

SCIENTIFIC RESEARCH & INTELLECTUAL PROPERTY: TALES FROM THE BENCH

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IL EST QUAND MEME QUI?

1. US Patent Appl. No. 13/420,479 of March 14/2012 - **Methods and Compositions for Preparing Noribogaine from Voacangine**. Robert M. Moriarty & Simon Mbua Ngale Efange.
2. US patent No. 6,846,817B2 (25/01/2005) – **Nicotine Receptor Ligands**; Inventor: Simon Mbua Ngale Efange.
3. US Patent No. 5,948,807 (07/09/1999) – **Spiroindanamines and Spiroindanamides**; Inventors: Simon Mbua Ngale Efange & Deborah C. Mash.
4. US Patent No. 5,929,087 (27/07/1999) - **Decahydroquinoline-based anti-cholinergic agents**; Inventors: Simon Efange and Stanley Parsons.
5. US Patent No. 5,876,694 (02/03/1999)– **Azavesamicols**; Inventors: Simon Mbua Ngale Efange & Stanley M. Parsons.

LIST OF PATENTS-2

6. US Patent No. 5,789,420 (04/08/1998) – *Azavesamicols*. Simon Mbua Ngale Efange & Stanley M. Parsons
7. US Patent No. 5,721,243 (24/02/1998) – *Radiopharmaceutical Agents for the Detection of Alzheimer's Disease*. Simon Mbua Ngale Efange & Stanley M. Parsons
8. US Patent No. 5,616,575 (01/04/1997) – *Bioactive Tricyclic Analogs*. Simon Mbua Ngale Efange and Deborah C. Mash.
9. US Patent No. 5,554,752 (10/09/1996) – *Spirovesamicols*. Simon Efange and Stanley Parsons
10. US Patent No. 5,457,207 (10/10/1995) – *Spirovesamicols*. Simon Mbua Ngale Efange & Stanley M. Parsons.

LIST OF PATENTS-3

11. US Patent No. 5,358,712 (10/25/94) – *Radiopharmaceutical Agents for the Detection of Alzheimer's Disease; Inventors*: Simon Mbua Ngale Efange & Stanley M. Parsons.
12. US Patent No. 5,338,852 (16/08/1994) – *Azavesamicols*; *Inventors*: Simon Mbua Ngale Efange & Stanley M. Parsons.
13. US Patent No. 4,895,937 (01/23/90) – *5-Iodo-2-pyrimidinone nucleoside*; *Inventors*: Thomas J. Bardos, Yung-Chi Cheng, Alan C. Schroeder & Simon Mbua Ngale Efange.
14. US Patent No. 4,782,142 (11/01/88) - *Novel 5-substituted 2-pyrimidinone nucleosides and methods of use; Inventors*: Thomas J. Bardos, Yung-Chi Cheng, Alan C. Schroeder & Simon Mbua Ngale Efange.

WHO ARE WE?

The University

- Teaching
- Research
- Outreach

WHAT IS OUR BUSINESS?

KNOWLEDGE

- Dissemination of knowledge
- Generation of new knowledge (Research)

WHAT IS RESEARCH?

“...any gathering of data, information and facts for the advancement of knowledge.”

“...performing a *methodical study* in order to *prove a hypothesis or answer a specific question.*”

WHAT ARE THE OUTCOMES OF RESEARCH?

- New molecules, designs, devices
- New methods
- New software
- New data

WHERE ARE WE IN THE LARGER PICTURE?

GLOBAL INNOVATION INDEX -2018 (WIPO)

- | | |
|-------------------|------------------|
| 1. Switzerland | 57. India |
| 2. Netherlands | 58. South Africa |
| 3. Sweden | 111. Cameroon |
| 4. United Kingdom | 118. Nigeria |
| 5. Singapore | |
| 6. U.S.A | |

WHERE ARE WE IN THE LARGER PICTURE? (THE MEANS)

UNIVERSITY OF MINNESOTA 2018 OPERATING BUDGET

\$3.8 billion (approx. 2,181.2 billion FCFA);

Research \$302.9 million (173.86 billion FCFA)

REPUBLIC OF CAMEROON - 2019 STATE BUDGET

Amt: 4,850.5 billion FCFA

MINESUP 2019 BUDGET – 55.95 billion FCFA

MINRESI 2019 BUDGET – 11.92 billion FCFA

WHAT MUST WE DO TO MAKE A DIFFERENCE?

- CREATE AND INNOVATE
- RE-THINK OUR APPROACH TO RESEARCH

(tunnel vision; 1-dimensional)

“Trop de chercheurs, pas de trouveurs.”

MESSAGE

Your ideas may be worth more than the paper they are written on, but you must be prepared to *work harder*.

HOW MAY WE BENEFIT FROM OUR IDEAS & INNOVATIONS?

INTELLECTUAL PROPERTY (IP)

A category of property that includes intangible creations of the human intellect.

HOW IS IP PROTECTED?

IP RIGHTS

Rights that are had by a person or by a company to have exclusive **rights** to use its own plans, ideas, or other intangible assets without the worry of competition, at least for a specific period of time.

