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(54) Title: METHOD FOR THE PREVENTION OR REDUCTION OF CARIOVASCULAR EVENTS ASSOCIATED WITH CORONARY INTERVENTION

(57) **Abstract**

This invention provides a method for the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal, particularly a human, which comprises administering to the subject N–(3',4'–dimethoxycinnamoyl)anthranilic acid (N–5') or a pharmaceutically acceptable salt thereof in a daily dose of from greater than 300 mg to about 1,200 mg for a treatment period of up to 89 days in association with coronary intervention.

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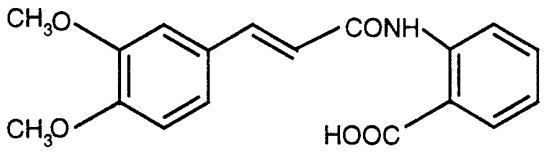
METHOD FOR THE PREVENTION OR REDUCTION OF CARDIOVASCULAR EVENTS ASSOCIATED WITH CORONARY INTERVENTION

Field of Invention

The present invention relates to a method for the prevention or reduction of cardiovascular events associated with coronary intervention.

More particularly, the method comprises administrating to a mammal, particularly a human patient, after coronary intervention an oral or parental dose of N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') (Tranilast) represented by the following formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient.



(I)

BACKGROUND OF THE INVENTION

1. Technical Field of the Invention

Coronary intervention is a percutaneous procedural approach to the treatment of ischemic heart disease such as angina pectoris and myocardial infarction. Coronary intervention technically involves mechanical revascularization of a stenosed lesion in a coronary artery by means of a balloon catheter, mechanical stent placement, an atherectomy catheter and the like. As a consequence, coronary intervention often causes restenosis due to damaged intima and media cells. Patients who experience restenosis may require revascularization procedures to correct the condition. Other cardiovascular events associated with coronary intervention include myocardial infarction and death.

Up to the present time, there has not been any effective drug for the prevention or reduction of cardiovascular events associated with coronary intervention.

2. DESCRIPTION OF THE RELATED ART

Tranilast is sold commercially as a drug for the treatment of allergic diseases, e.g., allergic bronchitis, allergic asthma, atopic dermatitis, and the like, based on the activity exhibited by the drug for inhibiting release of chemical mediators [The Journal of Allergy and Clinical Immunology, Vol. 57, No. 5, pp. 396-407, (1976)].

More recently, in Biochemical Pharmacology, Vol. 36, No. 4, pp. 469-474 (1987), it was reported that Tranilast inhibits fibroblast proliferation and collagen accumulation.

United States Patent No. 5,385,935 ('935) claims the use of Tranilast in the inhibition of restenosis associated with coronary intervention but indicates that a treatment period of at least three consecutive months is required for efficacy. The requirement of a three plus month treatment period was premised, in part, upon a publication in the Japanese College of Cardiology (1988), cited in the '935 patent. This publication discloses the treatment of patients subjected to the PTCA procedure with Tranilast in a daily oral dose of 300 mg for 30 consecutive days after the PTCA procedure. The clinical data obtained from this study did not indicate any significant efficacy for inhibiting a restenosis effect associated with the PTCA procedure at the tested dosage and duration. The '935 patent indicates that the lack of efficacy for inhibiting a restenosis effect with Tranilast after the 30 day protocol was due to a too short duration of treatment.

Conversely, the '935 patent demonstrated that an extended period of Tranilast treatment was effective for lowering the incidence of post-procedure restenosis associated with PTCA. It was found that dosing patients with Tranilast for a duration of at least about three months (i.e., a term of at least about 90 consecutive days of treatment) reduced the incidence of restenosis associated with the PTCA procedure. In one clinical study, when patients were administered Tranilast in a daily oral dose of 600 mg for three consecutive months after the PTCA procedure, the incidence of restenosis was less than about 20%. As reported in the '935 patent, the incidence of restenosis associated with the PTCA procedure usually is about 40%.

Additionally, in Nobuyoshi M. et al., J Am Coll. Cardiol. 1988; 12: 616 to 623, it was observed that most cases of restenosis after successful coronary angioplasty occur within 6 months after the procedure, particularly between 1 and 3 months after coronary angioplasty.

Thus, restenosis is considered to take place predominantly in the healing phase after coronary angioplasty and, using Tranilast, to require at least three months of treatment in order to show a therapeutic effect.

