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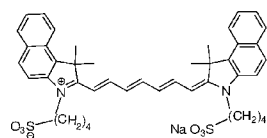
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[Continued on next page]

(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF INDOCYANINE GREEN



Formula I

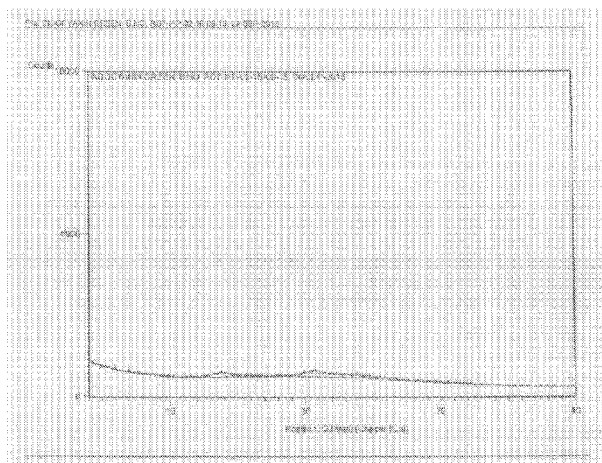


Fig. 1

(57) Abstract: The present invention involves an improved process for the preparation of Indocyanine green of Formula (I) having high purity of about 99%, wherein the process comprises steps of reacting 1,1,2-trimethyl-1H-benzo[e]indole with 1,4-butane sulfone in boiling solvent to give 4-(1,1,2-trimethyl-1H-benzo[e]indolium-3-yl)butane-1-sulfonate. Followed by reacting 4-(1,1,2-trimethyl-1H-benzo[e]indolium-3-yl)butane-1-sulfonate of Formula (IV) and N-phenyl-N-((1E,3E,5E)-5-(phenylimino)penta-1,3-dienyl)acetamide of formula (V) in presence of sodium acetate and alcohol; and extracting the title compound formula (I) with an ester solvent.



(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

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**AN IMPROVED PROCESS FOR THE PREPARATION OF INDOCYANINE
GREEN**

FIELD OF INVENTION

- 5 The present invention provides a novel process for the preparation of stable amorphous form of Indocyanine green.

BACKGROUND OF THE INVENTION

Indocyanine green, chemically known as sodium 4-[2-[(1*E*,3*E*,5*E*,7*Z*)-7-[1,1-dimethyl-3-
10 (4-sulfonatobutyl)benzo[*e*]indol-2-ylidene]hepta-1,3,5-trienyl]-1,1-dimethylbenzo[*e*]indol-3-ium-3-yl]butane-1-sulfonate, used in medical diagnostics. It is used for determining cardiac output, hepatic function, and liver blood flow, and for ophthalmic angiography.

15 Indocyanine green is a fluorescent dye which is used in medicine as an indicator substance (e.g. for photometric hepatic function diagnostics and fluorescence angiography) in cardiac, circulatory, hepatic and ophthalmic conditions. It is administered intravenously and, depending on liver performance, is eliminated from the body with a half life of approx. 3–4 minutes. Indocyanine green sodium salt is normally available in
20 powder form and can be dissolved in various solvents; 5% (<5% depending on batch) sodium iodide is usually added to ensure better solubility. The sterile lyophilisate of a water-Indocyanine green solution is approved many European countries and the United States under the names Indocyanine green-Pulsion and Indocyanine green as a diagnostic for intravenous use.

25

US2895955 describes a structure including Indocyanine green and its pharmaceutically acceptable salts. Indocyanine green as its pharmaceutical acceptable salts[iodide disodium salt]. In accordance with the US'955 patent, Indocyanine green can prepared by reacting 1,1,2-trimethyl-1H-benzo[*e*]indole with 1,4-butane sultone in without solvent to produce
30 4-(1,1,2-trimethyl-1H-benzo[*e*]indolium-3-yl)butane-1-sulfonate, followed by treatment with N-phenyl-N-((1*E*,3*E*,5*E*)-5-(phenylimino)penta-1,3-dienyl)acetamide triethyl amine in ethanol and extraction in ether, and making sodium iodide salt in alcoholic solvent. In

this process 4-(1,1,2-trimethyl-1H-benzo[e]indolium-3-yl)butane-1-sulfonate compound is not isolating or not easy filtration, also Indocyanine green not getting purity 99.0%.

