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Submission in opposition proceedings
made following summons to attend oral proceedings

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- representing the proprietor(s):	CELGENE CORPORATION
Proprietor/representative's reference	J100969PCEPOPPO

The information given below is pertaining to the following patent in opposition proceedings:

Patent No.	EP1667682
Application No.	EP04783095.5
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	02 November 2011
Title of the invention	Polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydroisoindol-2-yl)-piperidine-2,6-dione
Proprietor of the patent	Celgene Corporation

Documents attached:

	Description of document	Original file name	Assigned file name
1	Main request in opposition	J100969PCEPOPPOsubmission.pdf	MAINREQ-1.pdf
2	Auxiliary request in opposition	J100969PCEPOPPOauxreq6clean.pdf	AUXREQ-1.pdf
3	Auxiliary request in opposition	J100969PCEPOPPOauxreq5clean.pdf	AUXREQ-2.pdf
4	Auxiliary request in opposition	J100969PCEPOPPOauxreq4clean.pdf	AUXREQ-3.pdf
5	Auxiliary request in opposition	J100969PCEPOPPOauxreq3clean.pdf	AUXREQ-4.pdf
6	Auxiliary request in opposition	J100969PCEPOPPOauxreq6marked.pdf	AUXREQ-5.pdf
7	Auxiliary request in opposition	J100969PCEPOPPOauxreq5marked.pdf	AUXREQ-6.pdf
8	Auxiliary request in opposition	J100969PCEPOPPOauxreq4marked.pdf	AUXREQ-7.pdf
9	Auxiliary request in opposition	J100969PCEPOPPOauxreq3marked.pd	AUXREQ-8.pdf

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10	Any annexes (other than citation) to an opposition letter - Consolidated List of References	J100969PCEPOPPOConsolidatedRefs.pdf	OTHER-1.pdf

Evidence filed subsequently:

D26	Other evidence	Declaration of Ravi Natarajan, Ph.D. of March 6, 2015 with attachments 1 and 2 original file name: D26.pdf attached as: Other-evidence-1.pdf
D27	Other evidence	Copy of Pankaj Dutia, Chemical Weekly, August 10, 2004, p. 179-186 original file name: D27.pdf attached as: Other-evidence-2.pdf
D28	Other evidence	S. R. Chemburkar et al., Org. Process Res. Dev., (2000) 4:413-417 original file name: D28.pdf attached as: Other-evidence-3.pdf

Signatures

Place:	**Munich**
Date:	**09 March 2015**
Signed by:	**Bojan Savic 37009**
Association:	**JONES DAY (Association No. 215)**
Capacity:	**(Representative)**

D26

DECLARATION OF SWAMINATHAN (RAVI) NATARAJAN, Ph.D.

I, SWAMINATHAN (RAVI) NATARAJAN, do hereby declare and state:

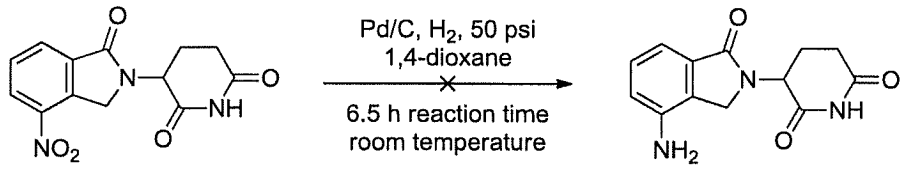
1. I received my Bachelor of Science degree in Chemistry from Jai Hind College, University of Bombay. I received my Masters of Science degree in Organic Chemistry from the Indian Institute of Technology Bombay in 1990. I received my Ph.D. in Organic Chemistry from the University of Illinois at Chicago in 1996. I was a post-doctoral researcher in the lab of Professor K. C. Nicolaou at The Scripps Research Institute from 1996 to 1999.

2. From 1999 to 2009 I was employed at Merck Research laboratories, serving as a Senior Research Chemist from 1999-2001, and as a Research Fellow from 2002-2009. Since 2009 I have been CEO of Kemxtree LLC, a company that provides drug discovery, synthesis, and analytical services to the pharmaceutical community. A copy of my curriculum vitae is enclosed herewith as ATTACHMENT 1.

3. Kemxtree LLC was engaged to perform the experiments described below. These experiments were conducted in Kemxtree laboratories under my supervision and control.

