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(54) **Title**: AN IMPROVED PROCESS FOR THE PREPARATION OF TERIFLUNOMIDE

(57) **Abstract**: The present invention relates to an improved process for the preparation of Teriflunomide with high yield and high purity. The present invention also relates to a process for the preparation of teriflunomide which is free from genotoxic impurities.

# AN IMPROVED PROCESS FOR THE PREPARATION OF TERIFLUNOMIDE

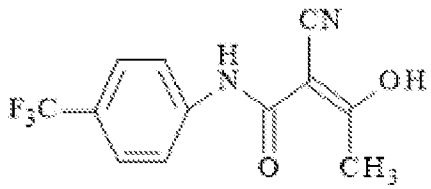
## Field of the Invention:

The present invention relates to an improved process for the preparation of Teriflunomide with high yield and high purity. The present invention also relates to a process for the preparation of teriflunomide which is free from genotoxic impurities.

## Background of the Invention:

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties, inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis.

Teriflunomide is chemically known as (Z)-2-cyano-3-hydroxy-but-2-enoic acid-(4-trifluoromethylphenyl) amide and structurally represented as below.



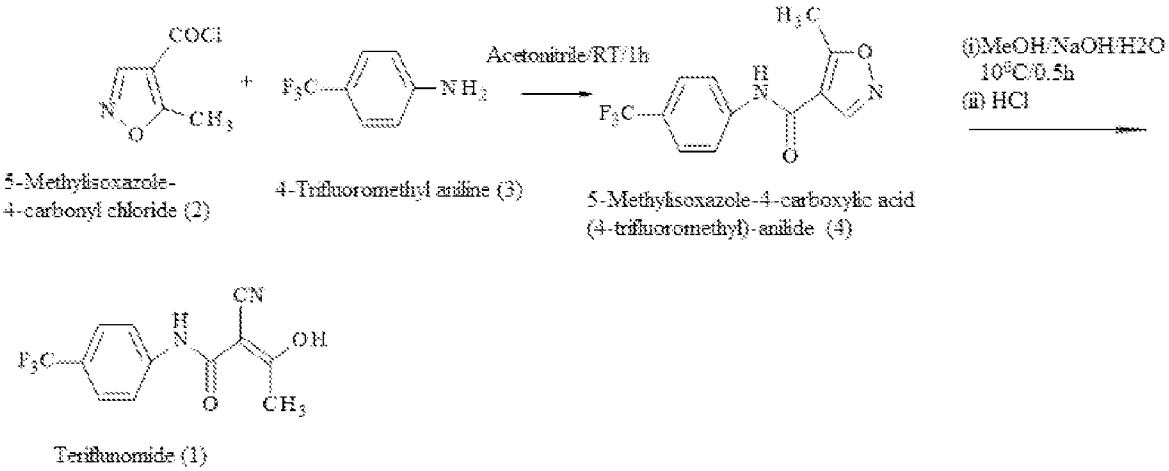

Teriflunomide

Formula-I

Teriflunomide is marketed under the brand name AUBAGIO®, and it is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

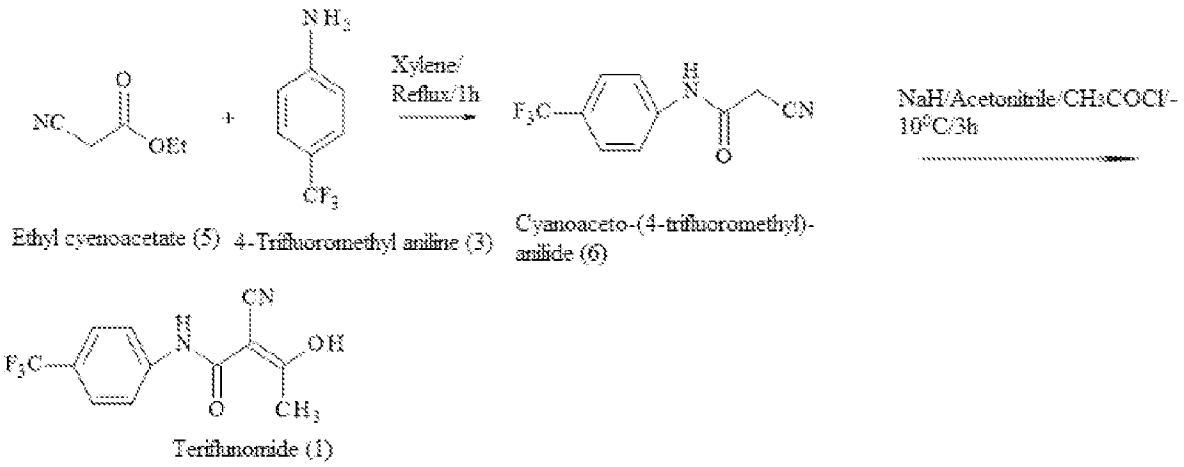
Teriflunomide was first disclosed and claimed in US5679709 but this application does not mention the process of preparation.