Numerous advantages would be realized if Tranilast could be efficaciously administered for the prevention or reduction of cardiovascular events associated with coronary intervention for a treatment period of less than three months. The advantages of a shorter dosing protocol include: increased patient compliance, less total medication taken by the patient, reduced side effect profile and providing a more cost effective treatment.

It has now surprisingly been discovered that Tranilast can be suitably administered in the prevention or reduction of cardiovascular events associated with coronary intervention for a period of less than three months.

SUMMARY OF THE INVENTION

This invention relates to a method for the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal, particularly a human, which comprises administering to the subject N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') or a pharmaceutically acceptable salt thereof in a daily dose of from greater than 300 mg to about 1,200 mg for a treatment period of up to 89 days in association with coronary intervention.

Other objects, features and advantages of the present invention will become apparent from the following description and examples.

DETAILED DESCRIPTION OF THE INVENTION

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

Illustrative of acceptable salts for use herein are inorganic salts such as sodium or calcium salt, or organic salts formed with amines such as morpholine, piperidine, arginine, and the like.

As coronary intervention in the present invention, for example, Percutaneous Transluminal Coronary Angioplasty (PTCA), Directional Coronary Atherectomy and Stent placement can be included.

By the term "cardiovascular events" as used herein, is preferably meant myocardial infarction, death and the need for revascularization procedures associated with coronary intervention. Also included in the definition of "cardiovascular events" is a restenosis effect associated with coronary intervention.

By the term "prevention or reduction" of cardiovascular events as used herein, is meant that the incidence of myocardial infarction and/or death and/or the need for revascularization procedures associated with coronary intervention in Trailast treated patients are prevented or reduced in comparison to untreated patients. Also, the incidence of a restenosis effect is prevented or reduced in Trailast treated patients in comparison to untreated patients.

By the term "in association with coronary intervention" as used herein, is meant that the treatment with Tranilast can commence immediately, for example within 4 to 8 hours, after coronary intervention, within a few days, for example 2 days, after coronary intervention or for a period of several days, for example about 7 days, prior to coronary intervention. Also contemplated within the term "in association with coronary intervention"

is a dosing protocol in which a dose or several doses are skipped, for example in the morning of or on the day of coronary invention.

By the term " collected over the observation period" as used herein, means a period of up to 12 months.

The present invention relates to a method for the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal, particularly a human, which comprises administering to the subject N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') (Tranilast) or a pharmaceutically acceptable salt thereof in a daily dose of from greater than 300 mg to about 1,200 mg for a treatment period of up to 89 days in association with coronary intervention.

A preferred daily dosage amount of Tranilast for use in the present invention is about 400 mg to about 1,200 mg. A more preferred daily dosage amount of Tranilast for use in the present invention is from about 500 mg to about 1,000 mg. The most preferred daily dosage amount of Tranilast for use in the present invention is from about 600 mg to about 900 mg. Particularly preferred is a daily dosage amount of about 600 mg of Tranilast for use in the present invention. Particularly preferred is a daily dosage amount of about 900 mg of Tranilast for use in the present invention.

A preferred treatment period for use in the present invention is about 60 days in association with coronary intervention. A more preferred treatment period for use in the present invention is about 45 days in association with coronary intervention. The most preferred treatment period for use in the present invention is about 30 days in association with coronary intervention. A preferred treatment period for use in the present invention is 14 days in association with coronary intervention.

A preferred method of use in the current invention is a method for preventing or reducing myocardial infarction associated with coronary intervention.

A preferred method of use in the current invention is a method for preventing or reducing death associated with coronary intervention.

A preferred method of use in the current invention is a method for preventing or reducing the need for revascularization procedures associated with coronary intervention.

A preferred method of use in the current invention is a method for preventing or reducing restenosis associated with coronary intervention.

The efficacy of the presently invented method is demonstrated by the Examples below.

The present invention therefor provides a method for the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal, particularly a human, which comprises administering to the subject N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') (Tranilast) or a pharmaceutically acceptable

salt thereof in a daily dose of from greater than 300 mg to about 1,200 mg for a treatment period of up to 89 days in association with coronary intervention.

The invention also provides for the use of Tranilast or a pharmaceutically acceptable salt thereof in the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal, particularly a human, in a daily dose of from greater than 300 mg to about 1,200 mg for a treatment period of up to 89 days in association with coronary intervention.

The invention also provides for a pharmaceutical composition for use in the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal, particularly a human, which comprises Tranilast or a pharmaceutically acceptable salt thereof in a daily dose of from greater than 300 mg to about 1,200 mg for a treatment period of up to 89 days in association with coronary intervention.

