMETHYLPHENYL)-AMIDE FOR TREATING INFLAMMATORY BOWEL DISEASE

FIELD OF THE INVENTION

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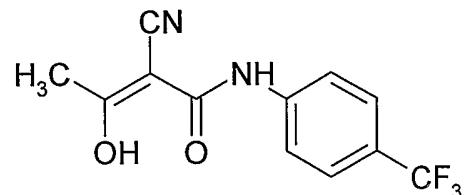
The present invention relates to methods of treating inflammatory bowel disease. In particular, the present invention relates to the treatment of inflammatory bowel disease with (Z)-2-cyano-3-hydroxy-but-2-enoic acid-(4'-trifluoromethylphenyl)-amide, commonly known as teriflunomide.

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BACKGROUND OF THE INVENTION

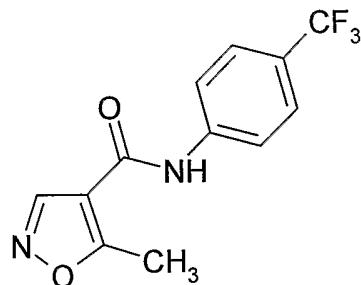
(Z)-2-cyano-3-hydroxy-but-2-enoic acid-(4'-trifluoromethylphenyl)-amide (teriflunomide) has the structure illustrated in Formula I:

25



Formula I

It is an active metabolite of the disease-modifying, antirheumatic drug 5-methylisoxazole-4-carboxylic -(4-trifluoromethyl)-anilide commonly known as leflunomide, the structure of which is shown in Formula II. Leflunomide was first disclosed generically in U.S. Patent 4,087,535, issued on May 2, 1978 and 5 specifically in U.S. Patent 4,284,786, issued on August 18, 1981, wherein it was disclosed that the compound could be used for the treatment of multiple sclerosis. Also, the successful use of leflunomide for the treatment of Crohn's disease in a small 10 number of patients, with azathioprine intolerance has been described (Prajapati, D.N., et al., 2001, American Journal of Gastroenterology, 96 (9): S305). Both of the aforementioned patents are incorporated herein by reference in their entirety.



Formula II

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(Z)-2-cyano-3-hydroxy-but-2-enoic acid-(4'-trifluoromethylphenyl)-amide (teriflunomide, Formula I) use in treating chronic graft-versus-host disease has been disclosed in U.S. Patent 4,965,276 issued on October 23, 1990. U.S. Patent 5,459,163 issued on October 21, 1997 and U.S. Patent 5,679,709 issued on October 20, 1997 disclose compositions useful for treating autoimmune diseases in particular lupus erythematosus. Both of the aforementioned patents are incorporated herein by reference in their entirety. Teriflunomide has been shown to produce antiproliferative effects on a wide variety of immune cells and cell lines (Cherwinski H. M., et al., J. Pharmacol. Exp. Ther. 1995;272:460-8; Prakash A., et al., Drugs 1999;58(6):1137-25 66; Bartlett R. R. et al., Agent Action 1991;32(1-2):10-21) and anti-inflammatory activity in an animal models of inflammation (Huang, W-H. et al. Chem. Pharm. Bull., 2003, 51(3): 313-314 and U.S. Patent 6,716,411 issued on April 6, 2004).

Additionally, it inhibits the enzyme dihydrooate dehydrogenase, an enzyme essential for the synthesis of pyrimidines (Bruneau J-M, et al., Biochem. J. 1998; 36:299–303).

Inflammatory bowel disease (IBD) is a general term used to identify a series of related intestinal diseases of unknown etiology characterized by chronic inflammation at various portions of the gastrointestinal tract. Representative of IBD are Crohn's disease, ulcerative colitis, indeterminate colitis, and infectious colitis.

Crohn's disease is an idiopathic chronic enteritis of unknown etiology. This disease occurs most frequently in human beings of both sexes in their twenties and becomes chronic. It is a granulomatous lesion with fibrosis or ulceration and may be present within the whole alimentary tract from mouth to anus. The clinical symptoms of Crohn's disease are celialgia, general malaise, diarrhea, melena and occult bleeding positive, fervescence, loss of body weight, anemia, ileus, abdominal tumor and peritonitis.