U.S. Patent No. 5,494,911, describes process for preparation of teriflunomide, wherein the process comprises reacting 5-methylisoxozole-4-carbonyl chloride (2) with 4-trifluoromethyl aniline (3) in acetonitrile to afford 5-methylisoxozole-4-carboxylic acid (4-trifluoromethyl)-anilide (4). Subsequent hydrolysis with aqueous sodium hydroxide in methanol to yield teriflunomide (1). The scheme representation is shown in scheme-1.



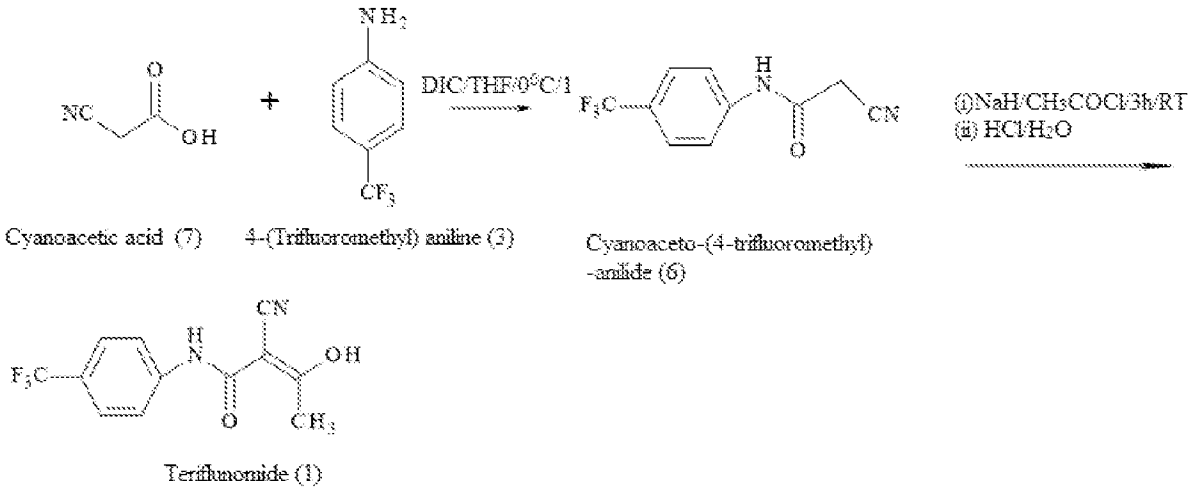

Scheme-I

U.S. Patent No. 5,990,141, describes the process for preparation of teriflunomide ,wherein the process involves reacting 4-trifluoromethyl aniline (3) with cyanoacetic acid ethyl ester (5) to yield intermediate (6), which is further reacted with sodium hydride in acetonitrile followed by acetyl chloride in tetrahydrofuran to produce teriflunomide. The product is purified by column chromatography to yield pure teriflunomide (1). The schematic representation is shown in scheme-II.




