

2020 EDITION

U.S. Patents granted between October 2018
to July 2020 for NCATS Inventions

Innovation at NCATS



National Center
for Advancing
Translational Sciences

ABOUT THE NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS):

NCATS conducts and supports research on the science and operation of translation – the process by which interventions to improve health are developed and implemented – to allow more treatments to get to more patients more quickly. For additional information about NCATS and its programs, visit <https://ncats.nih.gov>.

ABOUT THE NATIONAL INSTITUTES OF HEALTH (NIH):

NIH, the nation's medical research agency, includes 27 Institutes and Centers and is a component of the U.S. Department of Health and Human Services. NIH is the primary federal agency conducting and supporting basic, clinical and translational medical research and is investigating the causes, treatments and cures for both common and rare diseases. For more information about NIH and its programs, visit <https://www.nih.gov>.

Innovation at NCATS

2020 EDITION

U.S. Patents granted between October 2018
to July 2020 for NCATS Inventions

INTRODUCTION

The National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH) innovates to reduce, remove or bypass costly and time-consuming bottlenecks in the translational research pipeline. The Center emphasizes innovation to speed the delivery of new drugs, diagnostics and medical devices to patients.

The NCATS Office of Strategic Alliances (OSA) aims to enable interactions and partnerships between industry and academia and NCATS laboratories and scientists. One of OSA's core objectives is to facilitate the commercialization of inventions and discoveries made at NCATS for the benefit of the health of the nation and the world.

OSA has created this compilation of U.S. patents issued between October 2018 and July 2020 as a testimony to the many discoveries of NCATS Division of Preclinical Innovation (DPI) scientists. Many of these patents were developed through collaborative relationships with government, industry, academia, and patient and rare diseases communities, and they are consistent with DPI's mission to develop system approaches that improve the efficiency and effectiveness of the translation process. Granted U.S. patents include new technologies to make preclinical research more predictive and efficient and to de-risk potential drug targets or research projects to make them more attractive for commercial investment.

The tireless efforts of NCATS' DPI scientists cannot be captured fully in a simple patent listing. However, the breadth and scope of the inventive activity captured in these granted U.S. patents demonstrate outstanding contributions that impact public health.

We congratulate all of our DPI colleagues on their efforts.

The Office of Strategic Alliances, NCATS

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Issue Date: March 26, 2019

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Issue Date: May 28, 2019

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Issue Date: August 6, 2019

Patent Number: US 10,392,365

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Issue Date: August 27, 2019

Patent Number: US 10,392,646

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Patent Number: US 10,407,392

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Issue Date: September 17, 2019

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Issue Date: October 1, 2019

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Issue Date: November 12, 2019

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Issue Date: December 17, 2019

Patent Number: US 10,508,106

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Issue Date: December 24, 2019

Patent Number: US 10,513,521

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Issue Date: February 11, 2020

Patent Number: US 10,555,942

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Issue Date: February 18, 2020

Patent Number: US 10,561,666

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Issue Date: July 7, 2020

Patent Number: 10,703,746

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MODULATORS OF THE RELAXIN RECEPTOR 1

PATENT NUMBER: US 10,125,112

ISSUE DATE: November 13, 2018

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LEGAL ASSIGNEES:

The United States of America, as represented by The Secretary, Department of Health and Human Services, *Washington, DC (US)*;

The Florida International University Board of Trustees, *Miami, FL*

ABSTRACT:

Pulmonary arterial hypertension (PAH) is a rare, progressive condition affecting the heart and lungs. It is characterized by abnormally high blood pressure (hypertension) in the pulmonary artery that carries blood from the heart to the lungs. The most common symptoms are shortness of breath during exertion and fainting spells, and as the condition worsens, patients can experience dizziness, swelling of the lower extremities, chest pain and a racing pulse. Effective treatments are lacking for patients whose condition is driven by fibrotic processes that damage the lungs.

This innovation is directed to novel small molecule agonists of the mammalian relaxin family receptor 1 (RXFP1), including human RXFP1. Activation of RXFP1 induces: 1) widening of blood vessels due to up-regulation of the endothelin system; 2) extracellular matrix remodeling; 3) moderation of inflammation by reducing levels of inflammatory cytokines; and 4) angiogenesis. In an animal model of chemically induced fibrosis, these compounds have shown to reverse fibrotic damage. Small molecule agonists of RXFP1 may be useful in treating acute heart failure (AHF), scleroderma, fibrosis, other conditions associated with the biology of relaxin, and in improving reproductive health and wound healing. These compounds are the first and only small molecule agonists of RXFP1.

USPTO WEBSITE: <https://go.usa.gov/xf6vP>



US010125112B2

(12) **United States Patent**
Marugan et al.

(10) **Patent No.:** **US 10,125,112 B2**
(45) **Date of Patent:** **Nov. 13, 2018**

(54) **MODULATORS OF THE RELAXIN RECEPTOR 1**

(71) Applicants: **The United States of America, as Represented by the Secretary, Department of Health and Human Service, Washington, DC (US); The Florida International University Board of Trustees, Miami, FL (US)**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(h) by 0 days.

(21) Appl. No.: **15/247,438**

(22) Filed: **Aug. 25, 2016**

(65) **Prior Publication Data**
US 2017/0144984 A1 May 25, 2017

Related U.S. Application Data

(62) Division of application No. 14/398,830, filed as application No. PCT/US2013/032231 on Mar. 15, 2013, now Pat. No. 9,452,973.

(Continued)

(51) **Int. Cl.**
C07C 233/64 (2006.01)
A61K 31/166 (2006.01)
C07D 333/38 (2006.01)
C07C 237/42 (2006.01)
C07D 307/52 (2006.01)
C07D 333/20 (2006.01)
C07D 317/68 (2006.01)
C07D 213/81 (2006.01)
C07D 307/68 (2006.01)
C07D 213/82 (2006.01)
C07D 261/18 (2006.01)
C07D 209/08 (2006.01)
C07D 317/66 (2006.01)
C07C 317/40 (2006.01)

(Continued)

(52) **U.S. CL.**

CPC *C07D 333/38* (2013.01); *C07C 237/42* (2013.01); *C07C 251/24* (2013.01); *C07C 255/60* (2013.01); *C07C 317/40* (2013.01); *C07C 323/42* (2013.01); *C07D 209/08* (2013.01); *C07D 211/26* (2013.01); *C07D 213/81* (2013.01); *C07D 213/82* (2013.01); *C07D 235/08* (2013.01); *C07D 235/14* (2013.01); *C07D 257/04* (2013.01); *C07D 261/18* (2013.01); *C07D 295/088* (2013.01); *C07D 295/205* (2013.01); *C07D 307/52* (2013.01); *C07D 307/68* (2013.01); *C07D 317/66* (2013.01); *C07D 317/68* (2013.01); *C07D 333/20* (2013.01)

(58) **Field of Classification Search**

CPC *C07C 233/64*; *C07C 233/57*; *A61K 31/166*
USPC 564/155; 514/616
See application file for complete search history.

(56) **References Cited**

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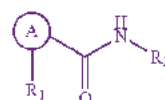
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Primary Examiner — Charanjit Aulakh

(74) *Attorney, Agent, or Firm* Cantor Colburn LLP

(57) **ABSTRACT**

Disclosed are modulators of the human relaxin receptor 1, for example, of formula (I), wherein A, R¹, and R² are as defined herein, that are useful in treating mammalian relaxin receptor 1 mediated facets of human health, e.g., cardiovascular disease. Also disclosed is a composition comprising a pharmaceutically suitable carrier and at least one compound of the disclosure, and a method for therapeutic intervention in a facet of mammalian health that is mediated by a human relaxin receptor 1.



(I)

3 Claims, 9 Drawing Sheets

ANTIFUNGAL COMPOUND PROCESS

PATENT NUMBER: US 10,173,998

ISSUE DATE: January 8, 2019

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ABSTRACT:

Cryptococcal meningitis (CM) results from fungal infections that are particularly prevalent in immune-compromised patients. CM is the second leading cause of HIV-related deaths in sub-Saharan Africa, with estimates of 500,000 deaths per year as current therapies are only marginally effective. CM results from infection by the encapsulated yeasts *Cryptococcus neoformans* and *Cryptococcus gattii* and is observed predominately in immune-compromised individuals. The most common drug treatment for CM in this patient population is high-dose fluconazole monotherapy, however, it achieves only a 40 percent survival rate after 10 weeks of treatment. A more potent anti-fungal drug that can be given orally once a day would likely provide a significant improvement in survival for this neglected population. VT-1129 is a novel fungus-specific Cyp51 inhibitor with potent in vitro activity against *Cryptococcus* species. This agent acts by inhibiting the fungal cytochrome P450 enzyme Cyp51 (lanosterol 14- α -demethylase), thus inhibiting the biosynthesis of ergosterol in a highly selective manner compared to that of clinically available azole antifungals.

The present invention provides novel methods of commercial scale manufacturing of VT-1129. The inventors have developed an optimized synthetic process for scaled-up production of drug at a low cost that will support treatment of patients in the developing world.

USPTO WEBSITE: <https://go.usa.gov/xf6vy>



US010173998B2

(12) **United States Patent**
Hoekstra et al.

(10) **Patent No.: US 10,173,998 B2**
(45) **Date of Patent: Jan. 8, 2019**

(54) **ANTIFUNGAL COMPOUND PROCESS**

(56) **References Cited**

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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **15/126,402**

(22) PCT Filed: **Mar. 19, 2015**

(86) PCT No.: **PCT/US2015/021491**

§ 371 (c)(1),

(2) Date: **Feb. 22, 2017**

(87) PCT Pub. No.: **WO2015/143172**

PCT Pub. Date: **Sep. 24, 2015**

(65) **Prior Publication Data**

US 2017/0088539 A1 Mar. 30, 2017

Related U.S. Application Data

(60) Provisional application No. 61/955,615, filed on Mar.
19, 2014.

(51) **Int. Cl.**

C07D 401/06 (2006.01)

C07D 213/26 (2006.01)

C07D 405/06 (2006.01)

C07D 213/38 (2006.01)

(52) **U.S. Cl.**

CPC **C07D 401/06** (2013.01); **C07D 213/26**
(2013.01); **C07D 213/38** (2013.01); **C07D**
405/06 (2013.01)

(58) **Field of Classification Search**

CPC **C07D 401/06**

USPC **546/268.4**

See application file for complete search history.

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Primary Examiner Patricia L. Morris

(74) *Attorney, Agent, or Firm* Brinks Gilson & Lione

(57) **ABSTRACT**

The present invention relates to a process for preparing
compound 1 that is useful as an antifungal agent. In par-
ticular, the invention seeks to provide new methodology for
preparing compound 1 and substituted derivatives thereof.

16 Claims, No Drawings

HETEROCYCLIC COMPOUNDS AND METHODS OF USE THEREOF

PATENT NUMBER: US 10,202,367

ISSUE DATE: February 12, 2019

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LEGAL ASSIGNEES:

The United States of America, as represented by the Secretary, Department of Health and Human Services, *Washington, DC (US)*; University of Kansas, *Lawrence, KS (US)*

ABSTRACT:

Most people infected with Hepatitis C Virus (HCV) have chronic infection of the liver. Over decades, this can lead to liver disease and liver cancer. In fact, HCV infection is the leading cause of liver transplants in the United States. Although, several new drugs have recently come into the market that have changed the HCV treatment paradigm, the effectiveness of these new drugs can vary depending on the HCV genotype. While most oral, interferon free therapeutic regimens for HCV infection will need combinations of drugs that target different aspects of the HCV life cycle, there is still the need for additional new therapeutics against HCV.

The present innovation provides aryloxazole based small molecules that are potent inhibitors of HCV infection and replication. The compounds represent a new class of anti-HCV compounds and exhibit synergy with currently available therapeutics for HCV. The compounds affect the entry step of HCV infection, a step not targeted by currently available therapeutics against HCV.

USPTO WEBSITE: <https://go.usa.gov/xf6vp>



US010202367B2

(12) **United States Patent**
Liang et al.

(10) **Patent No.:** US 10,202,367 B2
(45) **Date of Patent:** Feb. 12, 2019

(54) **HETEROCYCLIC COMPOUNDS AND METHODS OF USE THEREOF**

(2013.01): *A61K 31/7068* (2013.01); *A61K 38/07* (2013.01); *A61K 38/13* (2013.01);

(Continued)

(71) Applicants: **The United States of America, as represented by the Secretary, Department of Health and Human Services, Washington, DC (US); University of Kansas, Lawrence, KS (US)**

(58) **Field of Classification Search**
CPC C07D 413/14
See application file for complete search history.