Ulcerative colitis is an unaccountable disease of diffuse nonspecific inflammation of the colon, which attacks the mucous membrane and often forms an erosion or ulcer. The lesion is chiefly submucosal. The clinical symptoms of this disease are viscous-hemafecia, celialgia, hemafecia, watery stool, fervescence, loss of appetite, nausea and vomiting. Also, ulcerative colitis may be attended by such troubles as arthritis, stricture of the large intestine and copious bleeding, but their incidence is not high.

Current therapy for IBD includes anti-inflammatory drugs, immunosuppressive drugs and surgery. Sulfasalazine and related drugs having the bioactive 5-amino-salicylic acid (5-ASA) moiety are widely used to control moderate IBD symptoms and to maintain remission. Severe inflammation is often treated with corticosteroids and sometimes ACTH or with immunosuppressants such as 6-mercaptopurine, azathioprine, cyclosporine, and methotrexate. The most common surgical treatments for severe chronic IBD are intestinal resections and, ultimately, colostomy, which is a complete cure only for ulcerative colitis.

Severe side effects are associated with the drugs commonly prescribed for IBD, including nausea, dizziness, changes in blood chemistry (including anemia and leukopenia), skin rashes and drug dependence; and the surgical treatments are radical procedures that often profoundly alter the everyday life of the patient. Clearly

there is a need for novel agents for the treatment of IBD without some of the side-effect liabilities associated with current therapy.

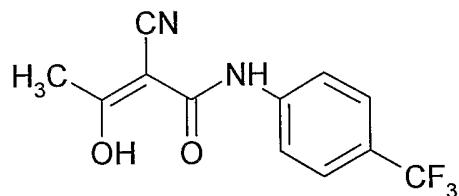
Teriflunomide itself has demonstrated efficacy in preclinical models of multiple sclerosis, and is in clinical trials for treatment of multiple sclerosis (MS). The 5 pathophysiology of MS (R.A. Adams, M.V. Victor and A.H. Ropper eds., *Principles of Neurology*, McGraw-Hill, New York, 1997, pp. 903-921.) and IBD (D.K. Poldosky, N. Eng. J. Med., 347, 6: 417-429) disorders is mediated substantially via T-lymphocytes, the activation of which is modulated by teriflunomide. Also, there is some evidence suggesting partial overlap of MS with inflammatory bowel disease. (Purman J et al. 10 J. Clin. Gastroenterol. 1992, 14, 1: 43-46 and Kimura K. Mayo Clin. Proc. 2000, 75, 8: 802-806).

Following administration of teriflunomide, high amounts of teriflunomide enter the intestinal lumen. This may be due to either enterohepatic recirculation or via the 15 intestinal mucosa. The intestinal mucosa is therefore exposed to relatively high amounts of teriflunomide, and therapeutic effects may be achieved at lower doses than those required to treat systemic autoimmune disease. Alterations in the integrity of the GI mucosa may provide further enhancement of local exposure. Thus, based upon the above discussions along with the good safety profile of teriflunomide even at 20 doses for treating systemic diseases, and coupled with the low likelihood of gastrointestinal side- effects, make teriflunomide a potentially useful drug for the treatment of IBD, which includes Crohn's disease, ulcerative colitis, indeterminate colitis and infectious colitis.

SUMMARY OF THE PRESENT INVENTION

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The present invention is a method of treating inflammatory bowel disease in patients by administering a compound of Formula I or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount to treat the disease.



Formula I

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DETAILED DESCRIPTION OF THE INVENTION

Terms used herein have the meanings defined in this specification.

a) "Pharmaceutically acceptable salts" means either an acid addition salt or a 10 basic addition salt, whichever is possible to make with the compounds of the present invention.

"Pharmaceutically acceptable acid addition salt" is any non-toxic organic or inorganic acid addition salt of the base compounds represented by Formula I.

Illustrative inorganic acids which form suitable salts include hydrochloric, 15 hydrobromic, sulfuric and phosphoric acid and acid metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic acids which form suitable salts include the mono-, di- and tri-carboxylic acids.

Illustrative of such acids are, for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, 20 benzoic, hydroxybenzoic, phenylacetic, cinnamic, salicyclic, 2-phenoxybenzoic, p-toluenesulfonic acid and sulfonic acids such as methanesulfonic acid and 2-hydroxyethanesulfonic acid. Either the mono- or di-acid salts can be formed, and such salts can exist in either a hydrated or substantially anhydrous form. In general, 25 the acid addition salts of these compounds are more soluble in water and various hydrophilic organic solvents and which in comparison to their free base forms, generally demonstrate higher melting points.