Scheme-II

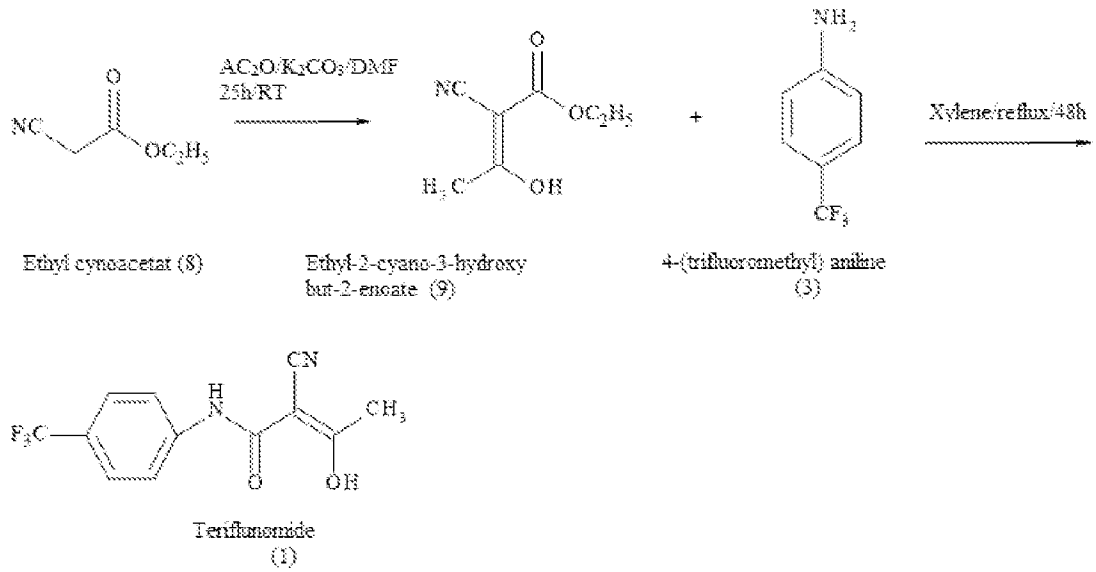
U.S. Patent No. 6,365,626 describes process for preparation of teriflunomide, wherein, the process involves reacting 4-trifluoromethyl aniline (3) with cyanoacetic acid (2) to give intermediate (4). This compound is further reacted first with sodium hydride and then with acetyl chloride to yield teriflunomide (1).The schematic representation is shown in scheme-III.




Scheme-III

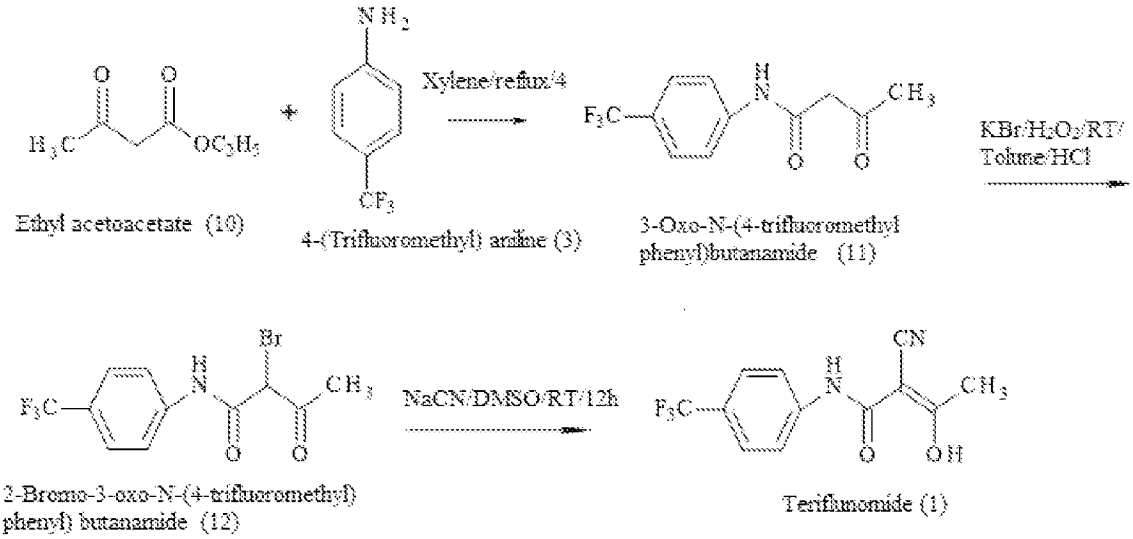
All of the above mentioned processes requires chromatography for purification/isolation.

U.S. Patent No. 8,389,757, describes the process for preparation of teriflunomide, wherein the process involves reacting ethyl acetoacetate (8) with acetic anhydride in presence of potassium carbonate in dimethylformamide to yield ethyl-2-cyano-3-hydroxy –but-2-enoate (9), which is further reacted with 4-trifluoromethyl aniline (3) at reflux temperature for 48h to give teriflunomide (I). Here the reaction conditions are drastic and severe and the patent does not describe the quality of product with respect to the impurities generated. The schematic representation is shown in scheme-IV.