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(56) **References Cited**

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(73) Assignees: **The United States of America, as represented by the Secretary, Department of Health and Human Services, Washington, DC (US); University of Kansas, Lawrence, KS (US)**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 15/317,864

(22) PCT Filed: Jun. 12, 2015

(86) PCT No.: PCT/US2015/035658

§ 371 (c)(1),

(2) Date: Dec. 9, 2016

(87) PCT Pub. No.: WO2015/192077

PCT Pub. Date: Dec. 17, 2015

(65) **Prior Publication Data**

US 2017/0114053 A1 Apr. 27, 2017

Related U.S. Application Data

(60) Provisional application No. 62/011,462, filed on Jun. 12, 2014.

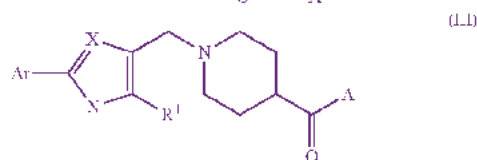
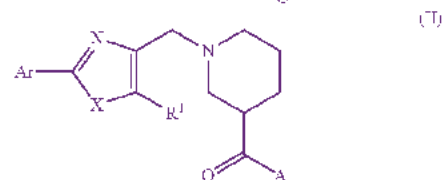
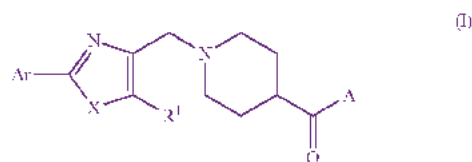
(51) **Int. Cl.**
C07D 413/14 (2006.01)
A61K 31/4545 (2006.01)

(Continued)

(52) **U.S. Cl.**
CPC *C07D 413/06* (2013.01); *A61K 31/4178* (2013.01); *A61K 31/454* (2013.01); *A61K 31/4545* (2013.01); *A61K 31/496* (2013.01); *A61K 31/5377* (2013.01); *A61K 31/7056*

(57) **ABSTRACT**

Disclosed are compounds of formula (I), formula (II), and formula (III): wherein Ar, R¹, A, and X are as defined in the specification. These compounds are antiviral agents and are contemplated for use in the treatment of viral infections, for example, hepatitis C. These compounds are also contemplated for use in treating or preventing cancers.



6 Claims, 3 Drawing Sheets

BENZENESULFONAMIDE UPREGULATORS OF NPCL FOR NEIMANN-PICK DISEASE AND OTHER LYSOSOMAL STORAGE DISORDERS

PATENT NUMBER: US 10,239,830

ISSUE DATE: March 26, 2019

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ABSTRACT:

Lysosomal storage disorders (LSDs), are a group of approximately 60 metabolic disorders that result from a deficiency of a lysosomal protein. Niemann-Pick disease, one example of the LSDs, refers to disorders in which cholesterol, sphingomyelin, and other lipids accumulate in lysosomes. Niemann-Pick type C is biochemically, genetically and clinically distinct from Niemann-Pick Types A and B. In Niemann-Pick type C, the protein product of the major mutated gene NPC 1 is not an enzyme but appears to function as a transporter in the endosomal-lysosomal system, whose deficiency leads to an accumulation of cholesterol, sphingolipids, gangliosides, and fatty acids in the endosomal-lysosomal system. Niemann-Pick C is always fatal. While the majority of children with this disease die before the age of 20, many die before the age of 10.

The invention is directed to pharmaceutical compositions and methods for upregulating the NPC1 promoter and thereby treating lysosomal storage disorders. The present invention provides methods and compositions for treating several lysosomal storage disorders including Niemann-Pick C, Niemann-Pick A/B, Fabry Disease, Farber Disease, Wolman Disease, Gaucher's Disease, Krabbe Disease, MPS VII (mucopolysaccharidosis VII), Neuronal Ceroid Lipofuscinosis Type 2 (CLN 2), and Pompe Disease.

USPTO WEBSITE: <https://go.usa.gov/xf6wN>



US010239830B2

(12) **United States Patent**
Patnaik et al.

(10) **Patent No.:** **US 10,239,830 B2**
(45) **Date of Patent:** **Mar. 26, 2019**

(54) **BENZENESULFONAMIDE UPREGULATORS OF NPC1 FOR NEIMANN-PICK DISEASE AND OTHER LYSOSOMAL STORAGE DISORDERS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **15/549,743**

(22) PCT Filed: **Feb. 11, 2016**

(86) PCT No.: **PCT/US2016/017504**

§ 371 (c)(1).

(2) Date: **Aug. 9, 2017**

(87) PCT Pub. No.: **WO2016/130774**

PCT Pub. Date: **Aug. 18, 2016**

(65) **Prior Publication Data**

US 2018/0044286 A1 Feb. 15, 2018

Related U.S. Application Data

(60) Provisional application No. 62/114,840, filed on Feb. 11, 2015.

(51) **Int. Cl.**
C07C 311/21 (2006.01)
A61K 31/4164 (2006.01)
A61K 31/44 (2006.01)

C07D 207/335 (2006.01)
C07D 213/46 (2006.01)
C07D 233/64 (2006.01)
A61K 31/165 (2006.01)

(52) **U.S. Cl.**
CPC **C07C 311/21** (2013.01); **A61K 31/165** (2013.01); **A61K 31/4164** (2013.01); **A61K 31/44** (2013.01); **C07D 207/335** (2013.01); **C07D 213/46** (2013.01); **C07D 233/64** (2013.01)

(58) **Field of Classification Search**
CPC ... **C07C 311/21**; **A61K 31/4164**; **A61K 31/44**; **C07D 207/335**; **C07D 213/46**; **C07D 233/64**

See application file for complete search history.

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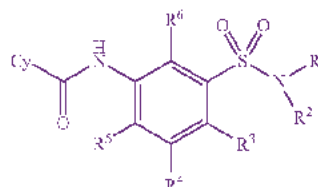
* cited by examiner

Primary Examiner Timothy R Rozof

(74) *Attorney, Agent, or Firm* Heslin Rothenberg Farley & Mesiti, P.C.; Philip Hansen

(57) **ABSTRACT**

Methods and compositions for treating lysosomal storage disorders are disclosed. The methods involve administering a genus of benzenesulfonamides, particularly N-[3-(amino-sulfonyl)phenyl]-benzanides and heteroaryl amides. A genus of suitable compounds is shown in formula 1:



28 Claims, No Drawings

4-((2-HYDROXY-3-METHOXYBENZYL)AMINO) BENZENESULFONAMIDE DERIVATIVES AS POTENT AND SELECTIVE INHIBITORS OF 12-LIPOXYGENASE

PATENT NUMBER: US 10,266,488

ISSUE DATE: April 23, 2019

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ABSTRACT:

Human lipoxygenases (LOXs) are a family of iron-containing enzymes involved in catalyzing the oxidation of polyunsaturated fatty acids to provide the corresponding bioactive hydroxyeicosatetraenoic acid (HETE) metabolites. These bioactive molecules are involved in several physiologic responses such as platelet aggregation, inflammation, and cell proliferation. Platelet-type 12-(S)-LOX(12-LOX) is of particular interest because of its demonstrated role in skin diseases, diabetes, platelet hemostasis, thrombosis, and cancer.

The present innovation provides for the identification of compounds of a 4-((2-hydroxy- 3-methoxybenzyl) amino) benzenesulfonamide-based scaffold. The compounds display nanomolar (nM) potency against 12-LOX and excellent selectivity over related lipoxygenases and cyclooxygenases. In addition to possessing favorable ADME properties, the compounds also inhibit PAR-4 induced aggregation and calcium mobilization in human platelets and reduce 12-HETE in mouse/human beta cells. The compounds can also be used in methods for treating or preventing a 12-lipoxygenase mediated disease or disorder.

USPTO WEBSITE: <https://go.usa.gov/xf6wn>



US010266488B2

(12) **United States Patent**
Maloney et al.

(10) **Patent No.:** US 10,266,488 B2
(45) **Date of Patent:** Apr. 23, 2019

(54) **4-(2-HYDROXY-3-METHOXYBENZYL)AMINO)BENZENESULFONAMIDE DERIVATIVES AS POTENT AND SELECTIVE INHIBITORS OF 12-LIPOXYGENASE**

(65) **Prior Publication Data**

US 2017/0001955 A1 Jan. 5, 2017

Related U.S. Application Data

(60) Provisional application No. 61/987,129, filed on May 1, 2014, provisional application No. 61/889,396, filed on Oct. 10, 2013.

(51) **Int. Cl.**
C07D 277/82 (2006.01)
C07D 235/30 (2006.01)

(Continued)

(52) **U.S. Cl.**
CPC *C07C 311/44* (2013.01); *A61P 7/02* (2018.01); *C07D 211/28* (2013.01);
(Continued)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

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(Continued)

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(57) **ABSTRACT**

Human lipoxigenases (LOXs) are a family of iron-containing enzymes involved in catalyzing the oxidation of polyunsaturated fatty acids to provide the corresponding bioactive hydroxyeicosatetraenoic acid (HETE) metabolites. These eicosanoid signaling molecules are involved in a

(Continued)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 15/028,386

(22) PCT Filed: Oct. 10, 2014

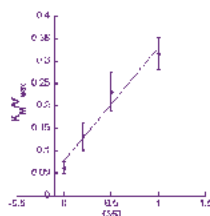
(86) PCT No.: PCT/US2014/060174

§ 371 (c)(1),

(2) Date: Apr. 8, 2016

(87) PCT Pub. No.: WO2015/054662

PCT Pub. Date: Apr. 16, 2015



INHIBITORS OF HUMAN 12/15-LIPOXYGENASE

PATENT NUMBER: US 10,287,279

ISSUE DATE: May 14, 2019

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ABSTRACT:

Lipoxygenases are a family of lipid-oxidizing enzymes, which generate eicosanoids and related compounds from arachidonic acid and other polyunsaturated fatty acids. Human lipoxygenases and their metabolites have been implicated in numerous diseases. 5-LOX has been implicated in cancer, asthma, COPD, allergic rhinitis, osteoarthritis, and atherosclerosis, while platelet-type 12-LOX has been implicated in diabetes, blood coagulation, psoriasis, and cancer. Human reticulocyte 15-lipoxygenase-1 (12/15-LOX, aka 15-LOX-1) is also an attractive therapeutic target, particularly for its role in atherogenesis, diabetes, Alzheimer's, newborn periventricular leukomalacia, breast cancer, and stroke. The difficulty in developing inhibitors that target LOX homologues in both species is that they have different substrate and inhibitor specificities. Thus, existing inhibitors of 12/15-LOX are typically not very selective with regards to other LOX isoforms, and many additionally are strong antioxidants.

The present invention provides compositions and methods for treating a condition involving 12/15-lipoxygenase. Through a systematic succession of high throughput screening steps, the inventors have identified novel inhibitors of human 12/15-lipoxygenase (12/15-LOX), which also targets the mouse 12/15-LOX homologue. The compositions and methods of the present invention can be used for the treatment of a condition involving 12/15-lipoxygenase such as stroke, periventricular leukomalacia, cardiac arrest with resuscitation, atherosclerosis, Parkinson's disease, Alzheimer's disease, and breast cancer.

USPTO WEBSITE: <https://go.usa.gov/xf6wd>



US010287279B2

(12) **United States Patent**
Van Leyen et al.

(10) **Patent No.:** **US 10,287,279 B2**
(45) **Date of Patent:** **May 14, 2019**

(54) **INHIBITORS OF HUMAN
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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **15/048,330**

(22) Filed: **Feb. 19, 2016**

(65) **Prior Publication Data**

US 2016/0168137 A1 Jun. 16, 2016

Related U.S. Application Data

(63) Continuation-in-part of application No.
PCI/US2014/052269, filed on Aug. 22, 2014.

(60) Provisional application No. 61/868,611, filed on Aug.
22, 2013.

(51) **Int. Cl.**
C07D 413/04 (2006.01)
C07D 277/56 (2006.01)
C07D 263/48 (2006.01)
A61K 31/421 (2006.01)
A61K 31/422 (2006.01)
A61K 31/426 (2006.01)
A61K 31/4709 (2006.01)
A61K 31/4725 (2006.01)
A61K 31/4245 (2006.01)
C07D 277/42 (2006.01)
C07D 213/85 (2006.01)
C07D 239/42 (2006.01)

(52) **U.S. CL.**
CPC **C07D 413/04** (2013.01); **A61K 31/421**
(2013.01); **A61K 31/422** (2013.01); **A61K**
31/426 (2013.01); **A61K 31/4245** (2013.01);
A61K 31/4709 (2013.01); **A61K 31/4725**
(2013.01); **C07D 213/85** (2013.01); **C07D**
239/42 (2013.01); **C07D 263/48** (2013.01);
C07D 277/42 (2013.01); **C07D 277/56**
(2013.01)

(58) **Field of Classification Search**
CPC .. **C07D 413/04**; **C07D 213/85**; **C07D 239/42**;
C07D 263/48; **C07D 277/42**; **C07D**
277/56; **A61K 31/421**; **A61K 31/422**;
A61K 31/4245; **A61K 31/426**; **A61K**
31/4709; **A61K 31/4725**
USPC **548/240**
See application file for complete search history.