4. In particular, I was asked to synthesize 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline, now known as lenalidomide, by exactly following the procedures of Example 1 of WO 98/03502 and Example 1 of U.S. Patent No. 5,635,517 ("the '517 patent"). I note that these examples are identical and are directed to the synthesis of 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-5-aminoisoindoline starting from 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-5-nitroisoindoline. I was asked to exactly duplicate these reaction conditions using 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-nitroisoindoline as the starting material instead of 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-5-nitroisoindoline.

5. I hereby confirm that the following reaction was performed in our laboratory.



A mixture of 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-nitroisoindoline (1 g; the same amount of starting material as in the '517 patent) and 10% Pd/C (0.13 g; the same amount as in the '517 patent) in 1,4-dioxane (200 mL; the same amount as in the '517 patent) was hydrogenated at 50 psi for 6.5 hours (the same pressure and time as in the '517 patent). The full procedure can be found in ATTACHMENT 2.

6. No lenalidomide was formed in the hydrogenation reaction, according to analysis of the reaction by LC-MS, TLC and ^{1}H-NMR. The starting material was recovered nearly quantitatively (985 mg), and a small amount of decomposition was observed by TLC.

7. I, Ravi Natarajan, declare under penalty of perjury under the laws of the United States that all statements made in this Declaration are of my own knowledge to be true and that all statements made on information and belief are believed to be true.

Respectfully submitted,

6th march 2015

(Date)

Swaminathan (Ravi) Natarajan, Ph.D.

ATTACHMENT 1

Swaminathan (Ravi) Natarajan

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EDUCATION & EXPERIENCE

2009 – Present	**Founder & CEO,** Kemxtree Research laboratories, NJ
2002 – 2009	**Research Fellow**, Merck Research laboratories, Rahway, NJ.
1999 – 2001	**Senior Research Chemist**, Merck Research laboratories, Rahway, NJ.
1996 – 1999	**Post-Doctoral Fellow / Team Leader**, The Scripps Research Institute, La Jolla, Ca Advisor : Professor KC Nicolaou
1991 – 1996	**Ph. D.**, Department of Chemistry, University of Illinois, Chicago, IL. Advisor : Professor David Crich
1988 – 1990	**M. Sc.**, Department of Chemistry, Indian Institute of Technology, Bombay, India
1985 – 1988	**B. Sc.**, Jai Hind College, University of Bombay, Bombay, India.

Key Accomplishments at Kemxtree

1. **Set-up Kemxtree LLC** **2009**

   - Set up Medicinal Chemistry and Drug Metabolism Infrastructure for Kemxtree LLC
   - Hired and Trained staff of 35 chemists

2. **Discovery & Development of Novel Immunosuppressant Drug (KM-1016; IND)** **2009**

   - Licensed early drug discovery program
   - Novel natural product derived Immunosuppressant Drug Candidate
   - Scientific Management and Responsibility

- Liaison with Pharmacology, Drug Metabolism, Formulation and pre-Clinical Safety groups
- Co-authored Chemistry, Drug Metabolism, Pharmacology (therapeutic and Safety) and Toxicology Sections of IND document
- Liaison with pre-IND committee with US-FDA
- On Track to file IND by 1Q-2014

3. **Discovery & Development of Novel Bone Anabolic Drug for Accelerated Fracture Healing and Secondary Osteoporosis (KM-0102; IND)** **2010**

- Licensed early drug discovery program
- Novel Orally Bioavailable Bone Anabolic Agents
- Scientific Management and Responsibility
- Liaison with Pharmacology, Drug Metabolism, Formulation and pre-Clinical Safety groups
- Responsibility to produce IND document and Filing
- Liaison with pre-IND committee with US-FDA
- On Track to file IND by 2Q-2014

Key Accomplishments at Merck

4. **Discovery & Development of P38 MAP Kinase inhibitor (L#'798; Ph-IA, Ph-IB and Ph-IB (POC))** **2002**

5. **Discovery & Development of Maxi-K Blocker (L#'839; Ph-IA, Ph-IB, Ph-IIB (POC))** **2004**

6. **Discovery & Development of Maxi-K Blocker B/up (L#'955; pre-clinical)** **2005**

7. **Discovery of P38 MAP Kinase Inhibitor B/up (L#575; Ph-IA, Ph-IB and Ph-IB (POC))** **2005**