Scheme-IV

U.S. Patent No. 8,420,856, describes the process for preparation of teriflunomide, wherein ethyl acetoacetate (10) and 4-trifluoromethylaniline (3) are refluxed in xylene to give 3-oxo-N-(4-trifluoromethyl phenyl) butanamide (11), which is further brominated to give 2-bromo-3-oxo-N-(4-trifluoromethylphenyl) butanamide (12). This intermediate (12) is reacted with sodium cyanide in DMSO at room temperature to yield teriflunomide (1). The schematic representation is shown in scheme-V.




Scheme-V

The inventors of the present of invention have developed an alternate improved process for the preparation of Teriflunomide with high yield and purity. The present process is cost effective and feasible in large scale production also. The present process controls the genotoxic impurities content in final API which can arise from the starting materials.

**Summary of the Invention:**

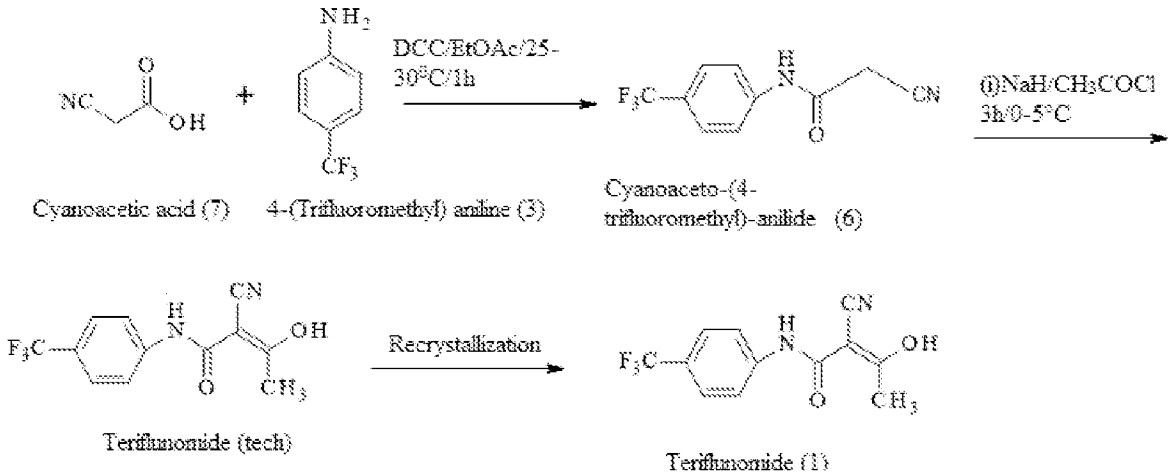
One aspect of the present invention is related to preparation of Teriflunomide, comprising the steps of:

a) purifying 4-trifluoromethyl aniline (3),

b) reacting 4-trifluoromethyl aniline (3) obtained from step a) with cyanoacetic acid (7) in presence of a carbodiimide in ethyl acetate to get 2-cyano-N-(4-trifluoromethylphenyl) acetamide (6),

c) reacting the intermediate (6) with sodium hydride, followed by acetyl chloride to yield crude teriflunomide, which is further recrystallized in ethyl acetate to get pure teriflunomide.

The present invention is shown in below scheme.




**Detailed description of the Invention:**

The present invention is relates to an improved process for the preparation of teriflunomide, wherein purifying the 4-trifluoromethyl aniline (3), followed by reacting with cyanoacetic acid (7) in presence of a carbodiimide in ethyl acetate to get 2-cyano-N-(4-trifluoromethylphenyl) acetamide (6), further reacted with sodium hydride, followed by acetyl chloride to yield crude teriflunomide, which is further recrystallized in ethyl acetate to get pure teriflunomide.

One embodimentof the present invention is related to preparation of Teriflunomide, comprising the steps of:

a) purifying 4-trifluoromethyl aniline (3),
b) reacting 4-trifluoromethyl aniline (3) obtained from step a) with cyanoacetic acid (7) in presence of a carbodiimide in ethyl acetate to get 2-cyano-N-(4-trifluoromethylphenyl) acetamide (6),
c) reacting the intermediate (6) with sodium hydride, followed by acetyl chloride to yield crude teriflunomide, which is further recrystallized in ethyl acetate to get pure teriflunomide.