Tranilast is generally described in United States Patent 3,940,422. Tranilast and pharmaceutically acceptable salts and compositions thereof can be readily prepared by known methods such as described in United States Patent 3,940,422.

When Tranilast or a pharmaceutically acceptable salt thereof is employed therapeutically, it can be administered orally or parentally in appropriate dosage forms, such as powder, granules, tablets, capsules, injectable solutions, and the like.

A Tranilast pharmaceutical composition can be formulated by admixing suitable carriers such as excipients, disintegrators, binders, brighteners, and the like, and preparing in accordance with conventional molding methods and dosage forms.

For example, a powdered dosage form can be formulated by admixing Tranilast or a pharmaceutically acceptable salt thereof with suitable excipients, binders, brighteners, and the like.

Tablets can be formulated by admixing Tranilast or a pharmaceutically acceptable salt thereof with suitable excipients, disintegrators, binders, brighteners, and the like, and compressing the mixture with conventional molding equipment. The tablets also can be coated to provide film coated tablets, sugar-coated tablets, enteric-coated tablets, and the like.

Capsules can be formulated by admixing Tranilast or a pharmaceutically acceptable salt thereof thereof with suitable excipients, brighteners, and the like, and filling the mixture in capsules, or by forming granules containing Tranilast or a pharmaceutically acceptable salt thereof with conventional molding equipment, and filling the formed granules in capsules.

When a pharmaceutical composition of the present invention is employed therapeutically, the daily dosage of Tranilast or a pharmaceutically acceptable salt thereof as an active ingredient will be an efficacious, nontoxic quantity selected from the range of

from above 300 mg to about 1,200 mg of active compound, preferably from about 500 mg to about 1,000 mg of active compound, particularly preferred is a dosage of about 600 mg, particularly preferred is a dosage of about 900 mg, per adult patient preferably by oral administration for a treatment period of up to 89 days, preferably for about 60 days and most preferably for about 30 days in association with coronary intervention. The dosage and term of administration can be changed depending upon the weight and age and sex of the patient, the severity of the condition to be treated, and the like.

When treating a human patient in need of treatment of cardiovascular events associated with coronary intervention, the above indicated dose may be split and administered preferably from 1-6 times daily, preferably about 2 times a day, orally or parenterally. Preferred forms of parenteral administration include topically, rectally, transdermally, by injection and continuously by infusion. Oral administration is preferred.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular patient being treated will result in a need to adjust dosages, including patient age, weight, diet, and time of administration.

No unacceptable toxicological effects are expected when compound of the invention is administered in accordance with the present invention.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

EXAMPLE I

Efficacy of the invented method for treatment of restenosis associated with the PCTA procedure is demonstrated by the following.

One hundred forty nine lesions with a partial occlusion, which undergo successful PTCA procedures with smooth dilation, are selected for study. These lesions are divided into two groups, and both groups do not differ significantly with sex, distribution of coronary artery or ratio of lesions restenosed after PTCA; One group (about 49 lesions) receives Tranilast in a daily dose of 600 mg, preferably in two 300 mg tablets administered 12 hours apart (hereinafter identified as group I), and another group (about 100 lesions) does not receive Tranilast (hereinafter identified as group II). In addition, patients may also be given a calcium antagonist, nitrates and/or anti-platelet agents. These drugs are

administered for 30 consecutive days after PTCA, and follow-up coronary angiography is performed within one year after PTCA.

The measurements are made in two projections and all measurements (before and immediately after PTCA and at final follow-up) are made in the same projection for more accurate comparisons.

Diameter stenosis is calculated as the mean of measurements, and restenosis is defined as a loss of at least 50% of the initial gain in luminal diameter accomplished by dilation or by 50% stenosis of a dilated vessel.

The comparative clinical data collected over the observation period demonstrate the efficacy of 30 days Tranilast treatment for the prevention or reduction of restenosis in patients after PTCA procedures.

EXAMPLE II

Efficacy of the invented method for preventing or reducing incidence of myocardial infarction associated with the PCTA procedure is demonstrated by the following.