According to PCT application WO2014/165216 patent, intermediate of N-((1E,3E,5E)-5-(phenylimino)penta-1,3-dien- 1-yl) benzenaminium chloride treated with acetic anhydride
5 in presence of triethylamine at -20°C to give N-phenyl-N-((1E,3E,5E)-5-(phenylimino)penta-1,3-dienyl)acetamide, reaction carried out concentrated under high vacuum.

10 According to PCT application WO 2014192972 patent, intermediate of N-((1E,3E,5E)-5-(phenylimino)penta-1,3-dien- 1-yl) benzenaminium chloride treated with acetic anhydride in presence of sodium acetate at 100°C to give N-phenyl-N-((1E,3E,5E)-5-(phenylimino)penta-1,3-dienyl)acetamide, reaction 4-(1,1,2-trimethyl-1H-benzo[e]indolium-3-yl)butane-1-sulfonate in water.

15 US5750722 disclosed a process for preparing Indocyanine green acetone as purification solvent. And also US20090069573 patent purification solvent is methylene dichloride.

Wang, Dun; Jin, Wenshu; Qin, Enwei; Wang, Shuobing; Li, Peng Zhongguo Yiyao
20 Gongye Zazhi Volume 37, Issue 9, Pages 584-585(2006) process for making indocyanine green.

Kundu, Kousik; Knight, Sarah F.; Willett, Nick; Lee, Sungmun; Taylor, W. Robert; Murthy, Niren Angewandte Chemie, International Edition Volume 48, Issue 2, Pages 299-
25 303(2009) disclosed process for making Hydrocyanines: a class of fluorescent sensors that can image reactive oxygen species in cell culture, tissue, and in vivo.

According to PCT application WO2007/120579 patent describe process for making Indocyanine green as sodium iodide salt.

30

OBJECTIVE OF THE INVENTION

The main objective of the present invention is to provide an improved process for the preparation of Indocyanine green

- 5 Yet another objective of the present invention is to provide an improved process for preparing a high purity NLT (Not Less Than) 98.0 % of intermediate compound formula(IV).

- Yet another objective of the present invention is to provide a simple and environmentally friendly process for the preparation of Indocyanine green, which avoids use of hazardous and expensive reagents.
- 10

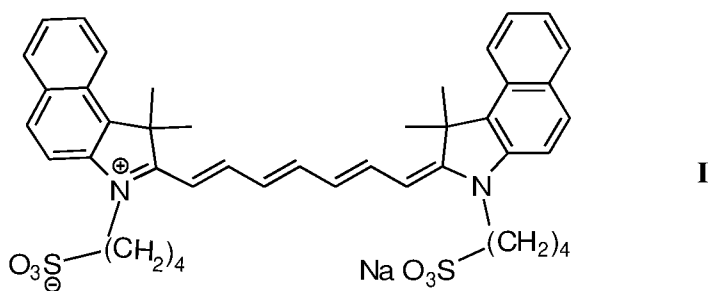
Yet another objective of the present invention is to provide a process with a good yield and high purity NLT(Not Less Than) 99.0%

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Yet another objective of the present invention is to provide an improved process for Indocyanine green, which is simple and industrially applicable.

SUMMARY OF INVENTION

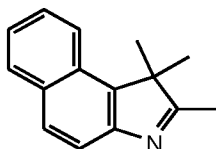
- 20 In one aspect the present invention provides a novel and improved one-pot process for the preparation of sodium iodide Indocyanin green of Formula (I) having >99.0%



said process comprises the steps of:

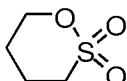
- a) reacting 1,1,2-trimethyl-1H-benzo[e]indole Formula (II)

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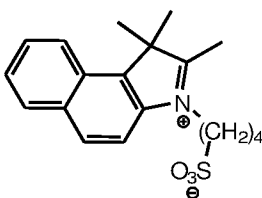
II

with 1,4-butane sultone of Formula (III)



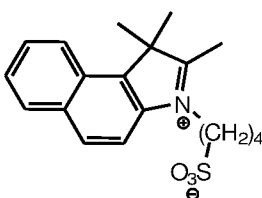
III

in boiling solvent to give 4-(1,1,2-trimethyl-1H-benzo[e]indolium-3-yl)butane-1-sulfonate of Formula (IV);