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Primary Examiner Kristin Vajda

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(57) **ABSTRACT**

A systematic screening has revealed a family of compounds
that exhibit inhibitory effects on 12/15-lipoxygenase.
Accordingly, the present invention relates to the use of these
compounds for the inhibition of 12/15-lipoxygenase and for
the treatment of a condition involving 12/15-lipoxygenase.
Exemplary conditions include, but are not limited to, stroke,
periventricular leukomalacia, cardiac arrest with resuscita-
tion, atherosclerosis, Parkinson's disease, Alzheimer's dis-
ease, and breast cancer.

19 Claims, 12 Drawing Sheets

COMPOUNDS AND METHODS FOR THE PREVENTION AND TREATMENT OF TUMOR METASTASIS AND TUMORIGENESIS

PATENT NUMBER: US 10,301,314

ISSUE DATE: May 28, 2019

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Chen Wang, *Chicago, IL*

LEGAL ASSIGNEES:

The United States of America, as represented by the Secretary, Department of Health and Human Services, *Washington, DC (US)*;
University of Kansas, *Lawrence, KS (US)*;
Northwestern University, *Evanston, IL (US)*

ABSTRACT:

Pancreatic cancer is the fourth leading cause of cancer-related deaths. As the disease progresses, cancer cells travel (metastasize) from the pancreas to other parts of the body. Despite substantial improvements in cancer patient survival, metastatic diseases remain ineffectively treated. The majority of pancreatic cancer patients are diagnosed only after the cancer has spread, and nearly all patients die because of the metastasis spreading to other organs.

The perinucleolar compartment (PNC) is a subcellular structure whose formation closely associates with metastatic potential of cancer cells. It is highly prevalent in metastatic tumors, metastatically transformed cancer cell lines, and cancer stem cells. A high PNC prevalence positively correlates with disease progression (stages and grades) in tested primary tumors, including breast, colorectal, and ovarian cancers, and inversely correlates with patient outcomes.

To identify compounds selectively targeting the metastatic state, the inventors used the perinuclear compartment (PNC), a complex nuclear structure associated with metastatic behaviors of cancer cells, as a phenotypic marker for a high-content screen of over 140,000 structurally diverse compounds. Metarrestin, was identified during a high content screen of ~140,000 compounds, as able to disassemble PNCs in multiple cancer cell lines, inhibit invasion in vitro, block metastatic development in three mouse models of human cancer, and extend survival of mice in a metastatic pancreatic cancer with no organ toxicity or discernable adverse effects. Altogether, metarrestin represents a potential therapeutic approach for the treatment of metastatic cancer.

USPTO WEBSITE: <https://go.usa.gov/xf6Jv>



US010301314B2

(12) **United States Patent**
Frankowski et al.

(10) **Patent No.:** **US 10,301,314 B2**

(45) **Date of Patent:** ***May 28, 2019**

(54) **COMPOUNDS AND METHODS FOR THE PREVENTION AND TREATMENT OF TUMOR METASTASIS AND TUMORIGENESIS**

(71) **Applicants:** **The United States of America, as represented by the Secretary, Department of Health and Human Services, Washington, DC (US); University of Kansas, Lawrence, KS (US); Northwestern University, Evanston, IL (US)**

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(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
This patent is subject to a terminal disclaimer.

(21) **Appl. No.:** **15/606,740**

(22) **Filed:** **May 26, 2017**

(65) **Prior Publication Data**

US 2017/0260192 A1 Sep. 14, 2017

Related U.S. Application Data

(63) Continuation of application No. 14/364,759, filed as application No. PCI/US2012/070155 on Dec. 17, 2012.

(60) Provisional application No. 61/576,780, filed on Dec. 16, 2011.

(51) **Int. Cl.**
A61K 31/519 (2006.01)
A61P 35/04 (2006.01)
C07D 487/04 (2006.01)
C07F 7/18 (2006.01)
A61K 31/695 (2006.01)
A61K 45/06 (2006.01)

(52) **U.S. CL.**

CPC **C07D 487/04** (2013.01); **A61K 31/519** (2013.01); **A61K 31/695** (2013.01); **A61K 45/06** (2013.01); **C07F 7/1804** (2013.01)

(58) **Field of Classification Search**

CPC **C07D 487/04**; **A61K 31/519**
See application file for complete search history.

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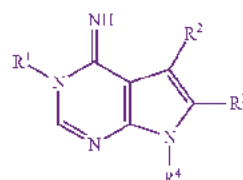
(Continued)

Primary Examiner — Susanna Moore

(74) *Attorney, Agent, or Firm* — Leydig, Voit & Mayer, Ltd.

(57) **ABSTRACT**

The disclosure provides compounds for reducing the prevalence of the perinucleolar compartment in cells, for example, of formula (I), wherein R¹, R², R³, and R⁴ are as defined herein, that are useful in treating a disease or disorder associated with increased prevalence of the perinucleolar compartment, such as cancer. Also disclosed is a composition containing a pharmaceutically acceptable carrier and at least one compound embodying the principles of the invention, and a method of treating or preventing cancer in a mammal.



(I)

SMALL MOLECULE INHIBITORS OF LACTATE DEHYDROGENASE AND METHODS OF USE THEREOF

PATENT NUMBER: US 10,351,532

ISSUE DATE: July 16, 2019

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LEGAL ASSIGNEES:

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ABSTRACT:

Agents that target enzymes involved in cancer cell metabolism offer an attractive therapeutic route in view of the potential to preferentially target cancer tissue over normal tissue. While normal tissue typically uses glycolysis as a major cellular metabolic path only when the oxygen supply is low, cancer tissue relies heavily on aerobic glycolysis regardless of the oxygen supply level. Lactate dehydrogenase (LDH) is involved in the final step of glycolysis, in which pyruvate is converted to lactate and the conversion of NADH to NAD⁺. There are two different genes of LDH, LDHA, and LDHB, but both proteins have the same active site and catalyze the conversion of pyruvate to lactate or lactate to pyruvate. LDH inhibition is expected to reduce the ability of the cell to effectively metabolize glucose and reduce tumor cell proliferation and tumor growth and other pathologies which involve a glycolytic metabolic switch. Thus, compounds that inhibit LDH activity have potential for the development of anti-cancer therapeutics. Previously developed LDH inhibitors have significant drawbacks, including poor potency and/or poor bioavailability, limiting their utility as therapeutics.

The present technology provides novel 1 H-PYRAZOL-1 -YL-THIAZOLE based LDH compounds with improved potency, selectivity, and/or bioavailability for the treatment of cancer.

USPTO WEBSITE: <https://go.usa.gov/xf6Sh>



US010351532B2

(12) **United States Patent**
Maloney et al.

(10) **Patent No.:** **US 10,351,532 B2**
(45) **Date of Patent:** **Jul. 16, 2019**

(54) **SMALL MOLECULE INHIBITORS OF LACTATE DEHYDROGENASE AND METHODS OF USE THEREOF**

(71) Applicants: **THE UNITED STATES OF AMERICA AS REPRESENTED BY THE SECRETARY, DEPARTMENT OF HE**, Bethesda, MD (US); **VANDERBILT UNIVERSITY**, Nashville, TN (US); **The UAB Research Foundation**, Birmingham, AL (US); **The Trustees of the University of Pennsylvania**, Philadelphia, PA (US)

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(73) Assignees: **THE UNITED STATES OF AMERICA, AS REPRESENTED BY THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES**, Washington, DC (US); **VANDERBILT UNIVERSITY**, Nashville, TN (US); **THE UAB RESEARCH FOUNDATION**, Birmingham, AL (US); **THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA**, Philadelphia, PA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **15/540,893**

(22) PCT Filed: **Dec. 29, 2015**

(86) PCT No.: **PCT/US2015/067895**

§ 371 (c)(1),

(2) Date: **Jun. 29, 2017**

(87) PCT Pub. No.: **WO2016/109559**

PCT Pub. Date: **Jul. 7, 2016**

(65) **Prior Publication Data**

US 2018/0273488 A1 Sep. 27, 2018

Related U.S. Application Data

(60) Provisional application No. 62/097,226, filed on Dec. 29, 2014.

(51) **Int. Cl.**

C07D 231/20 (2006.01)

C07D 231/38 (2006.01)

(Continued)

(52) **U.S. Cl.**

CPC **C07D 231/20** (2013.01); **A61K 31/415**

(2013.01); **A61K 31/4155** (2013.01);

(Continued)

(58) **Field of Classification Search**

CPC .. **C07D 231/20**; **C07D 231/38**; **C07D 401/04**;

C07D 403/04; **C07D 403/06**;

(Continued)

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(Continued)

Primary Examiner — Timothy R Rozof

(74) Attorney, Agent, or Firm Cantor Colburn LLP

(57) **ABSTRACT**

Provided is a compound of formula (I), in which Ar¹, R¹, U, V, W, X, and p are as described herein. Also provided are methods of using a compound of formula (I), including a method of treating cancer, a method of treating a patient with cancer cells resistant to an anti-cancer agent, and a method of inhibiting lactate dehydrogenase A (LDHA) and/or lactate dehydrogenase B (LDHB) activity in a cell.

(Continued)

TOCOPHEROL AND TOCOPHERYL QUINONE DERIVATIVES AS CORRECTORS OF LYSOSOMAL STORAGE DISORDERS

PATENT NUMBER: US 10,370,348

ISSUE DATE: August 6, 2019

INVENTORS:

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Wei Zheng, *Potomac, MD*
Jingbo Xiao, *Rockville, MD*
John McKew, *Poolesville, MD*

LEGAL ASSIGNEES:

The United States of America, as represented by the Secretary, Department of Health and Human Services, *Washington, DC (US)*;

ABSTRACT:

This innovation provides for novel tocopherol derivatives and tocopheryl quinone derivatives useful in the decrease of lysosomal substrate accumulation, the restoration of normal lysosomal size, and the treatment of lysosomal storage disorders (LSDs). The inventors have discovered that tocopherol and tocopheryl quinone derivatives with side chain modifications (such as terminal tri-halogenated methyl groups) exhibit improved pharmacokinetics, modulation of mitochondrial potential and restoration of some LSDs phenotypes. These molecules by themselves or in combination with Cyclodextrins (CDs) increase intracellular Ca²⁺ and enhance exocytosis.

Also, the treatment with these compounds reduced the pathological changes in LSD cells as observed using electron microscopy analysis. The inventors also found that there is a synergy between CDs and the new tocopherol analogues when tested on the NPC cells and cells from six other lysosomal storage diseases including Wolman, Niemann Pick Type A, Farber, TaySachs, MSIIIB, and CLN2 (Batten) diseases.

USPTO WEBSITE: <https://go.usa.gov/xf6hC>



US010370348B2

(12) **United States Patent**
Marugan et al.

(10) **Patent No.:** **US 10,370,348 B2**
(45) **Date of Patent:** ***Aug. 6, 2019**

(54) **TOCOPHEROL AND TOCOPHERYL
QUINONE DERIVATIVES AS CORRECTORS
OF LYSOSOMAL STORAGE DISORDERS**

(71) Applicant: **The United States of America, as
represented by the Secretary, Dept. of
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(72) Inventors: **Juan Jose Marugan, Gaithersburg, MD
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Jingbo Xiao, Rockville, MD (US);
John McKew, Poolesville, MD (US)**

(73) Assignee: **The United States of America, as
Represented by the Secretary,
Department of Health and Human
Services, Washington, DC (US)**

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-
claimer.

(21) Appl. No.: **15/608,753**

(22) Filed: **May 30, 2017**

(65) **Prior Publication Data**

US 2018/0105506 A1 Apr. 19, 2018

Related U.S. Application Data

(63) Continuation of application No. 14/442,637, filed as
application No. PCT/US2013/070156 on Nov. 14,
2013, now Pat. No. 9,663,485.

(60) Provisional application No. 61/727,296, filed on Nov.
16, 2012.