8. **Discovery & Development of alpha-selective P38 MAP Kinase Inhibitor (MK-2684; Ph-IA, Ph-IB)** **2006**

9. **Identification, Validation and POC studies on Substrate Selective MAP Kinase Inhibitors for Inflammatory Disorders** **2007**

10. **Discovery & Development of Substrate Selective Kinase Inhibitor for Inflammatory Disorders; (MK-7708; Ph-IA, Ph-IB)** **2008**

11. **Identification, Target Validation and POC studies on VAP-1 inhibitors for Inflammatory Disorders** **2007**

12. **Identification, Target Validation and POC studies on Chitinase inhibitors for Inflammatory (Respiratory) Disorders** **2007**

13. **Early Liaison for Drug Discovery Outsourcing Activities** **2006 - 2008**

14. **Development of Renin Inhibitors (MK-1597; Ph-IA, Ph-IB, Ph-IIA and Ph-IIB)** **2008**

15. **Development of Renin Inhibitors (Back-up) (MK-5632; Ph-IA, Ph-IB)** **2008**

Modalities of Accomplishments

1. Mentored a team of Ph.Ds and associates for discovery of all clinical candidates.

2. Explored research relationship with CROs in China, Russia for early drug discovery activities and validated three drug targets.

3. Created a liaison between Medicinal Chemistry and Drug Metabolism to forge a synergistic working relationship aimed at maximizing the qualities of drug candidates and lowering attrition in the Clinic.

4. Core member on drug development teams and co-authored sections of IND documents for filing.

5. Extensively represented drug discovery teams on organizational forums within Merck.

PRESENTATIONS, PUBLICATIONS and PATENTS

Presentations

1. July 3 – 8th 2004; Gordon Conference on Heterocyclic Chemistry, Newport Beach, RI

"Synthesis of the 2H-Quinolizin-2-one Scaffold via a Stepwise / Tandem Acylation- Intramolecular Annulation Strategy"

2. Dec 15 – 20th 2005; Pacifichem 2005, Honolulu, Hawaii.

"Development of a new class of potent, highly selective and orally bio-available p38 inhibitors"

3. June 25 – 29th 2005; Chemistry Council Conference, La Sapeniere, Montreal, Canada.

"Maxi-K channel Blockers for the Treatment of Glaucoma and Ocular Hypertension"

5. May 10th 2005; Inter-Site Invited Seminar Series, Merck-Frosst, Montreal, Canada.

" Maxi-K Channel Blockers for the treatment of Glaucoma ad Ocular Hypertension"

6. Oct 15 – 19th 2005; Target to Proof of Concept Symposium, Big Boulder Resort, Arizona.

"S-Selective Inhibitors of P38-MAP Kinase"

7. April 17-18th 2006; Ion Channel Retreat 2006, Red Bank, New Jersey.

" Maxi-K Channel Blockers for the treatment of Glaucoma ad Ocular Hypertension"

8. May 27th – June 2nd 2006; Chemistry, Biology and Medicine 2006, Cyprus, Greece.

"Discovery of Orally Efficacious p38 Inhibitors for the cure of Inflammatory Disorders"

9. June 25 – 29th 2006; Chemistry Council Conference, La Sapeniere, Montreal, Canada.

"S-Selective Inhibitors of P38-MAP Kinase: A Conceptually New Strategy for the Discovery of Selective Kinase Inhibitors"

10. July 2 – 7th 2006; Gordon Conference on Heterocyclic Chemistry, Newport Beach, RI

"Development of a new class of potent, highly selective and orally bio-available p38 inhibitors"

11. March 25 -29th 2007; Target to Proof of Concept Symposium, Elan Chateau Winery and Resort, Atlanta.

"Maxi-K Blockers for ocular Hypertension: a missed opportunity??"

12. May 15th 2007; Department of Chemistry, University of Illinois, Chicago.

"Discovery of Highly Potent, Selective and Orally Efficacious Inhibitors of p38 MAP Kinase"

13. May 31 – June 1st 2007; 2nd Protein Kinases in Drug Discovery Conference, Boston, Ma.

"Designing Selectivity, Potency and Oral Efficacy in the Discovery of Novel p38 MAP Kinase Inhibitors"

14. October 15th 2008; Invited lecture at Advinus Therapeutics

"Designing Selectivity, Potency and Oral Efficacy in the Discovery of Novel p38 MAP Kinase Inhibitors"