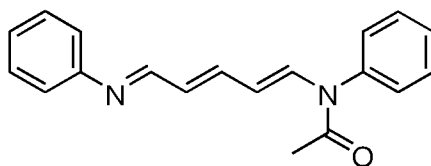
IV

b) reacting 4-(1,1,2-trimethyl-1H-benzo[e]indolium-3-yl)butane-1-sulfonate of Formula
5 (IV)



IV

and N-phenyl-N-((1E,3E,5E)-5-(phenylimino)penta-1,3-dienyl)acetamide compound
formula(V)

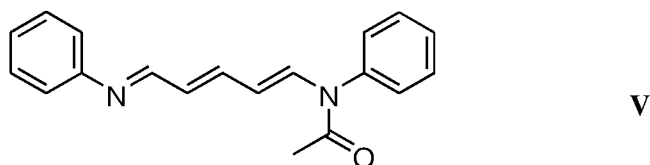


V

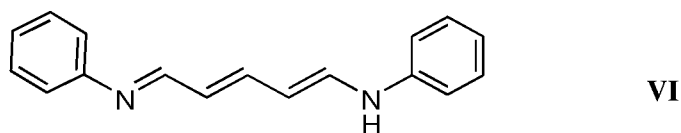
in presence of sodium acetate and alcohol as solvent to give title compound formula(I).

5

In another aspect the present invention provides a process for preparation of the compound of formula(V)



- 5 wherein the process comprises reacting (E)-N,N'-((1E,3E)-penta-1,3-diene-1-yl-5-ylidene)dianiline or hydrochloride of compound formula (VI)



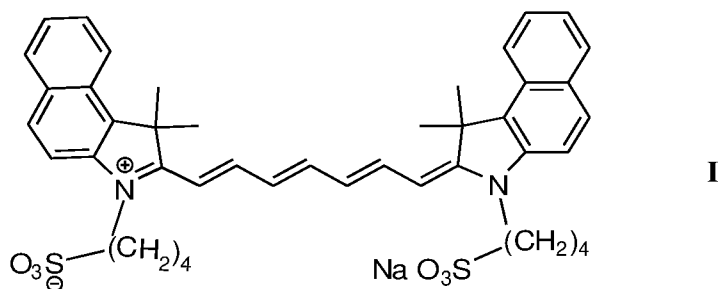
with acetic anhydride in presence of organic base.

10 **BRIEF DESCRIPTION OF ACCOMPANYING DRAWINGS:**

Figure-I: X-Ray Powder Diffraction (XRPD) pattern of Indocyanine green Formula (I) as a stable Amorphous form

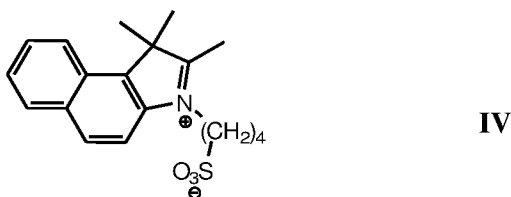
DETAILED DESCRIPTION OF THE INVENTION

- 15 An improved process for the preparation of Indocyanine green of Formula (I) having >99.0% and without using sodium iodide.

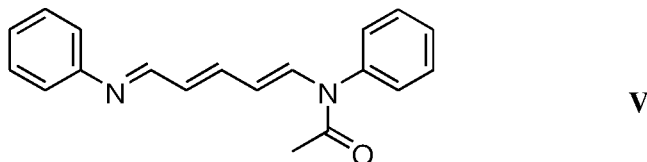


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condensation of the 4-(1,1,2-trimethyl-1H-benzo[e]indolium-3-yl)butane-1-sulfonate of Formula (IV)



and N-phenyl-N-((1E,3E,5E)-5-(phenylimino)penta-1,3-dienyl)acetamide compound formula(V)



in presence of sodium acetate and alcohol as solvent followed by extraction using an extraction solvent to give title compound formula(I).

The condensation reaction is carried out in presence of alkali metal acetate salt, such as sodium, potassium, lithium salt of acetate, preferably sodium acetate.

10 The present invention is carried out in alcohol as solvent, alcohol solvent define as methanol, ethanol, isopropanol, n-butanol but preferably solvent is methanol.

It is carried out at temperature range about 50°C to 90°C, but preferably temperature is 60°C to 70°C.

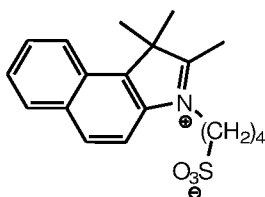
15 The extraction is carried out in ester solvents such as ethyl acetate, isopropyl acetate, methyl acetate, preferably ethyl acetate.