"Pharmaceutically acceptable basic addition salts" means non-toxic organic or inorganic basic addition salts of the compounds of Formula I. Examples are alkali metal or alkaline-earth metal hydroxides such as sodium, potassium, calcium, 30 magnesium or barium hydroxides; ammonia, and aliphatic, alicyclic, or aromatic

organic amines such as methylamine, trimethylamine and picoline. The selection of the appropriate salt may be important so that the ester is not hydrolyzed. The selection criteria for the appropriate salt will be known to one skilled in the art.

5 b) “Patient” means a warm blooded animal, such as for example rat, mice, dogs, cats, guinea pigs, and primates such as humans.

10 c) “Treat” or “treating” means any treatment, including, but not limited to, alleviating symptoms, eliminating the causation of the symptoms either on a temporary or permanent basis, or preventing or slowing the appearance of symptoms and progression of the named disorder or condition.

15 d) “Therapeutically effective amount” means an amount of the compound, which is effective in treating the named disorder or condition.

15 e) “Pharmaceutically acceptable carrier” is a non-toxic solvent, dispersant, excipient, adjuvant or other material which is mixed with the compound of the present invention in order to permit the formation of a pharmaceutical composition, i.e., a dosage form capable of administration to the patient. One example of such a carrier is pharmaceutically acceptable oil typically used for parenteral administration.

20 f) “Stereoisomers” is a general term for all isomers of the individual molecules that differ only in the orientation of their atoms in space. It includes mirror image isomers (enantiomers), geometric (cis/trans) isomers, and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereoisomers).

25 g) “Leflunomide” is the generic name for 5-methylisoxazole-4-carboxylic-(4-trifluoromethyl)-anilide.

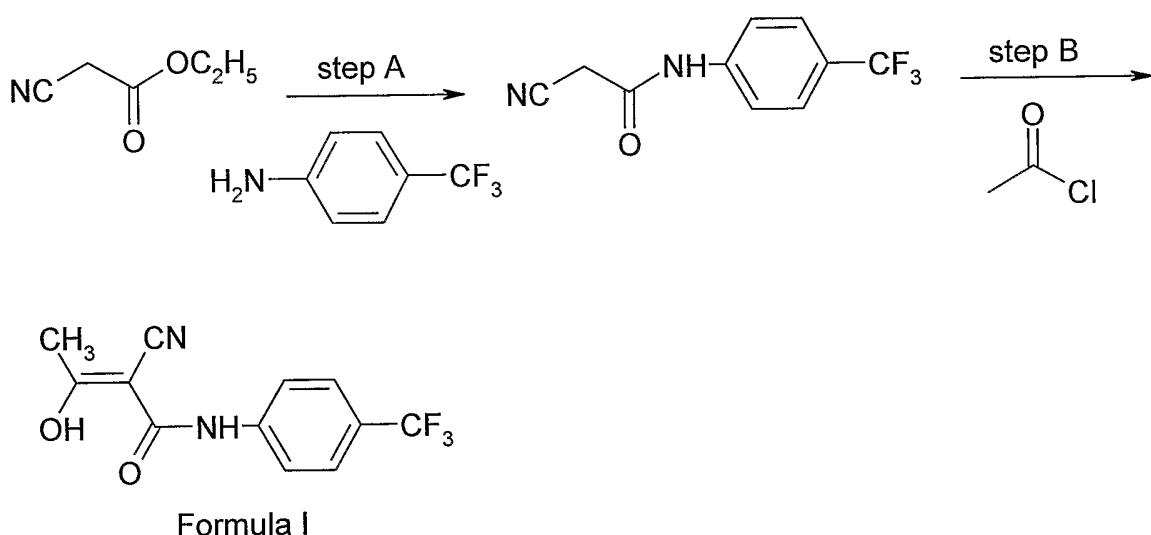
h) “Teriflunomide “ is the generic name for (Z)-2-cyano-3-hydroxy-but-2-enoic acid-(4’-trifluoromethylphenyl)-amide.