(51) **Int. Cl.**

A01N 43/16 (2006.01)
A61K 31/355 (2006.01)
C07D 311/58 (2006.01)
A61K 31/335 (2006.01)
A61K 31/35 (2006.01)
A61K 31/352 (2006.01)
A61K 31/353 (2006.01)
C07D 311/72 (2006.01)
A61K 31/122 (2006.01)
A61K 31/724 (2006.01)
C07C 50/02 (2006.01)
C07C 50/06 (2006.01)
C07C 50/24 (2006.01)

(52) **U.S. Cl.**

CPC **C07D 311/58** (2013.01); **A61K 31/122**
(2013.01); **A61K 31/335** (2013.01); **A61K**
31/35 (2013.01); **A61K 31/352** (2013.01);
A61K 31/353 (2013.01); **A61K 31/724**
(2013.01); **A61K 31/724** (2013.01); **C07C**
50/02 (2013.01); **C07C 50/06** (2013.01); **C07C**
50/24 (2013.01); **C07D 311/72** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

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PCT International Search Report & Written Opinion, International
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Primary Examiner Patrick T Lewis

(57) **ABSTRACT**

The subject invention relates to improved tocopheryl qui-
nine derivatives and tocopherol derivatives having improved
pharmacokinetics in vivo that can, in some embodiments, be
useful in the treatment of Lysosomal Storage Disorder,
restoration of normal mitochondrial ATP production, modu-
lation of intracellular calcium ion concentration and other
treatments or therapies. The tocopheryl quinone derivatives
and tocopherol derivatives have side chains that have ter-
minally halogenated carbon atoms.

1 Claim, 7 Drawing Sheets

ANTIFUNGAL COMPOUND PROCESS

PATENT NUMBER: US 10,392,365

ISSUE DATE: August 27, 2019

INVENTORS:

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LEGAL ASSIGNEES:

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The United States of America, as represented
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Human Services, *Rockville, MD (US)*

ABSTRACT:

Cryptococcal meningitis (CM) results from fungal infections that are particularly prevalent in immune-compromised patients. CM is the second leading cause of HIV-related deaths in sub-Saharan Africa, with estimates of 500,000 deaths per year as current therapies are only marginally effective. CM results from infection by the encapsulated yeasts *Cryptococcus neoformans* and *Cryptococcus gattii* and is observed predominately in immune-compromised individuals. The most common drug treatment for CM in this patient population is high-dose fluconazole monotherapy, however, it achieves only a 40 percent survival rate after 10 weeks of treatment. A more potent anti-fungal drug that can be given orally once a day would likely provide a significant improvement in survival for this neglected population. VT-1129 is a novel fungus-specific Cyp51 inhibitor with potent in vitro activity against *Cryptococcus* species. This agent acts by inhibiting the fungal cytochrome P450 enzyme Cyp51 (lanosterol 14- α -demethylase), thus inhibiting the biosynthesis of ergosterol in a highly selective manner compared to that of clinically available azole antifungals.

The present invention provides novel methods of commercial scale manufacturing of VT-1129. The inventors have developed an optimized synthetic process for scaled-up production of drug at a low cost that will support treatment of patients in the developing world.

USPTO WEBSITE: <https://go.usa.gov/xf6hV>



US010392365B2

(12) **United States Patent**
Hoekstra et al.

(10) **Patent No.:** **US 10,392,365 B2**
(45) **Date of Patent:** **Aug. 27, 2019**

(54) **ANTIFUNGAL COMPOUND PROCESS**

(71) Applicants: **Mycovia Pharmaceuticals, Inc.**,
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of America, as represented by the
Secretary, Department of Health and
Human Services**, Rockville, MD (US)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/241,036**

(22) Filed: **Jan. 7, 2019**

(65) **Prior Publication Data**

US 2019/0161469 A1 May 30, 2019

Related U.S. Application Data

(62) Division of application No. 15/126,402, filed as
application No. PCT/US2015/021491 on Mar. 19,
2015, now Pat. No. 10,173,998.

(60) Provisional application No. 61/955,615, filed on Mar.
19, 2014.

(51) **Int. Cl.**
C07D 213/26 (2006.01)
C07D 401/06 (2006.01)
C07D 405/06 (2006.01)
C07D 213/38 (2006.01)

(52) **U.S. Cl.**
CPC **C07D 401/06** (2013.01); **C07D 213/26**
(2013.01); **C07D 213/38** (2013.01); **C07D**
405/06 (2013.01)

(58) **Field of Classification Search**
CPC C07D 213/26
USPC 546/334
See application file for complete search history.

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(Continued)

Primary Examiner Patricia I. Morris

(74) *Attorney, Agent, or Firm* — Brinks Gilson & Lione

(57) **ABSTRACT**

The present invention relates to a process for preparing
compound 1 that is useful as an antifungal agent. In par-
ticular, the invention seeks to provide new methodology for
preparing compound 1 and substituted derivatives thereof.

2 Claims, No Drawings

DEVICE AND METHODS OF USING DEVICE FOR DETECTION OF AMINOACIDOPATHIES

PATENT NUMBER: US 10,392,646

ISSUE DATE: August 27, 2019

INVENTORS:

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Marshall Lynn Summar, *Washington, DC*
Juan Manuel Cabrera-Luque, *Rockville, MD*
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Anton Simeonov, *Bethesda, MD*
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LEGAL ASSIGNEES:

University of Maryland, College Park,
College Park, MD (US);
Children's National Medical Center,
Washington, DC (US);
The United States of America, as represented
by The Secretary, Department of Health and
Human Services, *Bethesda, MD (US)*

ABSTRACT:

Numerous metabolic disorders, such as hyperammonemia and aminoacidopathies, are characterized by a chronic elevation of a specific metabolite due to dysfunction of enzymes involved in metabolic regulation, process and clearance. It would be of great utility and convenience to develop enzyme-based sensors that can detect specific plasma metabolites in real-time, similar to the measurement of glucose in diabetics.

In the present invention, specific enzymes are immobilized within a polymer and attached to an electrode that then measures the electron flow produced by the redox transformation of the specific metabolite being analyzed. The biosensor described here is capable of measuring one or more amino acids with the use of a point of care system that comprises an electrode modified by hydrogel that contains one or more enzymes that can oxidize the relevant amino acids. This invention is used to measure metabolites in blood of patients in real time. The invention also provides a method of monitoring the concentrations of one or more amino acids in a sample of bodily fluid of a person diagnosed or suspected as having one or more aminoacidopathies.

USPTO WEBSITE: <https://go.usa.gov/xf6hf>



US010392646B2

(12) **United States Patent**
Ayyub et al.

(10) **Patent No.:** **US 10,392,646 B2**
(45) **Date of Patent:** **Aug. 27, 2019**

(54) **DEVICE AND METHODS OF USING DEVICE FOR DETECTION OF AMINOACIDOPATHIES**

(71) Applicants: **UNIVERSITY OF MARYLAND, OFFICE OF TECHNOLOGY COMMERCIALIZATION**, College Park, MD (US); **CHILDREN'S NATIONAL MEDICAL CENTER**, Washington, DC (US); **THE UNITED STATES OF AMERICA**, as represented by the Secretary, Department of Health and Human Services, Washington, DC (US)

(72) Inventors: **Omar Bilal Ayyub**, Potomac, MD (US); **Adam Michael Behrens**, Olney, MD (US); **Peter Kofinas**, Bethesda, MD (US); **Marshall Lynn Summar**, Washington, DC (US); **Juan Manuel Cabrera-Luque**, Rockville, MD (US); **Gary Cunningham**, Washington, DC (US); **Anton Simeonov**, Bethesda, MD (US); **Juan Marugan**, Gaithersburg, MD (US)

(73) Assignees: **University of Maryland, College Park**, College Park, MD (US); **Children's National Medical Center**, Washington, DC (US); **The United States of America**, as Represented by The Secretary, Department of Health and Human Services, Bethesda, MD (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 376 days.

(21) Appl. No.: **14/436,844**

(22) PCT Filed: **Oct. 17, 2013**

(86) PCT No.: **PCT/US2013/065548**

§ 371 (c)(1),

(2) Date: **Apr. 17, 2015**

(87) PCT Pub. No.: **WO2014/062985**

PCT Pub. Date: **Apr. 24, 2014**

(65) **Prior Publication Data**

US 2016/0168613 A1 Jun. 16, 2016

Related U.S. Application Data

(60) Provisional application No. 61/714,870, filed on Oct. 17, 2012, provisional application No. 61/776,371, filed on Mar. 11, 2013.

(51) **Int. Cl.**
G01N 33/68 (2006.01)
C12N 9/02 (2006.01)
C12N 9/06 (2006.01)
C12Q 1/00 (2006.01)
C12N 11/04 (2006.01)
C12N 11/10 (2006.01)
G01N 27/327 (2006.01)

(52) **U.S. CL.**

CPC **C12Q 1/005** (2013.01); **C12N 9/0018** (2013.01); **C12N 9/0071** (2013.01); **C12N 11/04** (2013.01); **C12N 11/10** (2013.01); **G01N 27/3277** (2013.01); **G01N 33/6812** (2013.01); **G01N 2800/04** (2013.01); **G01N 2800/52** (2013.01)

(58) **Field of Classification Search**

CPC **C12N 11/04**; **C12N 11/10**; **C12N 9/0018**; **C12N 9/0071**; **C12Q 1/005**; **G01N 27/3277**; **G01N 2800/52**; **G01N 33/68121**; **G01N 2800/04**; **G01N 33/6812**
See application file for complete search history.

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Primary Examiner — Aaron J Kosar

(74) *Attorney, Agent, or Firm* — Ballard Spahr LLP; John A. Zurawski

(57) **ABSTRACT**

The present invention relates to a biosensor capable of measuring the total concentration of one or a plurality of amino acids with the use of a reagentless system comprising an electrode modified by hydrogel that comprises at least one enzyme that oxidizes at least one substrate that is at least one amino acid. In some embodiments, the biosensor comprises a hydrogel comprising alginate. In some embodiments, the biosensor comprises use of a thermophilic bacterial metabolic enzyme immobilized or attached to the hydrogel.

19 Claims, 23 Drawing Sheets

Specification includes a Sequence Listing.

ANTIFUNGAL COMPOUND PROCESS

PATENT NUMBER: US 10,399,943

ISSUE DATE: September 3, 2019

INVENTORS:

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Mark Behnke, *Poolesville, MD*
Asaf Alimardanov, *North Bethesda, MD*
Scott A. David, *Huntsburg, OH*
Douglas Franklin Fry, *Euclid, OH*

LEGAL ASSIGNEES:

Mycovia Pharmaceuticals, Inc.,
Durham, NC (US);
The United States of America, as represented
by the Secretary, Department of Health and
Human Services, *Rockville, MD (US)*

ABSTRACT:

Vulvovaginal candidiasis (VVC) and recurrent VVC (RVVC) remain major health problems for women. RVVC is a debilitating, chronic infectious condition that affects quality of life for nearly 138 million women worldwide each year and for which there is currently no approved treatment. The azole class of drugs targeting fungal cytochrome P45051 (CYP51) is widely used as a first-line treatment for fungal infections or as preemptive treatment. However, several side effects exist and are linked to inhibition of off-target human cytochromes P450 (CYPs). Additionally, the widespread use of azole antifungals, especially for prolonged treatment periods, has led to the emergence of azole-resistant strains of *Candida albicans* and other *Candida* species. Fungal CYP51 inhibitors with greater selectivity for fungal CYP51 (than off-target human CYPs) could overcome these limitations and therefore become a significant advancement in the field of fungal therapy.

VT-1161 was identified and developed to fill the growing need to develop new effective antifungal drugs to combat the increasing occurrence of *Candida* resistance, especially for the treatment of deep systemic infections. VT-1161 is a novel, oral therapy for RVVC that is designed to have greater selectivity, fewer side effects, and improved efficacy than current treatment options. The present invention provides novel methods of commercial scale manufacturing of VT-1161. The inventors have developed an optimized synthetic process for scaled-up production of VT-1161 at a low cost that will support treatment of patients in the developing world.

USPTO WEBSITE: <https://go.usa.gov/xf6hM>



US010399943B2

(12) **United States Patent**
Hoekstra et al.

(10) **Patent No.:** **US 10,399,943 B2**
(45) **Date of Patent:** ***Sep. 3, 2019**

(54) **ANTIFUNGAL COMPOUND PROCESS**

(56) **References Cited**

(71) Applicants: **Mycovia Pharmaceuticals, Inc.,**
Durham, NC (US); **The United States**
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Secretary, Department of Health and
Human Services, Washington, DC (US)

U.S. PATENT DOCUMENTS

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(73) Assignees: **Mycovia Pharmaceuticals, Inc.,**
Durham, NC (US); **The United States**
of America, as represented by the
Secretary, Department of Health and
Human Services, Rockville, MD (US)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 21 days.