The crude compound purification reaction is usually run in a suitable ketonic solvent such as water or a mixture of water and a ketonic solvent such as acetone, methyl ethyl ketone,

20 preferably solvent is acetone and water.

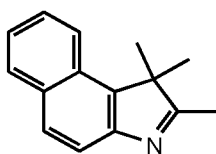
According to the present invention compound of formula(IV) is prepared

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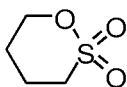
IV

using the 1,1,2-trimethyl-1H-benzo[e]indole compound formula(II) and 1,4-butane sultone compound formula(III)



II

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III

in high boiling solvent to give 4-(1,1,2-trimethyl-1H-benzo[e]indolium-3-yl)butane-1-sulfonate of Formula (IV)

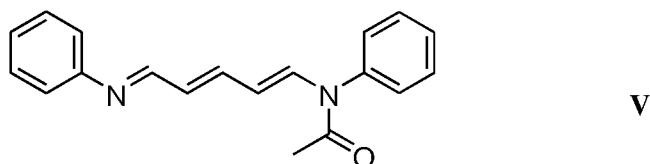
- 10 The solvents used in the reaction between compound of formula II and compound of formula III is selected from toluene, xylene, hexane, sulfolene, silicone oil but preferably solvent is sulfolene.

- The reaction for preparing compound formula(IV) reaction is carried out at temperature
15 range from about 110°C to about 180°C, preferably in the temperature range from 120°C to 140°C.

The present invention also provides a process for the preparation of the compound formula(V)

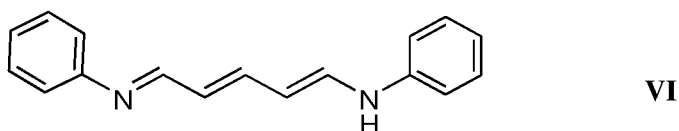
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Wherein the process comprises reacting (E)-N,N'-((1E,3E)-penta-1,3-diene-1-yl-5-ylidene)dianiline or hydrochloride of compound formula (VI)

5



with acetic anhydride in presence of organic base.

The preparation of compound of formula(V) reaction is carried out in an organic base such as primary amine, secondary, tertiary amine, methyl amine, ethyl amine, dimethyl amine, triethyl amine, preferably triethyl amine.

The solvent can also be selected from chlorinated solvent such as methylene dichloride, ethylene dichloride, preferably solvent is methylene dichloride.

15

The temperature range for carrying out the preparation of compound of formula V is from about 0°C to about 30°C, preferably a temperature range from 0°C to 5°C.

Throughout the description and claims the word "comprise" and variations of the word are not intended to exclude other technical features, additives, components, or steps. The content of the abstract of the present application is incorporated herein as reference. Additional objects, advantages and features of the invention will become apparent to those skilled in the art upon examination of the description or may be learned by practice

of the invention. The following examples are provided by way of illustration, and is not intended to be limiting of the present invention.

Example – 1

5 **Preparation of 4-(1,1,2-trimethyl-1H-benzo[e]indolium-3-yl)butane-1-sulfonate**

1,1,2-trimethyl-1H-benzo[e]indole (100 gm, 1.0 equivalent) was suspended in sulfolane (100 ml, 1.0 vol) and 1,4-Buane sultone was added and mixture was heated to 120-130°C for 3-4hrs, upon cooling to RT (Room temperature) add dichloromethane and stir for 4-5hrs at 25-30°C. The mixture was filtered and the resulting solid was washed with
10 dichloromethane. dried under vacuum and analyzed by HPLC (High performance liquid chromatography) (153g, 92.0 percent). Having HPLC more than 98.0%

Yield: 153 gm

Chromatographic Purity (by HPLC): ≥98 (% area),

15 **Example – 2**

Preparation of N-phenyl-N-((1E,3E,5E)-5-(phenylimino)penta-1,3-dienyl)acetamide

A solution of acetic anhydride (32.4g, 3.6 equivalent) was added to a cooled (0-5 °C), stirred suspension of N-((1E,3E',5Z)-5-(phenylimino)penta-1,3-dien-1-yl)benzen aminium chloride (25g, 1.0 equivalent) and triethylamine (28.3g, 4.47 equivalent) in CH₂Cl₂ (500
20 mL). The resulting clear solution was stirred for another 3h at RT (Room temperature). Add water and stir for 5min, separated dichloromethane and concentrated under high vacuum. The residue containing N-phenyl-N-((1E,3E',5Z)-5-(phenylimino)penta-1,3-dien-1-yl)acetamide to yield the title compound as an oily residue.