15. Nov 30th 2009; Drug Discovery in India – A Perspective, Chaired by Dr. Mashelkar, Lalit Intercontinental, Mumbai

"Maxi-K Blockers for ocular Hypertension"

Publications

1. Selective Inhibition of p38 protein Kinase Signaling Cascades in Cells. O'Keefe, S. J.; Natarajan, S. R.; Cubbon, R.; Kuhn, R.; Wang, R.; Rasa, C.; Lowitz, K.; Visco, D.; Kumar, S.; Mitra, K.; Owens, K.; Thompson, J. E.; DeMartino, J.; Doherty, J. B.; Zaller, D. M. *Nature Chemical Biology*, **2007**, (manuscript on technical hold).

2. Rapid Access to Pyrazollo [3,4-c] pyridines via Alkyne Annulations. Limitations of Steric Control in Nickel catalyzed Alkyne Insertions. Heller, S. T.; Natarajan, S. R. *Organic Letters*, **2007**, 9 (24) 4947-4950.

3. P38 MAP Kinase Inhibitors Part 6: 2-Arylpyridazinone-3-ones as templates for

inhibitor design. Natarajan, S. R.; Heller, S. T.; Nam, K.; Singh, S. B.; Scapin, G.; Patel, S.; Fitzgerald, C. E.; Thompson, J. E.; O'Keefe, S. J. *Bioorganic. Med. Chem. Lett.* **2006**, *16*, 5809 - 5813.

4. P38 MAP Kinase Inhibitors Part 5: Discovery of orally bioavailable and highly efficacious compound based on a 7-amino-naphthyridone scaffold. Natarajan, S. R.; Liu, L.; Levorse, M.; Thompson, J. E.; O'Neill, E. A.; O'Keefe, S. J.;Cvetovich, R.; Chung, J. Y.; Carballo-Jane, E.; Visco, D. M. *Bioorganic. Med. Chem. Lett.* **2006**, *16*, 5468 - 5471.

5. 1,3-Diketones from Acid Chlorides and Ketones: A Rapid and General One-Pot Synthesis of Pyrazoles. Heller, S. T.; Natarajan, S. R. *Organic Letters*, **2006**, 8 (13) 2675-2678.

6. Synthesis of the 2H-quinolizin-2-one Scaffold via a Stepwise Acylation - Intramolecular Annulation Strategy. Natarajan, S. R.; Chen, M. H.; Heller, H. T.; Tynebor, R. M.; Crawford, E. M.; Minxiang, C.; Kaizheng, H.; Dong, J.; Hu, B.; Chen, S. H.; Doherty, J. B. *Tetrahedron Lett.*, **2006**, *47(29)*, 5063.

7. P38 MAP Kinase Inhibitors Part 3: SAR on 3,4-Dihydropyrmido[4,5-*d*]Pyrimidin-2-ones and 3,4-Dihydropyrido[4,3-*d*]Pyrimidin-2-ones. Natarajan, S. R; Wisnoski, D. W.; Thompson, J. E.; O'Neill, E. A.; O'Keefe, S. J. *Bioorganic. Med. Chem. Lett.* **2006**, *16*, 4400 – 4404.

8. P38 MAP Kinase Inhibitors: Evolution of imidazole-based and pyrido-pyrimidin-2-one lead classes. Natarajan, S. R.; Doherty, J. B. *Current Topics in Medicinal Chemistry* **2005**, 10 (5), 987 - 1003pp.

9. SAR of 3,4-Dihydropyrido[3,2-*d*]pyrimidone p38 inhibitors. Liu, L; Stelmach, J. E.; Natarajan, S. R.; Chen, M. H.; Singh, S. B.; Schwartz, C. D.; Fitzgerald, C. E.; O'Keefe, S. J.; Zaller, D. M.; Schmatz, D. M.; Doherty, J. B. *Bioorganic. Med. Chem. Lett.* **2003**, 13, 3979.

10. P38 MAP Kinase Inhibitors Part 1: Design and Development of a New Class of Potent and Highly Selective Inhibitors Based on 3,4-Dihydropyrido[3,2-*d*]Pyrimidone Scaffold. Natarajan, S. R; Wisnoski, D. W.; Singh, S. B.; Stelmach, J. E.; O'Neill, E. A.; Schwartz, C. A.; Thompson, C. M.; Fitzgerald, C. D.; O'Keefe, S. J.; Kumar, S.; Hop, E. C. A. C.; Zaller, D. A.; Schmatz, D. M.; Doherty, J. B. *Bioorganic. Med. Chem. Lett.* **2003**, 13, 273.