This patent is subject to a terminal dis-
claimer.

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(21) Appl. No.: **15/126,392**

(22) PCT Filed: **Mar. 19, 2015**

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(86) PCT No.: **PCT/US2015/021484**

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§ 371 (c)(1).

(2) Date: **Sep. 15, 2016**

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(87) PCT Pub. No.: **WO2015/143166**

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PCT Pub. Date: **Sep. 24, 2015**

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(65) **Prior Publication Data**

US 2017/0081285 A1 Mar. 23, 2017

International Search Report and Written Opinion dated Jun. 25, 2015 for Application No. PCT/US2015/021436.
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Related U.S. Application Data

(60) Provisional application No. 61/955,599, filed on Mar. 19, 2014.

(51) Int. Cl.

C07D 213/26	(2006.01)
C07D 401/06	(2006.01)
C07D 213/50	(2006.01)
C07D 405/06	(2006.01)
C07D 213/30	(2006.01)
C07D 213/38	(2006.01)

(52) U.S. Cl.

CPC **C07D 213/50** (2013.01); **C07D 213/30**
(2013.01); **C07D 213/38** (2013.01); **C07D**
401/06 (2013.01); **C07D 405/06** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

(57)

ABSTRACT

The present invention relates to a process for preparing compound 1 that is useful as an antifungal agent. In particular, the invention seeks to provide new methodology for preparing compound 1 and substituted derivatives thereof.

16 Claims, No Drawings

Primary Examiner Karen Cheng

(74) *Attorney, Agent, or Firm* — Brinks Gilson & Lione

ANTIFUNGAL COMPOUND PROCESS

PATENT NUMBER: US 10,407,392

ISSUE DATE: September 10, 2019

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LEGAL ASSIGNEES:

Mycovia Pharmaceuticals, Inc.,
Durham, NC (US);
The United States of America, as represented
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Human Services, *Rockville, MD (US)*

ABSTRACT:

Vulvovaginal candidiasis (VVC) and recurrent VVC (RVVC) remain major health problems for women. RVVC is a debilitating, chronic infectious condition that affects quality of life for nearly 138 million women worldwide each year and for which there is currently no approved treatment. The azole class of drugs targeting fungal cytochrome P45051 (CYP51) is widely used as a first-line treatment for fungal infections or as preemptive treatment. However, several side effects exist and are linked to inhibition of off-target human cytochromes P450 (CYPs). Additionally, the widespread use of azole antifungals, especially for prolonged treatment periods, has led to the emergence of azole-resistant strains of *Candida albicans* and other *Candida* species. Fungal CYP51 inhibitors with greater selectivity for fungal CYP51 (than off-target human CYPs) could overcome these limitations and therefore become a significant advancement in the field of fungal therapy.

VT-1161 was identified and developed to fill the growing need to develop new effective antifungal drugs to combat the increasing occurrence of *Candida* resistance, especially for the treatment of deep systemic infections. VT-1161 is a novel, oral therapy for RVVC that is designed to have greater selectivity, fewer side effects, and improved efficacy than current treatment options. The present invention provides novel methods of commercial scale manufacturing of VT-1161. The inventors have developed an optimized synthetic process for scaled-up production of VT-1161 at a low cost that will support treatment of patients in the developing world.

USPTO WEBSITE: <https://go.usa.gov/xfFqk>



US010407392B2

(12) **United States Patent**
Hoekstra et al.

(10) **Patent No.:** **US 10,407,392 B2**
(45) **Date of Patent:** ***Sep. 10, 2019**

(54) **ANTIFUNGAL COMPOUND PROCESS**

(71) Applicants: **Mycovia Pharmaceuticals, Inc.**,
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Bethesda, MD (US); **Scott A. David**,
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Franklin Fry, Euclid, OH (US)

(73) Assignees: **Mycovia Pharmaceuticals, Inc.**,
Durham, NC (US); **The United States**
of America, as represented by the
Secretary, Department of Health and
Human Services, Rockville, MD (US)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-
claimer.

(21) Appl. No.: **16/280,527**

(22) Filed: **Feb. 20, 2019**

(65) **Prior Publication Data**

US 2019/0185429 A1 Jun. 20, 2019

Related U.S. Application Data

(62) Division of application No. 15/126,392, filed as
application No. PCT/US2015/021484 on Mar. 19,
2015.

(60) Provisional application No. 61/955,599, filed on Mar.
19, 2014.

(51) Int. Cl.
C07D 213/26 (2006.01)
C07D 213/50 (2006.01)
C07D 405/06 (2006.01)
C07D 213/38 (2006.01)
C07D 213/30 (2006.01)
C07D 401/06 (2006.01)

(52) U.S. Cl.
CPC **C07D 213/50** (2013.01); **C07D 213/30**
(2013.01); **C07D 213/38** (2013.01); **C07D**
401/06 (2013.01); **C07D 405/06** (2013.01)

(58) **Field of Classification Search**
CPC C07D 213/50; C07D 213/30
See application file for complete search history.

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for Application No. PCT/US2015/021464 (70021W000).

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Primary Examiner Karen Cheng

(74) *Attorney, Agent, or Firm* — Brinks Gilson & Liore

(57) **ABSTRACT**

The present invention relates to a process for preparing
compound 1 that is useful as an antifungal agent. In par-
ticular, the invention seeks to provide new methodology for
preparing compound 1 and substituted derivatives thereof.

3 Claims, No Drawings

METHODS AND COMPOSITIONS FOR THE INHIBITION OF PIN1

PATENT NUMBER: US 10,413,548

ISSUE DATE: September 17, 2019

INVENTORS:

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Anton Momtchilov Simeonov, *Rockville, MD*
Shuo Wei, *Chestnut Hill, MA*
Xiao Zhen Zhou, *Newton, MA*

LEGAL ASSIGNEES:

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The United States of America, as represented
by the Secretary, Department of Health and
Human Services, *Bethesda, MD (US)*

ABSTRACT:

Pin1, a peptidyl-prolyl cis/trans isomerase (PPlase), is emerging as an important regulator of signal transduction pathways. It is a potential target molecule for cancer, infectious disease, immune disorder, and Alzheimer's disease (AD). Pin 1 belongs to the Parvulin family of peptidyl-prolyl cis-trans isomerases and is the only member that specifically isomerizes phospho-(Ser/Thr)-Pro ((Ser(P)/Thr(P))-Pro) motifs). It was shown that the unique proline isomerase Pin1 is pivotal for protecting against age-dependent neurodegeneration in Alzheimer's disease (AD). Pin1 is modified in human AD brains, but little is known about its regulatory mechanisms and pathological significance of such Pin1 modification. It is also known that Pin1 is prevalently overexpressed in human cancers and that high Pin1 marker levels correlate with poor clinical outcome in many cancers. Significantly, Pin1 activates at least 19 oncogenes/growth enhancers and also inactivates at least 12 tumor suppressors/growth inhibitors. Thus, there is a need for Pin1 inhibitors for treating proliferative disorders and neurodegenerative disorders.

To identify the small molecule inhibitors of Pin1, a fluorescence polarization assay was developed and used for quantitative high-throughput screening. A total of 393,181 small molecule compounds from Molecular Libraries Probe Production Centers Network (MLPCN) library were screened in concentration-response manner. The invention features compositions and methods for inhibiting the Pin1 protein, and the treatment of disorders characterized by elevated Pin1 levels.

USPTO WEBSITE: <https://go.usa.gov/xfFqR>



US010413548B2

(12) **United States Patent**
Lu et al.(10) **Patent No.:** **US 10,413,548 B2**
(45) **Date of Patent:** **Sep. 17, 2019**(54) **METHODS AND COMPOSITIONS FOR THE INHIBITION OF PIN1**(71) Applicants: **Beth Israel Deaconess Medical Center, Inc.**, Boston, MA (US); **The United States of America, as represented by the Secretary, Department of Health and Human Services**, Bethesda, MD (US)(72) Inventors: **Kun Ping Lu**, Newton, MA (US); **Matthew Brian Boxer**, Rockville, MD (US); **Mindy Irene Emily Davis**, Rockville, MD (US); **Rajan Pragani**, Rockville, MD (US); **Min Shen**, Rockville, MD (US); **Anton Momtchilov Simeonov**, Rockville, MD (US); **Shuo Wei**, Chestnut Hill, MA (US); **Xiao Zhen Zhou**, Newton, MA (US)(73) Assignees: **Beth Israel Deaconess Medical Center, Inc.**, Boston, MA (US); **The United States of America, as represented by the Secretary, Department of Health and Human Services**, Bethesda, MD (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **15/645,683**(22) Filed: **Jul. 10, 2017**(65) **Prior Publication Data**
US 2017/0304310 A1 Oct. 26, 2017**Related U.S. Application Data**

(63) Continuation of application No. 14/406,401, filed as application No. PCT/US2013/044747 on Jun. 7, 2013, now Pat. No. 9,730,941.

(60) Provisional application No. 61/656,806, filed on Jun. 7, 2012.

(51) **Int. Cl.**
A61K 31/5377 (2006.01)
A61K 31/473 (2006.01)
A61K 45/06 (2006.01)
A61K 31/185 (2006.01)
A61K 31/341 (2006.01)
A61K 31/357 (2006.01)
A61K 31/365 (2006.01)
A61K 31/381 (2006.01)
A61K 31/382 (2006.01)
A61K 31/402 (2006.01)
A61K 31/4025 (2006.01)
A61K 31/404 (2006.01)
A61K 31/405 (2006.01)
A61K 31/4245 (2006.01)
A61K 31/427 (2006.01)**A61K 31/428** (2006.01)
A61K 31/4704 (2006.01)
A61K 31/496 (2006.01)(52) **U.S. Cl.**
CPC **A61K 31/5377** (2013.01); **A61K 31/185** (2013.01); **A61K 31/341** (2013.01); **A61K 31/357** (2013.01); **A61K 31/365** (2013.01); **A61K 31/381** (2013.01); **A61K 31/382** (2013.01); **A61K 31/402** (2013.01); **A61K 31/404** (2013.01); **A61K 31/405** (2013.01); **A61K 31/4025** (2013.01); **A61K 31/427** (2013.01); **A61K 31/428** (2013.01); **A61K 31/4245** (2013.01); **A61K 31/473** (2013.01); **A61K 31/4704** (2013.01); **A61K 31/496** (2013.01); **A61K 45/06** (2013.01)(58) **Field of Classification Search**
CPC **A61K 31/5377**
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(Continued)*Primary Examiner* Svetlana M Ivanova(74) *Attorney, Agent, or Firm* — Clark & Halbig LLP(57) **ABSTRACT**

The invention features compositions and methods for inhibiting the Pin1 protein, and the treatment of disorders characterized by elevated Pin1 levels.

3 Claims, 15 Drawing Sheets

ANTIFUNGAL COMPOUND PROCESS

PATENT NUMBER: US 10,421,741

ISSUE DATE: September 24, 2019

INVENTORS:

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Christopher M. Yates, *Raleigh, NC*
Mark Behnke, *Poolesville, MD*
Asaf Alimardanov, *North Bethesda, MD*
Scott A. David, *Huntsburg, OH*
Douglas Franklin Fry, *Euclid, OH*

LEGAL ASSIGNEES:

Mycovia Pharmaceuticals, Inc.,
Durham, NC (US);
The United States of America, as represented
by the Secretary, Department of Health and
Human Services, *Rockville, MD (US)*

ABSTRACT:

Cryptococcal meningitis (CM) results from fungal infections that are particularly prevalent in immune-compromised patients. CM is the second leading cause of HIV-related deaths in sub-Saharan Africa, with estimates of 500,000 deaths per year as current therapies are only marginally effective. CM results from infection by the encapsulated yeasts *Cryptococcus neoformans* and *Cryptococcus gattii* and is observed predominately in immune-compromised individuals. The most common drug treatment for CM in this patient population is high-dose fluconazole monotherapy, however, it achieves only a 40 percent survival rate after 10 weeks of treatment. A more potent anti-fungal drug that can be given orally once a day would likely provide a significant improvement in survival for this neglected population. VT-1129 is a novel fungus-specific Cyp51 inhibitor with potent in vitro activity against *Cryptococcus* species. This agent acts by inhibiting the fungal cytochrome P450 enzyme Cyp51 (lanosterol 14- α -demethylase), thus inhibiting the biosynthesis of ergosterol in a highly selective manner compared to that of clinically available azole antifungals.