Yield: 25-26 gm (Oily liquid)

25 **Chromatographic Purity (by TLC): ≥95 (% area),**

Example – 3

Preparation of Indocyanine Green

Charge methanol to the assembly at 25-30°C and then charge 4-(1,1,2-trimethyl-1H-benzo[e]indolium-3-yl)butane-1-sulfonate(56.17g 1.95equivalennt) and anhydrous sodium acetate(35.1g, 2.6 Equivalent) stir solution for 5min, then heat to reflux (65-70°C) and maintain for 15-30min. Then added solution of N-phenyl-N-((1E,3E,5E)-5-

(phenylimino)penta-1,3-dienyl)acetamide (25gm) in methanol (25ml) at reflux temperature(65-70°C). Reaction progress monitored by TLC (Thin layer chromatography) or HPLC .4-(1,1,2-trimethyl-1H-benzo[e]indolium-3-yl)butane-1-sulfonate NMT (Not More Than) -1.0%. After completion of reaction cool to 25-30°C
5 and Charge 1000ml ethyl acetate and stir for 6 hrs at 25-30°C. Filter and wash with 50ml ethyl acetate. The desired product was obtained as a green colour crystalline powder (46-50.5gm, 80%). Having HPLC purity more than >98.0%.

Purification of Indocyanine Green

10 Example:1

Add DM 315ml water to the assembly at 25-30°C and then add 45g Indocyanine green (1.0 equivalent), heat to 55-60°C. And add 900ml acetone and reflux for 1hr.gradually cool to RT (Room temperature)and stir for 12hrs at 25-30°C. Filter and wash with acetone. The desired product was obtained as a green colour crystalline powder (25 to
15 35gm). Having HPLC purity more than >99.0%. XRPD pattern of powder diffractogram of Indocyanine green (FIG. I).

Example:2

Add DM (DE-mineralization water) 315ml water to the assembly at 25-30°C and then
20 add 45g Indocyanine green (1.0 equivalent) and sodium iodide(0.9g,2.0%w/w), heat to 55-60°C.and add 900ml acetone and reflux for 1hr.gradually cool to RT (Room temperature) and stir for 12hrs at 25-30°C. Filter and wash with acetone The desired product was obtained as a green color crystalline powder (25 to 35gm). Having HPLC purity more than >99.0%.

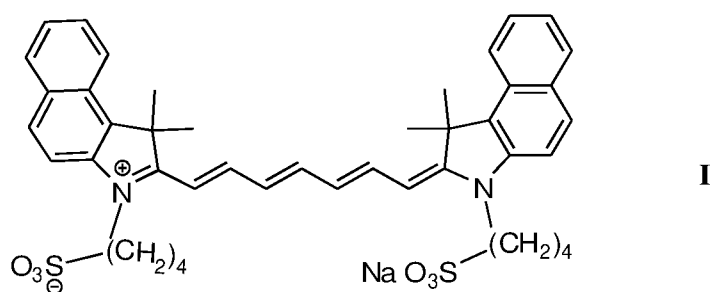
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Example:3

Add acetonitrile to the assembly at 25-30°C and then add 45g Indocyanine green (1.0 equivalent), heat to 55-60°C. And reflux for 1hr.gradually cool to RT (Room temperature) and stir for 2-3hrs at 25-30°C. Filter and wash with acetone. The desired
30 product was obtained as a green colour crystalline powder (25 to 35gm). Having HPLC purity more than >99.0%.

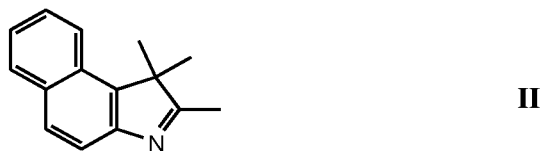
CLAIMS

1. An improved process for preparation of Indocyanine green of Formula (I) having high
 5 purity,



wherein the process comprises steps of:

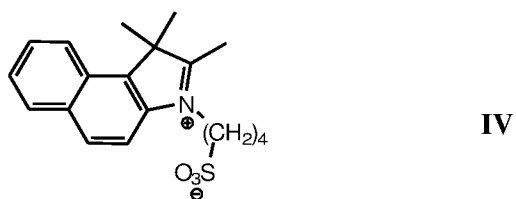
- a) reacting 1,1,2-trimethyl-1H-benzo[e]indole of Formula (II)