30 The synthesis of the compound of Formula 1 has been disclosed, and is accomplished by methods that are well known to those skilled in the art. For

example, US Patent 5,504,084, issued on April 2, 1996, and US Patent 5,990,141, issued on November 23, 1999 disclose methods of synthesis. The aforementioned patents are incorporated herein by reference. One synthesis as disclosed in US Patent 5,990,141 is illustrated in Scheme 1.

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Scheme 1



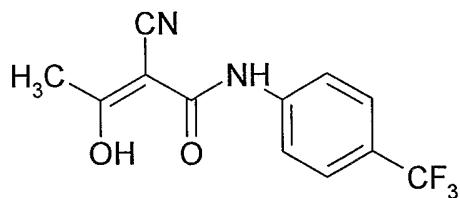
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In Scheme 1, step A, commercially available cyanoacetic acid ethyl ester is reacted with commercially available 4-trifluoromethylaniline neat at elevated temperature to give cyanoacet-(4-trifluoromethyl)anilide. In step B, the product from step A is dissolved in tetrahydrofuran and reacted with NaH in acetonitrile followed by reaction with acetyl chloride to produce the compound of Formula I.

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Thus in accordance with the practice of this invention is disclosed a method of treating inflammatory bowel disease which comprises administering to a patient having said disease a therapeutically effective amount of a compound of Formula I, its stereoisomer, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier,

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Formula I.

5 In another embodiment of the method of this invention said inflammatory bowel disease is Crohn's disease.

In a further embodiment of the method of this invention, said inflammatory bowel disease is ulcerative colitis.

10 In yet another embodiment of the method of this invention, said inflammatory bowel disease is indeterminate colitis.

In still another embodiment of the method of this invention, said inflammatory bowel disease is infectious colitis.

15 In a further embodiment of the method of this invention, said therapeutically effective amount of compound is an amount less than that required to treat systemic autoimmune diseases.

In another embodiment of the method of this invention, said therapeutically effective amount of compound is an amount less than about 10 mg/kg/day.

20 In yet another embodiment of the method of this invention, said therapeutically effective amount of compound is an amount from less than 1.0 mg/kg/day to about 10 mg/kg/day.

25 In treating a patient afflicted with a condition described above, a compound of Formula I can be administered in any form or mode which makes the compound bioavailable in therapeutically effective amounts, including orally, sublingually, buccally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, topically, and the like. One skilled in the art of preparing formulations can determine the proper form and mode of administration depending upon the particular characteristics of the compound selected for the condition or disease to be treated, the stage of the disease, the condition of the patient and other relevant circumstances. For example, see Remington's Pharmaceutical Sciences, 18th
30 Edition, Mack Publishing Co. (1990), incorporated herein by reference.

The compound of the present invention may be administered orally, for example, in the form of tablets, troches, capsules, elixirs, suspensions, solutions, syrups, wafers, chewing gums and the like and may contain one or more of the following adjuvants: binders such as microcrystalline cellulose, gum tragacanth or 5 gelatin; excipients such as starch or lactose, disintegrating agents such as alginic acid, Primogel, corn starch and the like; lubricants such as magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; and sweetening agents such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may 10 contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials, which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric 15 coating agents. A syrup may contain, in addition to the present compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The compound of Formula I of this invention may also be administered 20 topically, and when done so the carrier may suitably comprise a solution, ointment or gel base. The base, for example, may comprise one or more of petrolatum, lanolin, polyethylene glycols, bee wax, mineral oil, diluents such as water and alcohol, and emulsifiers and stabilizers.

The solutions or suspensions may also include one or more of the following 25 adjuvants: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials.

The dosage range at which the compound of Formula I exhibits its ability to act 30 therapeutically can vary depending upon its severity, the patient, the formulation, other underlying disease states that the patient is suffering from, and other medications that may be concurrently administered to the patient. Generally, the compound of Formula I will exhibit their therapeutic activities at dosages of between

about 0.001 mg/kg of patient body weight/day to about 100 mg/kg of patient body weight/day.

All of the references described herein are incorporated herein by reference in their entirety.

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DESCRIPTION OF THE DRAWING

Figure 1 shows the effect of teriflunomide on symptoms in the Rat Experimental Allergic Encephalomyelitis (EAE) at 3 different doses when administered orally (p.o.) as compared to vehicle and dexamethasone.