11. New Synthetic Technology for the Mild and Selective One-Carbon Homologation of Hindered Aldehydes in the Presence of Ketones. Nicolaou, K. C.; Vassilikogiannakis, G.; Kranich, R.; Baran, P. S.; Zhong, Y. L.; Natarajan, S. *Organic Letters*, **2000**, 2, 13, 1895.

12. The Total Synthesis of Vancomycin – Part 1: Design and Development of Methodology. Nicolaou, K. C.; Li, H.; Boddy, C. N. C.; Ramanjulu, J.; Yeu, T-Y.; Natarajan, S.; Chu, X. J.; Brase, S.; Rubsam, F. *Chemistry – A European Journal*, **1999**, 5, 2584.

13. The Total Synthesis of Vancomycin – Part 2: Retrosynthetic Analysis, Synthesis of Amino Acid Building Blocks and Strategy Evaluation. Nicolaou, K. C.; Boddy, C. N. C.; Li, H.; Koumbis, A. E.; Hughes, R.; Natarajan, S.; Jain, N. F.; Ramanjulu, J.; Brase, S.; Solomon, M. E. *Chemistry – A European Journal*, **1999**, 5, 2602.

14. The Total Synthesis of Vancomycin – Part 3: Total Synthesis of the Aglycon. Nicolaou, K. C.; Koumbis, A. E.; Takayanagi, M.; Natarajan, S.; Jain, N. F.; Bando, T.; Li, H.; Hughes, R. *Chemistry – A European Journal* **1999**, 5, 2622.

15. The Total Synthesis of Vancomycin – Part 4: Attachment of the Sugar Moieties and Completion of the Synthesis. Nicolaou, K. C.; Mitchell, H. J.; Jain, N. F.; Bando, T.; Hughes, R.; Winssinger, N.; Natarajan, S.; Koumbis, A. E. *Chemistry – A European Journal* **1999**, 5, 2648.

16. The Total Synthesis of Vancomycin Aglycone – Part 1: Synthesis of Amino Acids 4 – 7 and Construction of the *AB-COD* Ring System of Vancomycin. Nicolaou, K. C.; Natarajan, S.; Li, H.; Jain, N. F.; Hughes, R.; Solomon, M. E.; Ramanjulu, J. M.; Boddy, C.N.; Takayanagi, M. *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 2708.

17. The Total Synthesis of Vancomycin Aglycone - Part 2: Synthesis of Amino Acids 1 –3 and Construction of the *AB – COD – DOE* Ring Framework of Vancomycin. Nicolaou, K. C.; Jain, N. F.; Natarajan, S.; Hughes, R.; Solomon, M. E.; Li, H.; Ramanjulu, J. M.; Takayanagi, M.; Koumbis, A. E.; Bando, T. *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 2714.

18. The Total Synthesis of Vancomycin Aglycone – Part 3: Final Stages. Nicolaou, K. C.; Takayanagi, M.; Jain, N. F.; Natarajan, S.; Koumbis, A. E.; Bando, T.; Ramanjulu, J. *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 2717.

19. New Synthetic Technology for the Synthesis of Aryl Ethers: Construction of *C-O-D* and *D-O-E* ring Model Systems of Vancomycin. Nicolaou, K. C.; Boddy, C. N. C.; Natarajan, S.; Yeu, T. Y.; Li, H.; Brase, S.; Ramanjulu, J. *J. Am Chem. Soc. 1997, 119, 3421.*

20. New Technology For the Synthesis of Vancomycin-Type Biaryl Systems. Nicolaou, K. C.; Chu, X. J.; Ramanjulu, J.; Natarajan, S.; Brase, S.; Rubsam, F.; Boddy, C. N. C. *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1539.

21. A Macrolactonization Approach to the *AB-COD* Bicyclic System of Vancomycin. Nicolaou, K. C.; Ramanjulu, J.; Natarajan, S.; Brase, S.; Li, H.; Boddy, C. N. C.; Rubsam, F.; *J. Chem. Soc. Chem. Commun.* **1997**, 1899.

22. Synthesis of the Taxol AB Ring System by Olefination of an A-Ring C1 Ketone and Direct B-ring closure. Crich, D.; Natarajan, S.; Crich, J. Z. *Tetrahedron* **1997**, 53, 7158.