- 10 with 1,4-butane sultone of Formula (III)

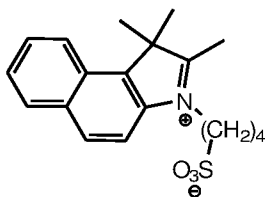


in boiling solvent to give 4-(1,1,2-trimethyl-1H-benzo[e]indolium-3-yl)butane-1-sulfonate of Formula (IV);



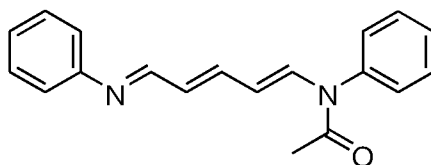
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b) condensing 4-(1,1,2-trimethyl-1H-benzo[e]indolium-3-yl)butane-1-sulfonate of Formula(IV)



IV

and N-phenyl-N-((1E,3E,5E)-5-(phenylimino)penta-1,3-dienyl)acetamide of formula(V)

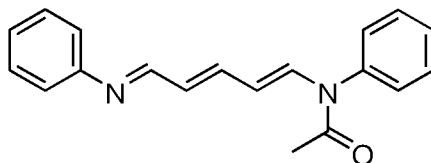


V

in presence of sodium acetate and an alcohol; and

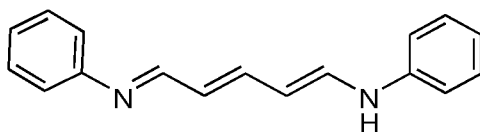
5 c) extracting the title compound formula(I) with an ester solvent.

2) The process according to claim 1, wherein preparation of compound of formula V comprises



V

10 reacting (E)-N,N'-((1E,3E)-penta-1,3-diene-1-yl-5-ylidene)dianiline or hydrochloride of compound of formula (VI) with an acetic anhydride in presence of an organic base.



VI

3) The process according to claim 1, wherein the solvent in step-(a) is sulfolene, toluene, xylene or silicone oil.

4) The process according to claim 1, wherein the reaction in step-(a) is performed at a temperature range from about 110°C to about 150°C, preferably a temperature range from about 120°C to about 140°C.

5

5) The process according to claim 1, where the reaction in step-(b) is performed at a temperature range from about 50°C to about 90°C, preferably a temperature range from about 60°C to about 70°C.

10 6) The process according to claim 1, wherein the alcohol in step-(b) is selected from methanol, ethanol, and isopropanol, preferably methanol

7) The process according to claim 1, wherein the ester solvent in step-(c) is methyl acetate or ethyl acetate, preferably ethyl acetate.

15

8) The process according to claim 1, wherein the process comprises a further step of purification.

9) The process according to claim 8, wherein the purification is carried out in a solvent
20 selected from C₁ to C₅ alcohols.

10) The process according to claim 8, wherein the purification is carried out in ketonic solvents like acetone and acetonitrile with water.

25 11) The process according to claim 2, wherein the solvent is a chlorinated solvent.

12) The process according to claim 11, wherein the chlorinated solvent is methylene dichloride or ethylene dichloride, preferably methylene dichloride.

30 13) The process according to claim 2, wherein the wherein the reaction is performed at a temperature range from about 50°C to about 90°C, preferably temperature range from about 60°C to about 70°C.

14) The process according to claim 2, wherein the organic base is methyl amine, dimethyl amine, triethyl amine, preferably triethyl amine

5 15) A stable Amorphous form of Indocyanine green of Formula(I) characterized by X-ray powder diffraction (XRPD) pattern.

16) A process for the preparation of Indocyanine green substantially as herein described with reference to the examples.