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The following examples are being presented to further illustrate the invention. However, it should not be construed as limiting the invention in any manner.

Example 1

Rat Experimental Allergic Encephalomyelitis (Rat EAE)

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This Example illustrates method for studying the inflammation of the brain and spinal cord associated with MS, a T-cell related autoimmune disease.. See Bolton, C. Multr. Scler. 1995; 1(3); 143-9.

20

Experimental allergic encephalomyelitis (EAE) is a T-cell-mediated autoimmune disease of the nervous system that develops in susceptible animals following sensitization with either whole spinal cord homogenate or a component (myelin basic protein). The EAE rodent model is an appropriate tool for studying the inflammation of the brain and spinal cord observed in MS patients. In rodents, injection of whole spinal cord or spinal cord components such as myelin basic protein induces an autoimmune response based on the activation of T-lymphocytes. Clinical disease typically becomes manifest around day 8-10 after inoculation, observed as a broad spectrum of behavioral anomalies ranging from mild gait disturbances and tail atony to complete paralysis and death. Weight loss typically occurs. In animals that survive, spontaneous recovery occurs, accompanied by variable recovery of most motor function. Depending on the species, allergen, and methodology used, animals tested by the EAE model may experience a single (acute EAE) or several (chronic relapsing EAE) attacks. Several treatment paradigms may be used: the drug or

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treatment of choice may be administered before immunization, during the nonsymptomatic period or during the clinical disease.

Animals:

5 Female Lewis rats, 160-220g (Charles River)

Antigen:

Whole Guinea Pig spinal cord (Harlan Biosciences).

Complete Freund's adjuvant H37 Ra [1mg/ml Mycobacterium Tuberculosis H37 Ra] (Difco).

10 Additional antigen:

Mycobacterium Tuberculosis (Difco).

Bordetella Pertussis [Heat Killed] (Difco).

Antigen preparation: (for approximately 720 animals)

15

1. Weigh 5 g of frozen guinea pig spinal cord.
2. Add 5g spinal cord to 5ml 0.9% saline (1g/ml) in a round bottom centrifuge tube
3. Homogenize on ice with the Tissue-tech until the tissue is completely disrupted (approximately 5 minutes).

20

4. Add 10 ml Complete Freund's adjuvant H37 Ra supplemented with 200 mg Mycobacterium Tuberculosis (20 mg / ml Complete Freund's adjuvant H37 Ra).
5. Extract homogenate / adjuvant from tube by sucking it into a 10 ml syringe fitted with an 18 gauge emulsifying needle.
6. Emulsify between two 30 ml glass syringes until it becomes difficult to continue passing the material through the needle. (Approximately 5 min {there must be no separation between the oil phase and the aqueous phase}).
7. Use immediately or keep on ice until needed (not more than 30 min) (do not freeze).

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Protocol

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1. Female Lewis rats (Charles River) are given free access to food and water and should be acclimated a minimum of 3 days before use in experiments.

2. Rats weighing 160 and 220 g are initially induced with 5% isoflurane (Aerrane, Fort Dodge), 30% O₂, 70% N₂O for 2-5 minutes.
3. The rat is then placed onto a circulating water heating blanket (Gaymar) (dorsal surface up) and into the nose cone for spontaneous respiration of anesthetic gases. The isoflurane is reduced to 2%.
5. Two subcutaneous injections (0.1 ml each) of either antigen or normal saline are made into ventral surface of the hind paws.
4. The animals are removed from the nose cone, weighed and numbered.
5. The rats are allowed to awake from anesthesia and are placed into individual
- 10 cages.
6. The animals are observed daily for signs of EAE induction (see criteria below)

STAGE:0 NORMAL

STAGE 1 Abnormal gate and tail atony

15 STAGE 2 Mild but definite weakness of one or both hind legs

STAGE: 3 Severe weakness of one or both hind legs or mild ataxia

STAGE: 4 Severe paraparesis and minimal hind leg movement

STAGE: 5 No hind leg movement and paraplegia

20 STAGE: 6 Moribund state with no spontaneous movement and impaired respiration.

Increasing degree of front leg involvement and urinary and fecal incontinence may also occur

STAGE:7 DEATH

25 Treatment was begun on day 10 after immunization. Since the disease symptoms in this model typically appear 10-11 days after inoculation, this time point may be considered to represent the initial phase of an acute episode of MS. It is judged that this delay of the start of treatment mimics the clinical situation more closely than the traditionally used protocols where drugs are administered at the time of, or even before, inoculation (Teitelbaum D. et al., Proc Natl Acad Sci USA 1999; 30 96: 3842-3847 and Brod S. A., et al., Ann Neurol 2000; 47: 127-131).