According to the present invention, commercially available 4-trifluoromethyl aniline (3) contains impurities such as 4-cyano aniline (genotoxic impurity) and isomeric 3-

trifluoromethyl aniline, 2-trifluoromethyl aniline. In the present process, all these impurities are eliminated by the vacuum distillation of 4-trifluoromethyl aniline to yield pure 4-trifluoromethyl aniline (3), which is subsequently employed to prepare high pure teriflunomide.

According to the present invention, 4-trifluoromethyl aniline (3) was condensed with cyanoacetic acid (7) in presence of dicyclohexylcarbodiimide and ethyl acetate. The reaction mixture was stirred at room temperature for 2h to give 2- cyano –N-(4-trifluoromethylphenyl)-acetamide (6) in 90% yield. Further 2- cyano –N-(4-trifluoromethylphenyl)-acetamide (6) is acetylated using acetyl chloride in presence of sodium hydride to yield crude teriflunomide. After the completion of reaction, reaction mass is quenched with acetic acid to neutralize followed by distillation to remove solvent and the crude material is washed with hexane, water and ethyl acetate.

According to the present invention, 4-trifluoromethyl aniline (3) is purified using high vacuum distillation.

According to the present invention, carbodiimide is dicyclohexylcarbodiimide. Which is a solid material and safe to handle.

According to the present invention, commercially available 4-trifluoromethyl aniline (3) contains impurities such as 4-cyano aniline (genotoxic impurity) and isomeric 3-trifluoromethyl aniline, 2-trifluoromethyl aniline. In the present process, all these impurities are eliminated by the vacuum distillation of 4-trifluoromethyl aniline to yield pure 4-trifluoromethyl aniline (3), which is subsequently employed to prepare teriflunomide of purity >99.9%.

The following examples are provided for illustrative purpose only and are not intended to limit the scope of invention in anyway.

**Example-1: Vacuum distillation of 4-trifluoromethylaniline (4-TFMA)(3)**

In a typical vacuum distillation set-up fitted with a 1-l., round-bottom flaks, a splash head, a condenser and a receiver flask assembly, 4- trifluoromethyl aniline (200 g) was taken. The contents of the flask were heated to 75°C under vacuum (650±20 mm Hg) with continuous

stirring. Distillate fractions were collected at specified temperatures and the purities determined by GC. The results are tabulated below.

| Fraction | Vapor temperature (°C) | Weight of fraction (g) | Purity % (GC) |
|---|---|---|---|
| 1 | 51-53 | 8.5 | 99.61% |
| 2 | 53-55 | 175.4 | 99.90% |
| 3 | 50-51 | 7.5 | 99.82% |

**Example-2: Preparation of 2-Cyano-N-(4-trifluoromethylphenyl) acetamide (6)**

In a 500-ml., four-necked, round-bottomed flask fitted with a mechanical stirrer, a 125-ml dropping funnel, and a thermometer were placed 8.34g. (0.098 moles) of cyanoacetic acid (**7**) and 165- ml., of ethyl acetate and the mixture was stirred for 10 minutes under nitrogen atmosphere and then added 10.0 g. ( 0.62 moles) of 4-trifluoromethyl aniline (**3**). From a clean dropping funnel 14.1 g. (0.068 moles, dissolved in ethyl acetate 85mL) of dicyclohexylcarbodiimide was added dropwise over a period of about 1 hour at the same temperature. The reaction mixture was stirred for additional 1.0 hour at 25-30$^0$C.After completion of the reaction precipitated urea was filtered and slurry washed successively with two 50-ml. portions of ethyl acetate and filtered. The organic extracts were combined and washed successively with two 50-ml. portions of 5% sodium bicarbonate solution, 25-ml.of 5% hydrochloric acid solution, and again with 50-ml. of 5% sodium chloride solution. Separated organic layer was evaporated under reduced pressure to yield solid material. To the solid 170-ml isopropyl alcohol was added and the mixture was heated to70-75°C, obtained clear solution and filtered. The filtrate was concentrated to 10 volumes and cooled to 15-20°C. The separated product was filtered and dried in a vacuum oven. Yield =12.5.g (88.15%), HPLC Purity: 99.6%