One hundred forty nine lesions with a partial occlusion, which undergo successful PTCA procedures with smooth dilation, are selected for study. These lesions are divided into two groups, and both groups do not differ significantly with sex, distribution of coronary artery or ratio of lesions restenosed after PTCA; One group (about 49 lesions) receives Tranilast in a daily dose of 900 mg, preferably in two 450 mg tablets administered 12 hours apart (hereinafter identified as group III), and another group (about 100 lesions) does not receive Tranilast (hereinafter identified as group IV). In addition, patients may also be given a calcium antagonist, nitrates and/or anti-platelet agents. These drugs are administered for 30 consecutive days after PTCA.

The comparative clinical data collected over the observation period demonstrate the efficacy of 30 days Tranilast treatment for the prevention or reduction of incidence of myocardial infarction in patients after the PTCA procedure.

EXAMPLE III

Efficacy of the invented method for preventing or reducing incidence of death associated with the PCTA procedure is demonstrated by the following.

One hundred forty nine lesions with a partial occlusion, which undergo successful PTCA procedures with smooth dilation, are selected for study. These lesions are divided into two groups, and both groups do not differ significantly with sex, distribution of coronary artery or ratio of lesions restenosed after PTCA; One group (about 49 lesions)

receives Tranilast in a daily dose of 600 mg, preferably in two 300 mg tablets administered 12 hours apart (hereinafter identified as group V), and another group (about 100 lesions) does not receive Tranilast (hereinafter identified as group VI). In addition, patients may also be given a calcium antagonist, nitrates and/or anti-platelet agents. These drugs are administered for 30 consecutive days after PTCA.

The comparative clinical data collected over the observation period demonstrate the efficacy of 30 days Tranilast treatment for the prevention or reduction of incidence of death in patients after PTCA procedures.

EXAMPLE IV

Efficacy of the invented method for preventing or reducing the need for revascularization procedures associated with PCTA procedure is demonstrated by the following.

One hundred forty nine lesions with a partial occlusion, which undergo successful PTCA procedures with smooth dilation, are selected for study. These lesions are divided into two groups, and both groups do not differ significantly with sex, distribution of coronary artery or ratio of lesions restenosed after PTCA; One group (about 49 lesions) receives Tranilast in a daily dose of 900 mg, preferably in two 450 mg tablets administered 12 hours apart (hereinafter identified as group VII), and another group (about 100 lesions) does not receive Tranilast (hereinafter identified as group VIII). In addition, patients may also be given a calcium antagonist, nitrates and/or anti-platelet agents. These drugs are administered for 30 consecutive days after PTCA.

The comparative clinical data collected over the observation period demonstrate the efficacy of 30 days Tranilast treatment for the prevention or reduction for the need for revascularization procedures in patients after PTCA procedures.

While the preferred embodiments of the invention are illustrated by the above, it is to be understood that the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming within the scope of the following claims is reserved.

What is claimed is:

1. A method for the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal which comprises administering to the subject N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') or a pharmaceutically acceptable salt thereof in a daily dose of from greater than 300 mg to about 1,200 mg for a treatment period of up to 89 days in association with coronary intervention.

2. The method of claim 1 wherein the mammal is a human.

3. The method of claim 2 wherein the dosage is from about 500-1000 mg of N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') or a pharmaceutically acceptable salt thereof.

4. The method of claim 2 wherein the dosage is from about 600-900 mg of N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') or a pharmaceutically acceptable salt thereof.

5. The method of claim 2 wherein the dosage is about 600 mg of N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') or a pharmaceutically acceptable salt thereof.

6. The method of claim 2 wherein the dosage is about 900 mg of N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') or a pharmaceutically acceptable salt thereof.

7. The method of claim 2 wherein the treatment period is about 60 days.

8. The method of claim 2 wherein the treatment period is about 45 days.

9. The method of claim 2 wherein the treatment period is about 30 days and commences immediately after coronary intervention.

10. The method of claim 2 wherein the treatment period is about 30 days and commences about 7 days prior to coronary intervention.

11. The method of claim 2 wherein the treatment period is about 14 days.

12. The method of claim 2 wherein the cardiovascular event is restenosis.

13. The method of claim 2 wherein the cardiovascular event is myocardial infarction.

14. The method of claim 2 wherein the cardiovascular event is death.

15. The method of claim 2 wherein the cardiovascular event is the need for a revascularization procedure.

16. A method in accordance with claim 2 wherein the dosage is administered orally.

17. A method in accordance with claim 2 wherein the coronary intervention is Percutaneous Transluminal Coronary Angioplasty.