The effect of teriflunomide on symptoms of EAE in rat at various doses is illustrated in Figure 1. Dexamethasone is included in the figure for comparison.

Example 2

2,4-Dinitrobenzenesulfonic Acid (DNBS) Induced Distal Colitis

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This Example illustrates the anti-inflammatory activity of one compound of this invention using a model of 2,4-dinitrobenzenesulfonic acid (DNBS) induced distal colitis (a model of inflammatory bowel disease).

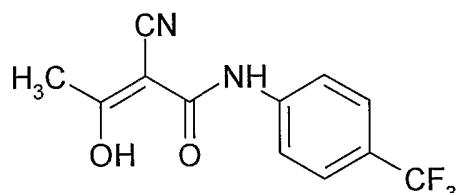
Use groups of 3 male or female rats fasted for 24 hours. Induce distal colitis by intra-colonic instillation of DNBS (2,4-dinitrobenzene sulfonic acid, 30 mg in 0.5 ml ethanol 30%) after which gently inject air (2 ml) through the cannula to ensure that the solution remains in the colon. Administer Test substance PO (30 mg/kg) at 24 and 2 hours before DNBS instillation. Then, the animals receive test compound every 24 hours for 5 consecutive days. Give the control group vehicle alone as compound dosing pattern. Sacrifice the animals 24 hours after the final dose of test compound administration and remove each colon and weigh. Obtain colon-to-body weight ratio from the percentage of the comparison between the animal colon weight and body weight. A 30 percent or more (.-.30%) reduction in colon-to-body weight ratio relative to the vehicle treated control group was considered significant. See C.M. Hogaboam et al. Eur. J. Pharmacol. 309:261 (1996).

25

CLAIMS

We claim:

5 1. A method of treating inflammatory bowel disease which comprises administering to a patient having said disease a therapeutically effective amount of a compound of Formula I, its stereoisomer, or a pharmaceutically acceptable salt thereof, optionally in combination with a pharmaceutically acceptable carrier,



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Formula I.