**Example-3: Preparation of 2-Cyano–3-hydroxy-but-2-enoic acid (4-trifluoromethylphenyl)-amide** (1)

In a 250-ml., four-necked, round-bottomed flask fitted with a mechanical stirrer, a 100-ml dropping funnel, and a thermometer were placed 3.7 g (0.0919 mole, 60% in mineral oil) of sodium hydride, 60-ml of tetrahydrofuran and the mixture was stirred for 10 minutes under nitrogen blanket. The mixture was cooled in an ice-salt bath to 0$^0$C, and a solution of 10.0 g (0.0438 mole) of 2-Cyano-N-(4-trifluoromethylphenyl) acetamide (**6**) in 100-ml. of

tetrahydrofuran was added dropwise at such a rate as to maintain the temperature below 5°C while stirred for 15-30 minutes. The mixture was further cooled to -5°C, from a clean dropping funnel 3.8 g. (0.048 mole) of acetyl chloride was added dropwise over a period of about 90 minutes while the temperature was maintained at -5 to $0^0$C. The mixture was held below $0^0$C for about 30 minutes and further maintained for 2 hours at 25-$30^0$C. After completion of reaction, 7.5 g. (0.125 mole) of glacial acetic acid was added to quench excess sodium hydride and then stirred for an additional 30 minutes and tetrahydrofuran was removed by distillation under reduced pressure to get solid material. The solid was washed successively with 100-ml. of hexane, two 100-ml. portions of water and then filtered the product. To the solid, 40-ml ethyl acetate was added, stirred for about 30 minutes at temperature 65 °C and cooled to 20-25°C, and further stirred 30 minutes then filtered and then dried in a vacuum oven. Yield = 9.5 g (80.3%), HPLC Purity: ~99.6%

**Example-4: Preparation of teriflunomide** (1)

Ten grams (0.037 mole) of crude teriflunomide (1), 400ml. of ethyl acetate were placed in a 1ltr three-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser. The mixture was heated to 40-50°C, 0.1g. activated charcoal was added, and the mixture was refluxed for about 1 hour. The warm mixture was filtered through sintered funnel under suction. The filtrate mother liquor was concentrated to half volumes under reduced pressure, then cooled to 15-20°C and stirred for 1 hour. The crystallized solid material was filtered, and then dried in a vacuum oven. Yield = 7.5 g (75%), HPLC Purity: ~99.92%.

**We Claim:**

1. A process for the preparation of Teriflunomide, comprising the steps of:
   a) purifying 4-trifluoromethyl aniline (3),
   b) reacting 4-trifluoromethyl aniline (3) obtained from step a) with cyanoacetic acid (7) in presence of a carbodiimide in ethyl acetate to get 2-cyano-N-(4-trifluoromethylphenyl) acetamide (6),
   c) reacting the intermediate (6) with sodium hydride, followed by acetyl chloride to yield crude teriflunomide, which is further recrystallized in ethyl acetate to get pure teriflunomide.

2. The process according to claim 1, wherein 4-trifluoromethyl aniline (3) is purified using high vacuum distillation.

3. The process according to claim 1, wherein carbodiimide is dicyclohexylcarbodiimide.

4. A process for the purification of Teriflunomide, comprising the steps of:
   a) dissolving teriflunomide in ethylacetate solvent,
   b) isolating teriflunomide.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2016/050059

A. CLASSIFICATION OF SUBJECT MATTER
C07C255/23,C07C253/14 Version=2016.01

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)

C07C

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 practicable, search terms used)

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | ELIZABETH ET AL; "Synthesis, Structure-Activity Relationships, and Pharmacokinetic Properties of Dihydroorotate Dehydrogenase Inhibitors: 2-Cyano-3-cyclopropyl-3-hydroxy-N-[3'-methyl-4'-(trifluoromethyl) phenyl]propenamide and Related Compounds", Journal of Medicinal Chemistry, 1996, Volume 39, Issue 23, Pages 4608-4621. Scheme 2, page 4610 | 1-4 |
| Y | WO2014177978 A2; VENKAT RAMAN ET AL, 06 Nov 2014 (06-11-2014). Examples, Claims | 1-4 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
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