The present invention provides novel methods of commercial scale manufacturing of VT-1129. The inventors have developed an optimized synthetic process for scaled-up production of drug at a low cost that will support treatment of patients in the developing world.

USPTO WEBSITE: <https://go.usa.gov/xfFq7>



US010421741B2

(12) **United States Patent**
Hoekstra et al.

(10) **Patent No.:** **US 10,421,741 B2**
(45) **Date of Patent:** ***Sep. 24, 2019**

(54) **ANTIFUNGAL COMPOUND PROCESS**

(56) **References Cited**

(71) Applicants: **Mycovia Pharmaceuticals, Inc.**,
Durham, NC (US); **The United States
of America, as represented by the
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U.S. PATENT DOCUMENTS

(72) Inventors: **William J. Hoekstra**, Durham, NC
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NC (US); **Mark Behnke**, Poolesville,
MD (US); **Asaf Alimardanov**, North
Bethesda, MD (US); **Scott A. David**,
Huntsburg, OH (US); **Douglas
Franklin Fry**, Euclid, OH (US)

(73) Assignees: **Mycovia Pharmaceuticals, Inc.**,
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Human Services**, Rockville, MD (US)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-
claimer.

(21) Appl. No.: **16/030,228**

(22) Filed: **Jul. 9, 2018**

(65) **Prior Publication Data**

US 2019/0010140 A1 Jan. 10, 2019

Related U.S. Application Data

(62) Division of application No. 15/126,420, filed as
application No. PCT/US2015/021511 on Mar. 19,
2015, now Pat. No. 10,017,494.

(60) Provisional application No. 61/955,650, filed on Mar.
19, 2014.

(51) **Int. Cl.**
C07D 401/06 (2006.01)
C07D 405/06 (2006.01)
C07D 213/30 (2006.01)
C07D 213/38 (2006.01)
C07D 213/56 (2006.01)
C07D 213/50 (2006.01)

(52) **U.S. Cl.**
CPC **C07D 401/06** (2013.01); **C07D 213/30**
(2013.01); **C07D 213/38** (2013.01); **C07D**
213/50 (2013.01); **C07D 213/56** (2013.01);
C07D 405/06 (2013.01)

(58) **Field of Classification Search**
CPC .. **C07D 401/06**; **C07D 213/30**; **C07D 405/06**;
C07D 213/50; **C07D 213/56**; **C07D**
213/38
USPC **546/268.4**
See application file for complete search history.

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Primary Examiner — Daniel R Carcamague

(74) *Attorney, Agent, or Firm* — Brinks Gilson & Lione

(57) **ABSTRACT**

The present invention relates to a process for preparing
compound 1 that is useful as an antifungal agent. In par-
ticular, the invention seeks to provide new methodology for
preparing compound 1 and substituted derivatives thereof.

2 Claims, No Drawings

ANTIFUNGAL COMPOUND PROCESS

PATENT NUMBER: US 10,428,025

ISSUE DATE: October 1, 2019

INVENTORS:

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Scott A. David, *Huntsburg, OH*
Douglas Franklin Fry, *Euclid, OH*

LEGAL ASSIGNEES:

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Human Services, *Rockville, MD (US)*

ABSTRACT:

Vulvovaginal candidiasis (VVC) and recurrent VVC (RVVC) remain major health problems for women. RVVC is a debilitating, chronic infectious condition that affects quality of life for nearly 138 million women worldwide each year and for which there is currently no approved treatment. The azole class of drugs targeting fungal cytochrome P45051 (CYP51) is widely used as a first-line treatment for fungal infections or as preemptive treatment. However, several side effects exist and are linked to inhibition of off-target human cytochromes P450 (CYPs). Additionally, the widespread use of azole antifungals, especially for prolonged treatment periods, has led to the emergence of azole-resistant strains of *Candida albicans* and other *Candida* species. Fungal CYP51 inhibitors with greater selectivity for fungal CYP51 (than off-target human CYPs) could overcome these limitations and therefore become a significant advancement in the field of fungal therapy.

VT-1161 was identified and developed to fill the growing need to develop new effective antifungal drugs to combat the increasing occurrence of *Candida* resistance, especially for the treatment of deep systemic infections. VT-1161 is a novel, oral therapy for RVVC that is designed to have greater selectivity, fewer side effects, and improved efficacy than current treatment options. The present invention provides novel methods of commercial scale manufacturing of VT-1161. The inventors have developed an optimized synthetic process for scaled-up production of VT-1161 at a low cost that will support treatment of patients in the developing world.

USPTO WEBSITE: <https://go.usa.gov/xfFaX>



US010428025B2

(12) **United States Patent**
Hoekstra et al.

(10) **Patent No.:** **US 10,428,025 B2**
(45) **Date of Patent:** ***Oct. 1, 2019**

(54) **ANTIFUNGAL COMPOUND PROCESS**

(71) Applicants: **Mycovia Pharmaceuticals, Inc.**,
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Huntsburg, OH (US); **Douglas**
Franklin Fry, Euclid, OH (US)

(73) Assignees: **Mycovia Pharmaceuticals, Inc.**,
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Secretary, Department of Health and
Human Services, Rockville, MD (US)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-
claimer.

(21) Appl. No.: **16/280,534**

(22) Filed: **Feb. 20, 2019**

(65) **Prior Publication Data**

US 2019/0185430 A1 Jun. 20, 2019

Related U.S. Application Data

(62) Division of application No. 15/126,392, filed as
application No. PCT/US2015/021484 on Mar. 19,
2015.

(60) Provisional application No. 61/955,599, filed on Mar.
19, 2014.

(51) **Int. Cl.**

C07D 213/30 (2006.01)
C07D 213/50 (2006.01)
C07D 405/06 (2006.01)
C07D 213/38 (2006.01)
C07D 401/06 (2006.01)

(52) **U.S. Cl.**

CPC **C07D 213/50** (2013.01); **C07D 213/30**
(2013.01); **C07D 213/38** (2013.01); **C07D**
401/06 (2013.01); **C07D 405/06** (2013.01)

(58) **Field of Classification Search**

CPC **C07D 213/30**; **C07D 213/50**
See application file for complete search history.

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Primary Examiner — Karen Cheng

(74) Attorney, Agent, or Firm Brinks Gilson & Lione

(57)

ABSTRACT

The present invention relates to a process for preparing
compound 1 that is useful as an antifungal agent. In par-
ticular, the invention seeks to provide new methodology for
preparing compound 1 and substituted derivatives thereof.

3 Claims, No Drawings

SMALL-MOLECULE INHIBITORS OF HUMAN GALACTOKINASE FOR THE TREATMENT OF GALACTOSEMIA AND CANCERS

PATENT NUMBER: US 10,471,061

ISSUE DATE: November 12, 2019

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Manshu Tang, *Salt Lake City, UT*
Douglas S. Auld, *Beverly, MA*

LEGAL ASSIGNEES:

The United States of America, as represented by the Secretary, Department of Health and Human Services, *Bethesda, MD (US)*; University of Utah Research Foundation, *Salt Lake City, UT (US)*

ABSTRACT:

Lactose, found in dairy products and other foods, is comprised of two simple sugars, glucose and galactose. In galactosemia, where galactose is not properly metabolized, build-up of toxic compounds, such as galactose-1-phosphate, can lead to liver disease, renal failure, cataracts, brain damage, and even death if this disorder is left untreated. Currently, the only treatment for galactosemia is elimination of lactose and galactose from the diet, but in some cases this is not sufficient to avoid long-term complications from the disorder.

This technology describes selective small-molecule inhibitors of human galactokinase, which inhibit the first step in galactose metabolism. These compounds could be used to treat galactosemia by eliminating the build-up of toxic metabolites in brain, liver, and other tissues, and could form the basis for the first effective treatment for this disorder. These compounds are also promising candidates for the treatment of certain cancers, such as PTEN/AKT mis-regulated cancers.

USPTO WEBSITE: <https://go.usa.gov/xfFas>



US010471061B2

(12) **United States Patent**
Boxer et al.

(10) **Patent No.:** **US 10,471,061 B2**

(45) **Date of Patent:** ***Nov. 12, 2019**

(54) **GALACTOKINASE INHIBITORS FOR THE TREATMENT AND PREVENTION OF ASSOCIATED DISEASES AND DISORDERS**

(71) Applicants: **The United States of America, as represented by the Secretary, Department of Health and Human Services, Bethesda, MD (US); UNIVERSITY OF UTAH RESEARCH FOUNDATION, Salt Lake City, UT (US)**

(72) Inventors: **Matthew B. Boxer, Frederick, MD (US); Martin J. Walsh, Carmel, IN (US); Li Liu, Germantown, MD (US); Cordelle D. Tanega, Rockville, MD (US); Min Shen, Boyds, MD (US); Kent Lai, Salt Lake City, UT (US); Manshu Tang, Salt Lake City, UT (US); Douglas S. Auld, Beverly, MA (US)**

(73) Assignees: **The United States of America, as represented by the Secretary, Department of Health and Human Services, Bethesda, MD (US); University of Utah Research Foundation, Salt Lake City, UT (US)**

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(h) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **16/152,735**

(22) Filed: **Oct. 5, 2018**

(65) **Prior Publication Data**

US 2019/0030031 A1 Jan. 31, 2019

Related U.S. Application Data

(63) Continuation of application No. 15/234,934, filed on Aug. 11, 2016, now abandoned, which is a continuation of application No. 14/346,400, filed as application No. PCT/US2011/053021 on Sep. 23, 2011, now Pat. No. 9,447,087.

(51) **Int. Cl.**
C07D 403/12 (2006.01)
A61K 31/517 (2006.01)
A61K 31/506 (2006.01)
C07D 413/14 (2006.01)
C07D 413/12 (2006.01)
C07D 493/10 (2006.01)
C07D 495/10 (2006.01)
C07D 417/14 (2006.01)
C07D 491/107 (2006.01)
A61K 31/527 (2006.01)

(52) **U.S. CL.**
CPC **A61K 31/517** (2013.01); **A61K 31/506** (2013.01); **A61K 31/527** (2013.01); **C07D 403/12** (2013.01); **C07D 413/12** (2013.01); **C07D 413/14** (2013.01); **C07D 417/14** (2013.01); **C07D 491/107** (2013.01); **C07D 493/10** (2013.01); **C07D 495/10** (2013.01)

(58) **Field of Classification Search**
CPC **C07D 403/12; A61K 31/506**
USPC **544/331; 514/275**
See application file for complete search history.

(56) **References Cited**

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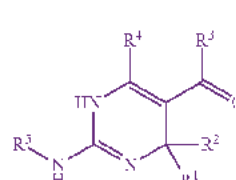
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Primary Examiner Deepak R Rao

(74) *Attorney, Agent, or Firm* Michael Best & Friedrich LLP

(57) **ABSTRACT**

Disclosed are inhibitors of human galactokinase of formula (I) that are useful in treating or preventing a galactokinase mediated disease or disorder, e.g., galactosemia. Also disclosed are a composition comprising a pharmaceutically acceptable carrier and at least one inhibitor of the invention, and a method of treating or preventing such disease or disorder in a mammal. Formula (I).



20 Claims, No Drawings

BICYCLIC BET BROMODOMAIN INHIBITORS AND USES THEREOF

PATENT NUMBER: US 10,508,106

ISSUE DATE: December 17, 2019

INVENTORS:

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Makoto Yoshioka, *Gaithersburg, MD*
David J. Maloney, *Point of Rocks, MD*
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Ajit Jadhav, *Chantilly, VA*
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LEGAL ASSIGNEES:

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The United States of America, as represented
by the Secretary, Department of Health and
Human Services, *Bethesda, MD (US)*

ABSTRACT:

The proteins containing bromodomain(s) are critical in the epigenetic regulation of gene transcription, and epigenetic dysregulation can lead to cancers and inflammatory diseases. Among identified bromodomains, the bromodomain and extra-terminal domain (BET) family, consisting of four members BRD2, BRD3, BRD4, and BRDT, have emerged as a potential therapeutic target. Thus, inhibiting the bromodomains of BET proteins can provide an effective mode of treatment for various diseases, including various cancers.

The present invention relates to compounds that bind to and otherwise modulate the activity of bromodomain-containing proteins, to processes for preparing these compounds, to pharmaceutical compositions containing these compounds, and to methods of using these compounds for treating a wide variety of conditions and disorders. Specifically, this invention relates to (S)-1-(4-(6-(3,5-dimethylisoxazol-4-yl)-4-(3-phenylmorpholino)quinazolin-2-yl)1H-pyrazol-1-yl)-2-methylpropan-2-ol and pharmaceutical compositions containing the same for treatment of variety of indications including cancer.