18. A method in accordance with claim 2 wherein the coronary intervention is Directional Coronary Atherectomy.

19. A method in accordance with claim 2 wherein the coronary intervention is Stent Placement.

20. Use N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal, particularly a human, when administered in association with coronary intervention in a daily dose of from about 300 mg to about 1,200 mg for a treatment period of up to 89 days.

21. The use according to claim 20 wherein the mammal is a human.

22. The use according to claim 21 wherein the dosage is from about 500-1000 mg of N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') or a pharmaceutically acceptable salt thereof.

23. The use according to claim 21 wherein the dosage is from about 600-900 mg of N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') or a pharmaceutically acceptable salt thereof.

24. The use according to claim 21 wherein the dosage is about 600 mg of N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') or a pharmaceutically acceptable salt thereof.

25. The use according to claim 21 wherein the dosage is about 900 mg of N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') or a pharmaceutically acceptable salt thereof.

26. The use according to claim 21 wherein the treatment period is about 60 days.

27. The use according to claim 21 wherein the treatment period is about 45 days.

28. The use according to claim 21 wherein the treatment period is about 30 days and commences immediately after coronary intervention.

29. The use according to claim 21 wherein the treatment period is about 30 days and commences about 7 days prior to coronary intervention.

30. The use according to claim 21 wherein the treatment period is about 14 days.

31. The use according to claim 21 wherein the cardiovascular event is restenosis.

32. The use according to claim 21 wherein the cardiovascular event is myocardial infarction.

33. The use according to claim 21 wherein the cardiovascular event is death.

34. The use according to claim 21 wherein the cardiovascular event is the need for a revascularization procedure.

35. The use according to claim 21 wherein the dosage is administered orally.

36. The use according to claim 21 wherein the coronary intervention is Percutaneous Transluminal Coronary Angioplasty.

37. The use according to claim 21 wherein the coronary intervention is Directional Coronary Atherectomy.

38. The use according to claim 21 wherein the coronary intervention is Stent Placement.

39. A pharmaceutical composition for use in the prevention or reduction of cardiovascular events associated with coronary intervention in a mammal, particularly a human, when administered in association with coronary intervention in a daily dose of from about 300 mg to about 1,200 mg for a treatment period of up to 89 days which comprises N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') or a pharmaceutically acceptable salt thereof.

40. A composition according to claim 39 wherein the mammal is a human.

41. A composition according to claim 40 wherein the dosage is from about 500-1000 mg of N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') or a pharmaceutically acceptable salt thereof.

42. A composition according to claim 40 wherein the dosage is from about 600-900 mg of N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') or a pharmaceutically acceptable salt thereof.

43. A composition according to claim 40 wherein the dosage is about 600 mg of N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') or a pharmaceutically acceptable salt thereof.

44. A composition according to claim 40 wherein the dosage is about 900 mg of N-(3',4'-dimethoxycinnamoyl)anthranilic acid (N-5') or a pharmaceutically acceptable salt thereof.

45. A composition according to claim 40 wherein the treatment period is about 60 days.

46. A composition according to claim 40 wherein the treatment period is about 45 days.

47. A composition according to claim 40 wherein the treatment period is about 30 days and commences immediately after coronary intervention.

48. A composition according to claim 40 wherein the treatment period is about 30 days and commences about 7 days prior to coronary intervention.

49. A composition according to claim 40 wherein the treatment period is about 14 days.

50. A composition according to claim 40 wherein the cardiovascular event is restenosis.

51. A composition according to claim 40 wherein the cardiovascular event is myocardial infarction.

52. A composition according to claim 40 wherein the cardiovascular event is death.

53. A composition according to claim 40 wherein the cardiovascular event is the need for a revascularization procedure.

54. A composition according to claim 40 wherein the dosage is administered orally.

55. A composition according to claim 40 wherein the coronary intervention is Percutaneous Transluminal Coronary Angioplasty.

56. A composition according to claim 40 wherein the coronary intervention is Directional Coronary Atherectomy.

57. A composition according to claim 40 wherein the coronary intervention is Stent Placement.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/02622

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/24
US CL :514/535, 563, 930; 549/441
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)

U.S. : 514/535, 563, 930; 549/441

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
none

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

STN, caplus, uspatfull, reg
tranilast, cardiovascular, restenosis, myocardial infarct, heart attack

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,385,935 A (TAMAI et al.) 31 January 1995, col. 3, lines 1-11.	1-38
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X		39-57
A	US 5,693,337 A (SUZUKI et al.) 02 December 1997, col. 6, line 35.	39-57

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

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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