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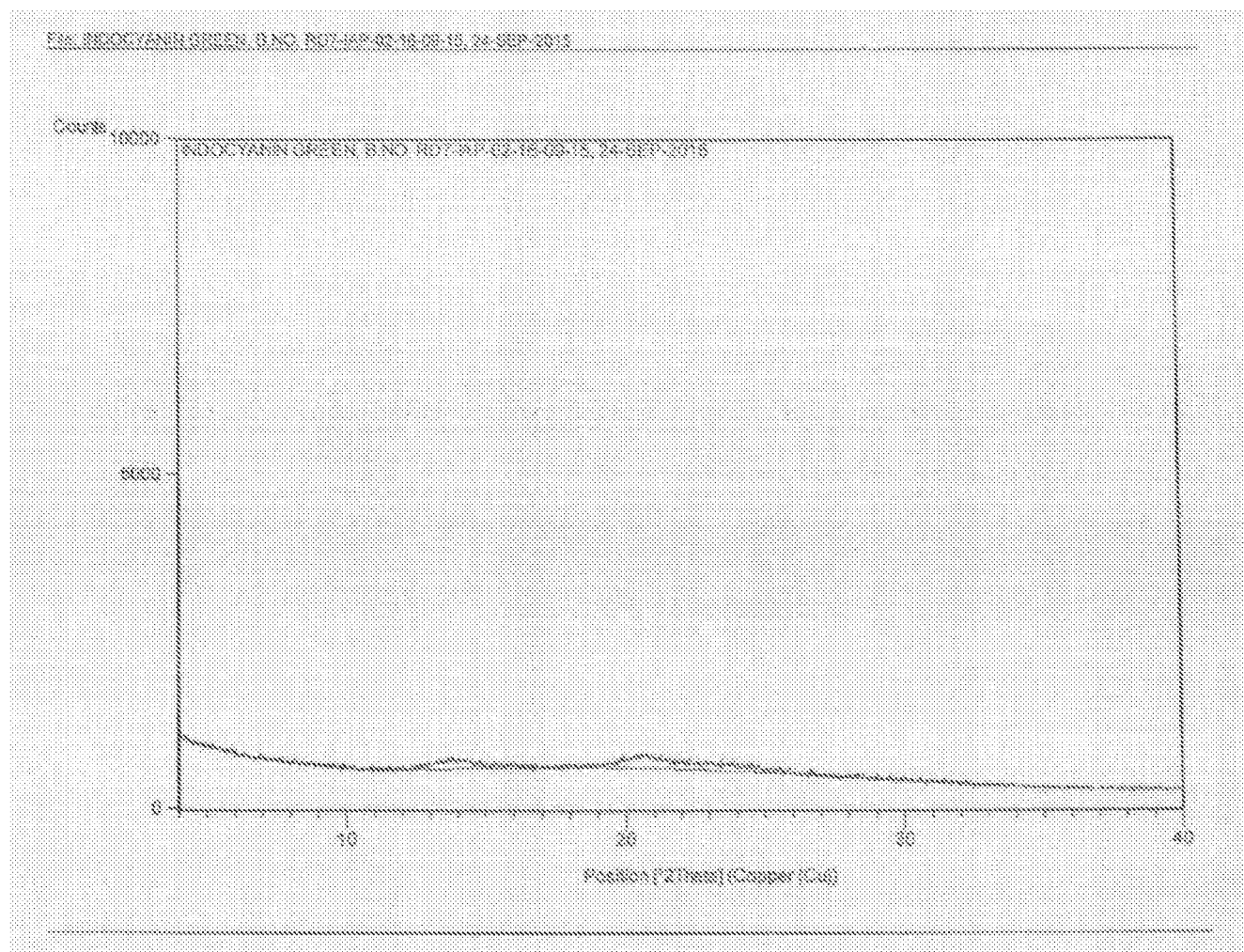


Fig. 1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2016/057178

Box No. 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.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 16
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:
Claim 16 is an omnibus claim as it refers to "the preparation of Indocyanine green substantially as herein described with reference to the examples".

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 No. 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 additional fees, this Authority did not invite payment of additional fees.

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 and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2016/057178

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 47/48; A61K 49/00; C07D 209/00; C07D 209/58; C07D 209/60 (2017.01)

CPC - A61K 47/48; A61K 49/00; C07D 209/00; C07D 209/58; C07D 209/60 (2017.01)

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)

See Search History document

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)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,750,722 A (HUYNH et al) 12 May 1998 (12.05.1998) entire document	1-15
A	✓ CN 104130178 A (LIAONING TIANHE PHARMACEUTICAL CO LTD) 05 November 2014 (05.11.2014) entire document	1-15
A	✓ PUBCHEM, Substance Record for SID 967. Create Date: 2005-03-27. [retrieved on 15 February 2017]. Retrieved from the Internet: <https://pubchem.ncbi.nlm.nih.gov/substance/967>. entire document	1-15

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

20 February 2017

Date of mailing of the international search report

23 MAR 2017

Name and mailing address of the ISA/US

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