USPTO WEBSITE: <https://go.usa.gov/xfFat>



US010508106B2

(12) **United States Patent**
Strovel et al.

(10) **Patent No.:** **US 10,508,106 B2**
(45) **Date of Patent:** **Dec. 17, 2019**

(54) **BICYCLIC BET BROMODOMAIN
INHIBITORS AND USES THEREOF**

(2013.01); *C07D 413/14* (2013.01); *C07D
417/14* (2013.01); *C07D 471/04* (2013.01);
C07D 471/10 (2013.01)

(71) Applicants: **ConverGene LLC**, Cambridge, MD
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(58) **Field of Classification Search**
CPC *C07D 239/48*; *A61K 45/06*
See application file for complete search history.

(72) Inventors: **Jeffrey William Strovel**, Laurel, MA
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Dryolestown, PA (US); **Ajit Jadhav**,
Chantilly, VA (US); **Daniel Jason
Urban**, Poolesville, MD (US)

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Primary Examiner Rei Tsang Shiao

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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(h) by 0 days.

(21) Appl. No.: **15/779,353**

(22) PCT Filed: **Nov. 23, 2016**

(86) PCT No.: **PCT/US2016/063485**

§ 371 (c)(1),

(2) Date: **May 25, 2018**

(87) PCT Pub. No.: **WO2017/091661**

PCT Pub. Date: **Jun. 1, 2017**

(65) **Prior Publication Data**

US 2018/0305344 A1 Oct. 25, 2018

Related U.S. Application Data

(60) Provisional application No. 62/259,894, filed on Nov.
25, 2015.

(51) **Int. Cl.**

C07D 413/04 (2006.01)

C07D 413/14 (2006.01)

C07D 401/04 (2006.01)

C07D 239/84 (2006.01)

C07D 471/04 (2006.01)

C07D 471/10 (2006.01)

A61P 39/00 (2006.01)

C07D 239/95 (2006.01)

C07D 401/14 (2006.01)

C07D 403/04 (2006.01)

C07D 417/14 (2006.01)

(52) **U.S. Cl.**

CPC *C07D 413/04* (2013.01); *A61P 39/00*

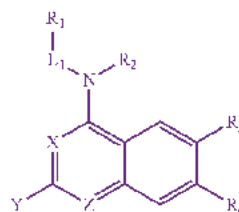
(2018.01); *C07D 239/84* (2013.01); *C07D*

239/95 (2013.01); *C07D 401/04* (2013.01);

C07D 401/14 (2013.01); *C07D 403/04*

(57) **ABSTRACT**

The present invention relates to compounds that bind to and
otherwise modulate the activity of bromodomain-containing
proteins, to processes for preparing these compounds, to
pharmaceutical compositions containing these compounds,
and to methods of using these compounds for treating a wide
variety of conditions and disorders.



(1)

2 Claims, No Drawings

BONE MORPHOGENETIC PROTEIN INHIBITORS TO TREAT FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

PATENT NUMBER: US 10,513,521

ISSUE DATE: December 24, 2019

INVENTORS:

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LEGAL ASSIGNEES:

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The United States of America, as represented
by the Secretary, Department of Health and
Human Services, *Bethesda, MD (US)*

ABSTRACT:

Fibrodysplasia ossificans progressiva (FOP) is a rare, fatal disease marked by inappropriate growth BMP signals have been known for decades to play essential roles in normal embryonic development. More recently, it has been recognized that BMP signals also play important roles in adults. In fact, excessive BMP signaling has been shown to contribute to the pathophysiology of two distinct diseases. The first of these, FOP, is caused by activating mutations in a gene encoding one of the type I BMP receptors. There are no available treatments for FOP patients.

The present invention provides small-molecule inhibitors of BMP signaling and compositions and methods for inhibiting BMP signaling. Specifically, the present invention provides bicyclic heteroaryl inhibitors of BMP signaling and compositions and methods for inhibiting BMP signaling. These compounds and compositions may be used to modulate cell growth, differentiation, proliferation, and apoptosis, and thus may be useful for treating diseases or conditions associated with BMP signaling, including inflammation, cardiovascular disease, hematological disease, cancer, and bone disorders. These compounds and compositions may also be used to reduce circulating levels of ApoB-100 or LDL and treat or prevent acquired or congenital hypercholesterolemia or hyperlipoproteinemia.

USPTO WEBSITE: <https://go.usa.gov/xfFrP>



US010513521B2

(12) **United States Patent**
Lee et al.

(10) **Patent No.:** US 10,513,521 B2
(45) **Date of Patent:** Dec. 24, 2019

(54) **COMPOSITIONS AND METHODS FOR INHIBITING BMP**

(71) Applicants: **The Brigham and Women's Hospital, Inc.**, Boston, MA (US); **The United States of America, as Represented by the Secretary, Department of Health and Human Services, National Institutes of Health**, Bethesda, MD (US); **University of Houston System**, Houston, TX (US)

(72) Inventors: **Arthur Lee**, San Jose, CA (US); **John C. McKew**, Boyds, MD (US); **Paresma R. Patel**, Rockville, MD (US); **Paul B. Yu**, Boston, MA (US); **Agustin H. Mohedas**, Somerville, MA (US); **Philip E. Sanderson**, Bethesda, MD (US); **Gregory D. Cuny**, Houston, TX (US); **Wei Zheng**, Potomac, MD (US); **Xiuli Huang**, Potomac, MD (US)

(73) Assignees: **The Brigham and Women's Hospital, Inc.**, Boston, MA (US); **University of Houston System**, Houston, TX (US); **The United States of America, as Represented by the Secretary, Department of Health and Human Services**, Bethesda, MD (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(h) by 0 days.

(21) Appl. No.: 15/326,262

(22) PCT Filed: Jul. 14, 2015

(86) PCT No.: PCT/US2015/040366

§ 371 (c)(1),

(2) Date: Jan. 13, 2017

(87) PCT Pub. No.: WO2016/011019

PCT Pub. Date: Jan. 21, 2016

(65) **Prior Publication Data**

US 2017/0197968 A1 Jul. 13, 2017

Related U.S. Application Data

(60) Provisional application No. 62/024,870, filed on Jul. 15, 2014.

(51) **Int. Cl.**
C07D 487/04 (2006.01)
C07D 519/00 (2006.01)

(52) **U.S. Cl.**
CPC C07D 487/04 (2013.01); C07D 519/00 (2013.01)

(58) **Field of Classification Search**
CPC C07D 487/04; C07D 471/04
USPC 544/281, 282; 546/121
See application file for complete search history.

(56) **References Cited**

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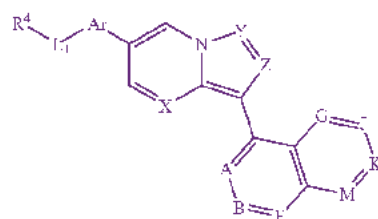
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Primary Examiner Jeffrey H Murray

(74) *Attorney, Agent, or Firm* David P. Halstead; Foley Hoag LLP

(57) **ABSTRACT**

The present invention provides bicyclic heteroaryl inhibitors of BMP signaling and compositions and methods for inhibiting BMP signaling. Exemplary compounds include those of Formula I:



These compounds and compositions may be used to modulate cell growth, differentiation, proliferation, and apoptosis, and thus may be useful for treating diseases or conditions associated with BMP signaling, including inflammation, cardiovascular disease, hematological disease, cancer, and bone disorders, as well as for modulating cellular differentiation and/or proliferation. These compounds and compositions may also be used to reduce circulating levels of ApoB-100 or LDL and treat or prevent acquired or congenital hypercholesterolemia or hyperlipoproteinemia; diseases, disorders, or syndromes associated with defects in lipid absorption or metabolism; or diseases, disorders, or syndromes caused by hyperlipidemia.

19 Claims, 5 Drawing Sheets

EMETINE COMPOUNDS FOR TREATMENT AND PREVENTION OF FLAVIVIRUS INFECTION

ABSTRACT

PATENT NUMBER: US 10,555,942

ISSUE DATE: February 11, 2020

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ABSTRACT:

Zika virus (ZIKV) and Ebola virus (EBOV) pose serious and continued threats to global public health, with no effective therapies. The present invention concerns the use of emetine compounds for the treatment or prevention of Flavivirus infections, such as Zika virus infections. The inventors showed that emetine, an anti-protozoal agent, potently inhibits ZIKV and EBOV infections at low nanomolar concentrations, both in-vitro and in-vivo. Two mechanisms of action for emetine are identified: the inhibition of ZIKV NS5 polymerase activity and disruption of lysosomal function. Emetine also inhibits EBOV entry. Cephaeline, a desmethyl analog of emetine, may be better tolerated in patients than emetine and exhibits a similar efficacy against both ZIKV and EBOV infections. Hence, emetine and cephaeline offer pharmaceutical therapies against both ZIKV and EBOV infection.

Aspects of the invention include methods for treating or preventing Flavivirus virus infection, such as Zika virus infection; pharmaceutical compositions; packaged dosage formulations; and kits for treating or preventing Flavivirus infections, such as Zika virus infections.

USPTO WEBSITE: <https://go.usa.gov/xfFYm>



US010555942B2

(12) **United States Patent**
Tang et al.

(10) **Patent No.:** **US 10,555,942 B2**
(45) **Date of Patent:** **Feb. 11, 2020**

(54) **EMETINE COMPOUNDS FOR TREATMENT AND PREVENTION OF FLAVIVIRUS INFECTION**

(71) Applicants: **FLORIDA STATE UNIVERSITY RESEARCH FOUNDATION, INC.**, Tallahassee, FL (US); **THE JOHNS HOPKINS UNIVERSITY**, Baltimore, MD (US); **The United States of America, as represented by the Secretary, Department of Health and Human Services**, Bethesda, MD (US)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/156,124**

(22) Filed: **Oct. 10, 2018**

(65) **Prior Publication Data**

US 2019/0105318 A1 Apr. 11, 2019

Related U.S. Application Data

(60) Provisional application No. 62/608,347, filed on Dec. 20, 2017; provisional application No. 62/570,553, filed on Oct. 10, 2017.

(51) **Int. Cl.**
A61K 31/4745 (2006.01)
A61K 45/06 (2006.01)
A61P 31/14 (2006.01)

(52) **U.S. Cl.**
CPC **A61K 31/4745** (2013.01); **A61K 45/06** (2013.01); **A61P 31/14** (2018.01)

(58) **Field of Classification Search**
CPC **A61K 31/4745**; **A61K 45/06**; **A61P 31/14**
See application file for complete search history.

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Primary Examiner—Sahar Javanmard

(74) Attorney, Agent, or Firm—Saliwanchik, Lloyd & Eisenschenk

(57) **ABSTRACT**

The present invention concerns the use of emetine compounds for the treatment or prevention of Flavivirus infections, such as Zika virus infections. Aspects of the invention include methods for treating or preventing Flavivirus virus infection, such as Zika virus infection, by administering an emetine compound such as emetine or cephaeline, or a combination of two or more emetine compounds, to a subject in need thereof; methods for inhibiting Flavivirus infections such as Zika virus infections in a cell in vitro or in vivo; pharmaceutical compositions; packaged dosage formulations; and kits for treating or preventing Flavivirus infections, such as Zika virus infections.

15 Claims, 7 Drawing Sheets

AMIDO COMPOUNDS AS ROR_γT MODULATORS AND USES THEREOF

PATENT NUMBER: US 10,561,666

ISSUE DATE: February 18, 2020

INVENTORS:

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LEGAL ASSIGNEES:

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ABSTRACT:

The retinoic acid receptor-related orphan nuclear receptor Gamma (ROR_γ) is a member of the nuclear hormone receptor superfamily. A single gene encodes for two isoforms, ROR_γ1 and ROR_γt, which differ only in their amino terminal domains. ROR_γ is widely expressed in many tissues, including liver, adipose tissue, skeletal muscle, and kidney. ROR_γt is expressed in CD4⁺/CD8⁺ thymocytes, lymphoid tissue inducer cells, and innate lymphoid cells. ROR_γt plays a pivotal role in the differentiation of TH17 cells and inhibiting ROR_γt activity presents a potential means to treat TH17-related autoimmune diseases.

This invention relates to the identification of a series of diphenylpropanamides as novel and selective ROR_γt antagonists. The amino compounds of this invention are useful to treat diseases or conditions related to ROR_γt activity. In particular, the compounds may be used to diminish inflammation due to an inflammatory disease or autoimmune disorder.

USPTO WEBSITE: <https://go.usa.gov/xfFYp>



US010561666B2

(12) **United States Patent**
Littman et al.