23. Synthesis of a Highly Functionalized AB Taxane Ring System: Formation of the Eight Membered Ring by an Efficient 8-exo-tet Alkylation of an α-Sulfonyl Anion. Crich, D.; Natarajan, S. *J. Chem. Soc. Chem. Commun.* **1995**, 85.

24. Chemistry of Cyclic Tautomers of Tryptophan: Free Radical Reactions at C2 Occur Preferentially on the endo-face of the Diazabicyclooctane Skeleton. Crich, D.; Natarajan, S. *J. Org. Chem.* **1995**, 60, 6237.

25. Coformational Analysis of Substituted Hexahydropyrrolo[2,3-b] indoles and Related Systems, an Unusual Example of Hindered Rotation About Sulfonamide S-N bonds: an X-ray cyrstallographic and NMR study. Crich, D.; Bruncko, M.; Natarajan, S.; Teo, B. K.; Tocher, D. A. *Tetrahedron* **1995**, 51, 2215.

26. Antiovulatory Antagonists of LHRH Related to Antide. Flouret, G.; Arnold, Z. S.; Majewski, T.; Petousis, N. H.; Kevin, M.; Farooqui, F.; Blum, K. A.; Konopinska, D.; Natarajan, S.; Crich, D. *J. Peptide Science* **1995**, 1, 89.

27. Enantiospecific Synthesis of Amino acids - Part 2: α-Alkylation of Tryptophan, a Chemical and Computational Investigation of Cyclic Tryptophan Tautomers. Crich, D.; Chan, C. O.; Davies, J. D.; Natarajan, S.; Vinter, J. G. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2233.

28. Enantiospecific Synthesis of Amino Acids: Preparation of R and S –α-Methyl Aspartic Acid Derivatives from (S)-Tryptophan. Chan, C. O.; Crich, D.; Natarajan, S. *Tetrahedron Lett.* **1992**, 33, 3405.

Patents:

1. Doherty, James B.; Stelmach, John E.; Chen, Meng-Hsin; Liu, Luping; Hunt, Julianne A.; Ruzek, Rowena D.; Goulet, Joung L.; Wisnoski, David D.; Natarajan, Swaminathan Ravi; Rupprecht, Kathleen M.; Bao, Jianming; Miao, Shouwu; Hong, Xingfang.
Preparation of 1,5-diaryl-7-heterocyclyl(alkyl)-2-quinolinones as p38 protein kinase inhibitors.
WO-2002-058695

2. Doherty, James B.; Stelmach, John E.; Chen, Meng-Hsin; Liu, Luping; Hunt, Julianne A.; Ruzek, Rowena D.; Goulet, Joung L.; Wisnoski, David D.; Natarajan, Swaminathan Ravi; Rupprecht, Kathleen M.; Bao, Jianming; Miao, Shouwu; Hong, Xingfang.
Preparation of 1,5-diaryl-7-heterocyclyl(alkyl)-2-quinolinones as p38 protein kinase inhibitors.
EP-1345603

3. Doherty, James B.; Natarajan, Swaminathan Ravi; Wisnoski, David D.
Halo-benzo-carbonyl Heterocyclic p38 Kinase Inhibiting Agents.
WO 2003 103590 A2

4. Doherty, James B.; Chen, Meng-H.; Liu, Luping; Natarajan, Swaminathan; Tynebor, Robert; Meinke, Peter T.; Parsons, William; Shen, Dong-Ming; Shu, Min; Stelmach, John E.; Wood, Harold; Zhang, Fengqi; Wisnoski, David.
Ophthalmic Compositions for Treatment of Ocular Hypertension.

WO2003105847 A1

5. Doherty, James B.; Chen, Meng-H.; Liu, Luping; Natarajan, Swaminathan; Tynebor, Robert; Shen, Dong-Ming.
Ophthalmic Compositions for Treatment of Ocular Hypertension.
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6. Doherty, James B.; Chen, Meng-H.; Liu, Luping; Natarajan, Swaminathan; Tynebor, Robert.
Ophthalmic Compositions for Treatment of Ocular Hypertension.
WO2004043932

7. Doherty, James B.; Chen, Meng-H.; Liu, Luping; Natarajan, Swaminathan; Tynebor, Robert.
Ophthalmic Compositions for Treatment of Ocular Hypertension.
WO2004043933