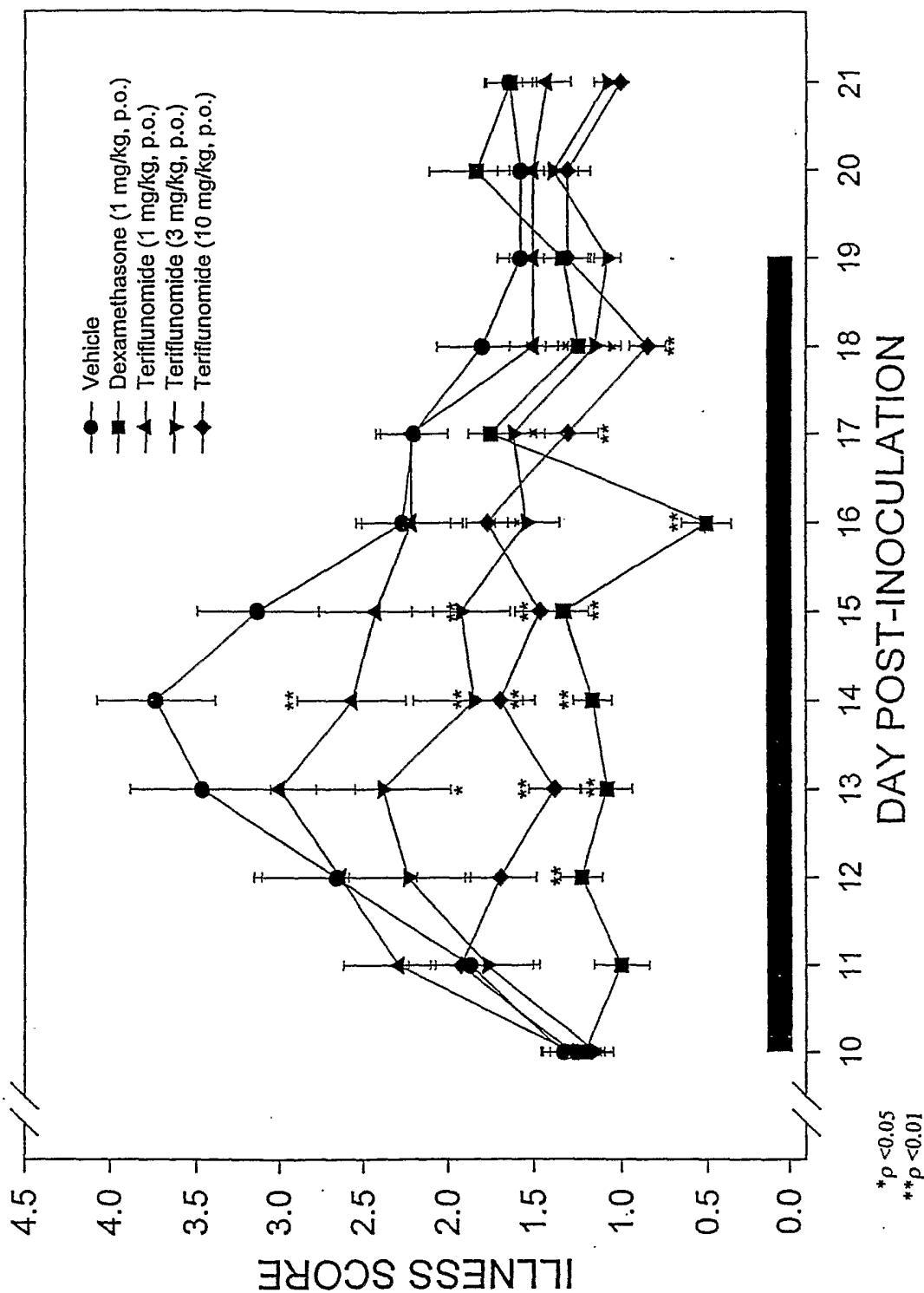
2. The method of claim 1 wherein said inflammatory bowel disease is Crohn's disease.

15 3. The method of claim 1 wherein said inflammatory bowel disease is ulcerative colitis.

4. The method of claim 1 wherein said inflammatory bowel disease is indeterminate colitis.

20 5. The method of claim 1 wherein said inflammatory bowel disease is infectious colitis.

FIG. 1
**Effect of Teriflunomide on
Symptoms of EAE in Rat**



INTERNATIONAL SEARCH REPORT

International application No
US2005/037161

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/165 A61P1/00 A61P29/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/54286 A (WAYNE HUGHES INSTITUTE) 28 October 1999 (1999-10-28) claims 1,18 table 1	1,2
X	US 5 780 592 A (MUELLNER ET AL) 14 July 1998 (1998-07-14) column 5, line 41 example 1 claim 3	1,3-5
A	WO 2004/024676 A (SCHEBO® EIGENBRODT, ERICH; SCHEEFERS, HANS; MAZUREK, SYBILLE) 25 March 2004 (2004-03-25) figure 2b page 9, paragraph 1 page 16, last paragraph claim 11	1-5

Further documents are listed in the continuation of Box C.

See patent family annex.

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Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
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Collura, A

INTERNATIONAL SEARCH REPORT

International application No US2005/037161

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, A	STEINHILBER D: "Pharmacology of immunosuppressive agents" PHARMAZIE IN UNSERER ZEIT 2005 GERMANY, vol. 34, no. 4, 2005, pages 276-281, XP002365151 ISSN: 0048-3664 page 280, right-hand column figure 9 -----	1-5
A	WO 02/080897 A (AVENTIS PHARMACEUTICALS INC; WETTSTEIN, JOSEPH) 17 October 2002 (2002-10-17) the whole document -----	1-5
A	KIMURA K ET AL: "Concurrence of inflammatory bowel disease and multiple sclerosis" MAYO CLINIC PROCEEDINGS 2000 UNITED STATES, vol. 75, no. 8, 2000, pages 802-806, XP009060726 ISSN: 0025-6196 cited in the application the whole document -----	1-5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/037161

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. Claims Nos.: 1-5 (with respect to IA)
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-5 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

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

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2005/037161

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