(10) **Patent No.:** **US 10,561,666 B2**
(45) **Date of Patent:** ***Feb. 18, 2020**

(54) **AMIDO COMPOUNDS AS ROR γ T
MODULATORS AND USES THEREOF**

C07D 317/54 (2013.01); *C07D 317/60*
(2013.01); *C07D 401/10* (2013.01); *C07D*
403/14 (2013.01);

(71) Applicants: **New York University**, New York, NY
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as Represented by the Secretary,
Department of Health and Human
Services, Bethesda, MD (US)

(Continued)

(58) **Field of Classification Search**
CPC A61K 31/55; A61K 31/12; A61K 31/33;
A61K 31/4025; A61K 31/404; A61K
31/4453; A61K 31/451; A61K 31/4525;
A61K 31/454; A61K 31/4545; A61K
31/4709; A61K 31/496; A61K 31/535;
A61K 31/5377
See application file for complete search history.

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(56) **References Cited**

(73) Assignees: **THE UNITED STATES OF**
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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

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This patent is subject to a terminal dis-
claimer.

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Registry No. 958981-75-4. File Registry, STN. entered STN Dec.
20, 2007.

(21) Appl. No.: **15/350,299**

(Continued)

(22) Filed: **Nov. 14, 2016**

(65) **Prior Publication Data**

US 2017/0065606 A1 Mar. 9, 2017

Primary Examiner Rebecca L. Anderson

(74) *Attorney, Agent, or Firm* — Hoffmann & Barton, LLP

Related U.S. Application Data

(63) Continuation of application No. 13/634,073, filed as
application No. PCT/US2011/000459 on Mar. 11,
2011, now Pat. No. 9,492,439.

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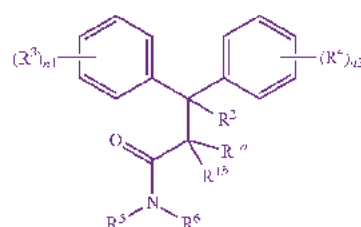
(51) **Int. Cl.**
A61K 31/55 (2006.01)
A61K 31/12 (2006.01)

(Continued)

(52) **U.S. Cl.**
CPC *A61K 31/55* (2013.01); *A61K 31/12*
(2013.01); *A61K 31/33* (2013.01); *A61K*
31/404 (2013.01); *A61K 31/4025* (2013.01);
A61K 31/4453 (2013.01); *A61K 31/451*
(2013.01); *A61K 31/454* (2013.01); *A61K*
31/4525 (2013.01); *A61K 31/4545* (2013.01);
A61K 31/4709 (2013.01); *A61K 31/496*
(2013.01); *A61K 31/535* (2013.01); *A61K*
31/5377 (2013.01); *C07C 235/34* (2013.01);
C07C 235/36 (2013.01); *C07D 211/06*
(2013.01); *C07D 211/16* (2013.01); *C07D*
307/52 (2013.01); *C07D 307/81* (2013.01);

(57) **ABSTRACT**

Amido compounds are disclosed that have a formula repre-
sented by the following:



and wherein n_1 , n_2 , R^{1a} , R^{1b} , R^2 , R^3 , R^4 , R^5 , and R^6 are as
described herein. The compounds may be prepared as phar-
maceutical compositions, and may be used for the preven-
tion and treatment of a variety of conditions in mammals
including humans, including by way of non-limiting
example, inflammatory conditions, autoimmune disorders,
cancer, and graft-versus-host disease.

8 Claims, 11 Drawing Sheets

Specification includes a Sequence Listing.

MUTANT IDH1 INHIBITORS USEFUL FOR TREATING CANCER

PATENT NUMBER: 10,703,746

ISSUE DATE: July 7, 2020

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ABSTRACT:

Isocitrate dehydrogenase 1 (IDH1) is an enzyme whose normal function is to convert isocitrate to α -ketoglutarate. Mutated forms of this enzyme (mIDH1) are common in a variety of cancers, including acute myeloid leukemia (AML), glioma, cholangiocarcinoma, chondrosarcoma, and melanoma. The IDH1 mutation at position 132 and similar IDH1 mutations result in the enzyme gaining the ability to catalyze the NADPH-dependent reduction of the wild type enzyme's product, α -ketoglutarate to R-2-hydroxyglutarate (2-HG). 2-HG is an oncometabolite, and its elevated levels have been shown to lead to de-differentiation of cells. Mutant IDH1 is an attractive target for anti-cancer therapeutics as inhibition reduces levels of 2-HG. It is expected that lower 2-HG levels will result in fewer undifferentiated cancer cells. Furthermore, inhibition of mutant IDH1 is expected to have little effect on non-cancerous cells, as these cells do not express the IDH1 mutation resulting in lower toxicity than typical cytotoxic anticancer agents.

The inventors of this innovation have discovered a series of novel compounds that potently and selectively inhibit mIDH1. These compounds reduce 2-HG levels in cell lines in vitro as well as in human cancer cells grown as xenografts in mice. These compounds possess very favorable in vivo rodent pharmacokinetics and bioavailability and are well tolerated in rodents, even when dosed at high levels. These compounds can potentially be used as treatments of cancer (AML or other solid tumors).

USPTO WEBSITE: <https://go.usa.gov/xfSQb>



US010703746B2

(12) United States Patent
Boxer et al.**(10) Patent No.: US 10,703,746 B2**
(45) Date of Patent: Jul. 7, 2020**(54) MUTANT IDH1 INHIBITORS USEFUL FOR TREATING CANCER****(71) Applicants:** THE UNITED STATES OF AMERICA, AS REPRESENTED BY THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICE, Bethesda, MD (US); THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL, Chapel Hill, NC (US)**(72) Inventors:** Matthew Brian Boxer, New Market, MD (US); Jason Matthew Rohde, Poolesville, MD (US); Rajan Pragani, Gaithersburg, MD (US); Li Liu, Germantown, MD (US); Mindy Irene Emily Davis, Rockville, MD (US); Kyle Ryan Brimacombe, Bethesda, MD (US); Min Shen, Boyds, MD (US); Anton Simeonov, Bethesda, MD (US); Surendra Karavadhi, Gaithersburg, MD (US); Daniel Jason Urban, Rockville, MD (US); Ajit Jadhav, Chantilly, VA (US); Xiaodong Wang, Chapel Hill, NC (US); Andrew Louis McIver, Durham, NC (US)**(73) Assignees:** THE UNITED STATES OF AMERICA, AS REPRESENTED BY THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES, Bethesda, MD (US); THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL, Chapel Hill, NC (US)**(*) Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 134 days.**(21) Appl. No.: 15/538,570****(22) PCT Filed: Dec. 22, 2015****(86) PCT No.: PCT/US2015/067406**

§ 371 (c)(1),

(2) Date: Jun. 21, 2017**(87) PCT Pub. No.: WO2016/106331****PCT Pub. Date: Jun. 30, 2016****(65) Prior Publication Data**

US 2019/0071434 A1 Mar. 7, 2019

Related U.S. Application Data**(60)** Provisional application No. 62/095,322, filed on Dec. 22, 2014.**(51) Int. Cl.**
C07D 417/04 (2006.01)
A61K 31/4709 (2006.01)

(Continued)

(52) U.S. Cl.
CPC **C07D 417/04** (2013.01); **A61K 31/435** (2013.01); **A61K 31/437** (2013.01);
(Continued)**(58) Field of Classification Search**
None
See application file for complete search history.**(56) References Cited**

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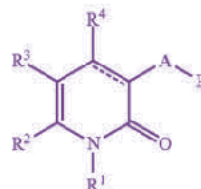
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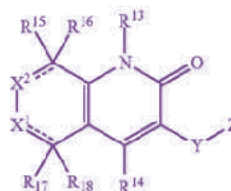
Primary Examiner — Po-Chih Chen**(74) Attorney, Agent, or Firm** — Cantor Colburn LLP**(57) ABSTRACT**

Compounds of Formula I and Formula II and the pharmaceutically acceptable salts thereof are disclosed. The variables A, B, Y, Z, X¹, X², R¹⁻⁴ and R¹³⁻¹⁸ are disclosed herein. The compounds are useful for treating cancer disorders, especially those involving mutant IDH1 enzymes. Pharmaceutical compositions containing compounds of Formula I or Formula II and methods of treatment comprising administering compounds of Formula I and Formula II are also disclosed.

Formula I



Formula II



(Continued)

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ANTON SIMEONOV			
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10,287,279 B2	5/14/2019	Inhibitors of human 12/15-lipoxygenase	Anton Simeonov; Ganesha Rai Bantukallu
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DIANE LUCI			
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PATENT NUMBER	ISSUE DATE	TITLE	NCATS INVENTORS
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JOHN MCKEW			
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JUAN MARUGAN			
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LI LU			
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MARC FERRER			
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10,202,367 B2	2/12/2019	Heterocyclic compounds and methods of use thereof	Marc Ferrer; Juan Marugan; Noel Southall; Xin Hu; Wei Zheng
10,125,112 B2	11/13/2018	Modulators of the relaxin receptor 1	Marc Ferrer; Juan Marugan; Catherine Chen; Noel Southall; Wei Zheng

PATENT NUMBER	ISSUE DATE	TITLE	NCATS INVENTORS
MIAO XU			
10,555,942 B2	2/11/2020	Emetine compounds for treatment and prevention of flavivirus infection	Wei Zheng, Miao Xu, Ruili Huang, Wenwei Huang, Khalida Shamim, Hao Li
MIN SHEN			
10,471,061 B2	11/12/2019	Galactokinase inhibitors for the treatment and prevention of associated diseases and disorders	Min Shen; Li Liu
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NOEL SOUTHALL			
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10,202,367 B2	2/12/2019	Heterocyclic compounds and methods of use thereof	Juan Marugan; Noel Southall; Xin Hu; Marc Ferrer; Wei Zheng
10,125,112 B2	11/13/2018	Modulators of the relaxin receptor 1	Juan Marugan; Marc Ferrer; Catherine Chen; Noel Southall; Wei Zheng
PATRICIA DRANCHAK			
10,239,830 B2	3/26/2019	Benzenesulfonamide upregulators of NPC1 for Neimann-Pick disease and other lysosomal storage disorders	Juan Marugan; Samarjit Patnaik; Noel Southall; Wei Zheng; Marc Ferrer; Raul Calvo; Patricia Dranchak
PHILIP SANDERSON			
10,513,521 B2	12/24/2019	Compositions and methods for inhibiting BMP	Philip Sanderson, Wei Zheng, Xiuli Huang
RAUL CALVO			
10,239,830 B2	3/26/2019	Benzenesulfonamide upregulators of NPC1 for Neimann-Pick disease and other lysosomal storage disorders	Juan Marugan; Samarjit Patnaik; Noel Southall; Wei Zheng; Marc Ferrer; Raul Calvo; Patricia Dranchak
RUILI HUANG			
10,561,666 B2	2/18/2020	Amido compounds as RORyt modulators and uses thereof	Wenwei Huang; Ruili Huang
10,555,942 B2	2/11/2020	Emetine compounds for treatment and prevention of flavivirus infection	Wei Zheng, Miao Xu, Ruili Huang, Wenwei Huang, Khalida Shamim, Hao Li

PATENT NUMBER	ISSUE DATE	TITLE	NCATS INVENTORS
SAMARJIT PATNAIK			
10,301,314 B2	5/28/2019	Compounds and methods for the prevention and treatment of tumor metastasis and tumorigenesis	Samarjit Patnaik, Juan Marugan, Noel Southall, Wei Zheng
10,239,830 B2	3/26/2019	Benzenesulfonamide upregulators of NPC1 for Neimann-Pick disease and other lysosomal storage disorders	Juan Marugan; Samarjit Patnaik; Noel Southall; Wei Zheng; Marc Ferrer; Raul Calvo; Patricia Dranchak
SHYH MING YANG			
10,508,106 B2	12/17/2019	Bicyclic BET bromodomain inhibitors and uses thereof	Shyh Ming Yang
10,351,532 B2	7/16/2019	Small molecule inhibitors of lactate dehydrogenase and methods of use thereof	Anton Simeonov; Shyh Ming Yang, Xin Hu, Ganesh Rai Bantukallu
WEI ZHENG			
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10,370,348 B2	8/6/2019	Tocopherol and tocopheryl quinone derivatives as correctors of lysosomal storage disorders	Juan Marugan; Wei Zheng
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WENWEI HUANG			
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10,555,942 B2	2/11/2020	Emetine compounds for treatment and prevention of flavivirus infection	Wei Zheng, Miao Xu, Ruili Huang, Wenwei Huang, Khalida Shamim, Hao Li
XIN XU			
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XIULI HUANG			
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