8. Doherty, James B.; Chen, Meng-H.; Liu, Luping; Natarajan, Swaminathan; Tynebor, Robert; Shen, Dong-Ming; Shu, Min.
Ophthalmic Compositions for Treatment of Ocular Hypertension.
WO2005002520 A2

9. Doherty, James B.; Chen, Meng-H.; Liu, Luping; Natarajan, Swaminathan; Tynebor, Robert.
Ophthalmic Compositions for Treatment of Ocular Hypertension.
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10. Doherty, James B.; Chen, Meng-H.; Liu, Luping; Natarajan, Swaminathan; Tynebor, Robert.
Ophthalmic Compositions for Treatment of Ocular Hypertension.
WO2005-026128

11. Doherty, James B.; Natarajan, Chen, Meng-Hsin, Swaminathan; Sahoo, Soumya P.; Li, Zhen;
Heterobicyclic compounds useful as p38 Kinase inhibiting agents
WO2007-021710

12. Doherty, James B.; Natarajan, Swaminathan; Sahoo, Soumya P.; Koyama, Hiroo; Hu, Zao; Yang, Ginger; Miller, Daniel; Li, Zhen;
P38 MAP Kinase inhibiting Agents.
Filed April 2005

13. Doherty, James B.; Natarajan, Swaminathan; Sahoo, Soumya P.; Koyama, Hiroo; Hu, Zao; Yang, Ginger; Miller, Daniel; Li, Zhen;
P38 MAP Kinase inhibiting Agents.
Filed April 2007

14. Doherty, James B.; Natarajan, Swaminathan; Chen, Meng-Hsin; Tynebor, Robert.
P39 MAP Kinase Inhibiting Agents.
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15. Doherty, James B.; Stelmach, John E.; Chen, Meng-Hsin; Liu, Luping; Hunt, Julianne A.; Ruzek, Rowena D.; Goulet, Joung L.; Wisnoski, David D.; Natarajan, Swaminathan Ravi; Rupprecht, Kathleen M.; Bao, Jianming; Miao, Shouwu; Hong, Xingfang.
Halo-benzocarbonyl) heterocyclo-fused phenyl p38 Kinase inhibiting agents
US2003-0092712

16. Doherty, James B.; Stelmach, John E.; Chen, Meng-Hsin; Liu, Luping; Hunt, Julianne A.; Ruzek, Rowena D.; Goulet, Joung L.; Wisnoski, David D.; Natarajan, Swaminathan Ravi; Rupprecht, Kathleen M.; Bao, Jianming; Miao, Shouwu; Hong, Xingfang.
Halo-benzocarbonyl) heterocyclo-fused phenyl p38 Kinase inhibiting agents
US-6809199

17. Doherty, James B.; Natarajan, Swaminathan; Chen, Meng-Hsin; Tynebor, Robert.
Ophthalmic compositions for treating ocular hypertension
US 2004-0097575

18. Doherty, James B.; Natarajan, Swaminathan; Chen, Meng-Hsin; Tynebor, Robert.
Ophthalmic compositions for treating ocular hypertension
US 2004-0097575

19. Doherty, James B.; Natarajan, Swaminathan; Stelmach, John E..
Halo-benzo-carbonyl Heterocyclic p38 Kinase Inhibiting Agents.
US 2005-0176723

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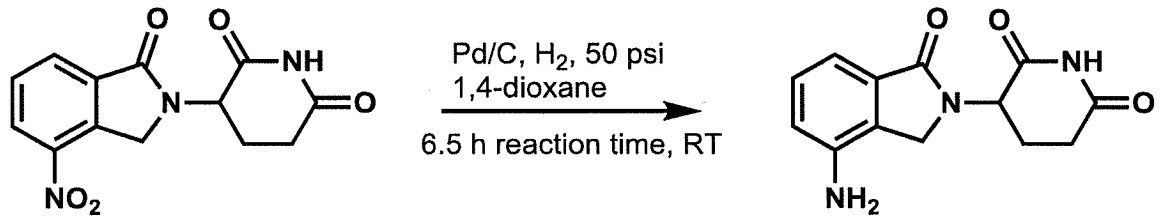
ATTACHMENT 2

Experimental Section: Reduction of 1-Oxo-2-(2,6-Dioxopiperidin-3-yl)-4-Nitro isoindoline



Material Batch Sheet:

Reagents	MW (density)	Amount	MMol.	Equiv.	Source (lot #)	Grade and Comment
1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-nitroisoindoline	289.07	1.0 g	3.46	1.0	Synthesized in-house (KM-121-70-25)	≥99%
Pd/C (10%)	106.42	0.13 g	0.122	3.5%	Sigma-Aldrich (#MKBR2016V)	
H_2	2.0			excess		50 psi in 500 mL steel autoclave in a Parr Shaker apparatus
Solvents and processing aids						
1,4-dioxane (anhydrous)	88.0 (1.03)	200 mL			SPECTROCHEM (#3302996)	Grade ≥ 99.9%

Major equipment used: Parr Shaker, 500 mL steel Autoclave.

Notebook/batch reference: KEMXTREE; KM-123-01-01, pages 1 and 2.

Process description:

To a 500 mL Steel Autoclave was charged 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-nitroisoindoline (1.0 g, 1.0 eq) and 1,4-dioxane (200 mL). Under a nitrogen atmosphere, Pd/C (0.13 g) was added and the reaction mixture was placed in the Parr Shaker. The autoclave was evacuated and

back-filled with hydrogen. Evacuation and backfilling was repeated one more time. Finally the reaction was pressurized with hydrogen until 50 psi and allowed to shake for 6.5 hours.

After 6.5 hours, the reaction was stopped by evacuation of the hydrogen atmosphere and backfilling with nitrogen. The evacuation and backfilling was repeated twice more after which the reaction mixture was filtered over a pad of Celite (pre-washed with anhydrous 1,4-dioxane). The resulting filtrate was concentrated under reduced pressure, to yield a solid (0.985 g). The resultant solid was analyzed by TLC, LC-MS and 1H NMR.

Analytical Section:

Analytical-1: HPLC/ LCMS conditions for analysis of reaction.

HPLC Equipment: AGILENT 1200 (with DAD detector and MWD)
MS Equipment: 6130 Quadrupole MS (micromass)
Injection Volume: 20µL
HPLC method: Method LENALI-TEST-03

Table 1: HPLC/LC-MS methods for testing compounds.

Method	LENALI-TEST-03
Column	Atlantis d18; 3 microns; 4.6 X 50 mm column
Column Temp.	Ambient
Detector	UV 195 nm
Mobile phase	A: Water + 0.1% Formic Acid B: Acetonitrile + 0.1% Formic Acid
Gradient	A B 0.00 min 100 00 5.00 min 50 50 7.00 min 90 10
Injection vol.	20 µL
Flow rate	0.8 mL/min

Sample Preparation: Prepare a 5-10 mg/mL sock solution using MeCN and MeOH (as needed for solubility). Dilute the stock solution to 0.5 to 1.0 mg/mL using diluent (50/50/1 MeCN/H_2O/TFA) to provide the sample for injection.

LC-MS Results:
LCMS data: (no sharp peaks)

1. LCMS of starting material (KM-121-70-25)
2. LCMS of reaction material (KM-123-01-01-1)
3. LCMS of standard (lenalidomide; KM-LEN-STD)

Analytical-2: Thin layer Chromatography

Sample preparation: 5 mg of resultant solid was dissolved in 15 mL of ethyl acetate and methanol (as needed for dissolution).

Method: Sample solution was spotted on standard 2 cm X 5 cm TLC plates (Merck) and eluted in 100% ethyl acetate solution. The sample solution was also co-spotted with starting material (1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-nitroisoindoline) and reference product (lenalidomide).

Analytical-2: 1H Nuclear Magnetic Resonance

Equipment used: Bruker 400 MHz Avance multi-probe Model

Sample Preparation: 5 mg of resultant solid from the reaction was dissolved in 500 μL of DMSO-d6 and loaded into a 5 mm NMR tube which was then inserted into a NMR probe.

KM-123-01-01-1 is the 1H NMR of the crude reaction mixture;
KM-121-70-25 is the 1H NMR of the starting material (1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-nitroisoindoline)

KM-123-01-01-1 NMR.pdf

KM-121-70-25.pdf

Results and Conclusion

1. Analysis of resultant solid obtained after reaction, by means of LC-MS, TLC and 1H NMR, did not detect any product formation.

2. The starting material (1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-nitroisoindoline) was recovered nearly quantitatively (985 mg).

3. A small amount of decomposition was observed per analysis by TLC and 1H NMR.