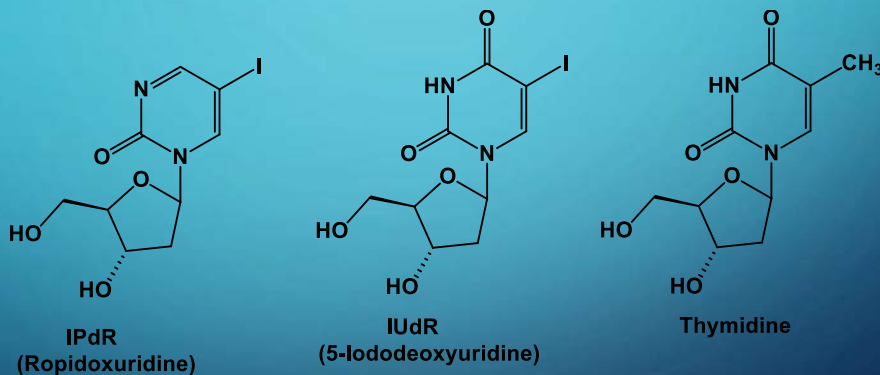
HOW IS IP CLASSIFIED?

- **Trade Secrets**
- **Trademarks.**
- **Copyrights**
- **Patents**

HOW DO WE PROCEED TO ACQUIRE IP? *CREATE! INNOVATE!*

- **CONCEPTUALIZATION**
- **DISCLOSURE** (*Publish or Protect?*)
- **PATENT APPLICATION** (*Costs and other considerations*)
- **COMMERCIALIZATION** (*Search for sponsors, licensees, ownership, benefits sharing etc.*)
- **PATENT MAINTENANCE**

THE CASE OF ROPIDOXURIDINE



The Case of IPdR (*Ropidoxuridine*)

- Synthesized 1982/83 (Efange et al., J. Med. Chem. 28:904-910, 1985)
- Anti-herpes activity confirmed in 1983
- Scale-up work in 1984
- GD Searle
- Monsanto
- Hana Biosciences
- Shuttle Pharmaceuticals Inc.

ROPIDOXURIDINE



US4895937.pdf



United States Patent [19] **Patent Number:** 4,895,937
Bardos et al. [45] **Date of Patent:** Jan. 23, 1990

[54] 5-ISO-2-PYRIMIDINONE NUCLEOSIDE

[75] Inventors: Thomas J. Bardos, Snyder, N.Y.;
 Tung-Chi Cheng, Chapel Hill, N.C.;
 Alan C. Schroeder, Silver Springs,
 Md.; Simon M. N. Efanje, Plymouth,
 Minn.

[73] Assignee: The Research Foundation of State
 University of New York, Albany,
 N.Y.

[21] Appl. No.: 263,183

[22] Filed: Oct. 27, 1988

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 641,770, Aug. 20,
 1984, Pat. No. 4,782,142, which is a continuation-in-
 part of Ser. No. 337,297, Jan. 5, 1982, Pat. No.
 4,468,384.

[51] Int. Cl.⁴ C07H 19/067

[52] U.S. Cl. 536/23

[58] Field of Search 536/23; 514/49

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Primary Examiner—Blondel Hazel
Attorney, Agent, or Firm—Howard M. Ellis, Michael L.
 Dunn

ABSTRACT

[57] The nucleoside 1-(2-Deoxy-β-D-ribofuranosyl)-5-
 (iodo)-2-pyrimidinone possesses a high level of antiviral
 activity and a low level of toxicity to the host cell mak-
 ing it an especially effective therapeutic agent for HSV-2.

1 Claim, No Drawings

ROPIDOXURIDINE



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<https://www.shuttlepharma.com>



Shuttle Pharmaceuticals Holdings, Inc.

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Investors



To improve the safety, efficacy and quality of life of cancer patients
 undergoing radiation therapy.

About Us

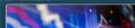
Shuttle Pharmaceuticals Holdings, Inc., through our subsidiary, Shuttle
 Pharmaceuticals, Inc. is developing first-in-class therapies to improve
 the outcomes of patients receiving radiation therapy for the treatment of
 cancers. The focus is on products with unique properties to sensitize
 cancer cells, protect normal tissues and monitor clinical responses to
 treatment.

Our Focus

We have built a platform technology to advance the discovery and
 development of novel small molecules to modify the effects of ionizing
 radiations on cancer cells and normal tissues. To accomplish this goal,
 we have developed strategic collaborations to leverage programs that
 include drug discovery, preclinical studies of radiation sensitizers,
 protectors and epigenetic therapeutics. A phase I clinical trial of a
 radiation sensitizer has been initiated.

Market Opportunity

The precision of radiation therapy (RT) delivery has reached
 a technical plateau, limited only by the tolerance of normal
 tissues surrounding tumors. Further improvements will come
 with drugs that modify cellular responses of cancers and
 normal tissues to radiation.



Unmet Need

- A non-cytotoxic radiation sensitizer for use in cancer treatment:
 - 80 percent of cancer patients undergo radiation therapy (RT)
 - > 1 million patients are treated annually in the U.S.
 - Annual estimated radiation oncology market is > \$4 billion dollars
 - Cancers treated with RT include prostate, lung, breast, brain

ROPIDOXURIDINE

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https://www.shuttlepharma.com

Shuttle Pharmaceuticals Holdings, Inc.

Home Company Technology Investors

Technology

OUR PRODUCTS

The Company's founding objective is to develop and commercialize cancer radiation sensitizing drugs and normal tissue radiation protectors for use in clinical radiation therapy. We are advancing two clinical stage drugs in the radiation sensitizer category (ropidoxuridine, a sensitizer of rapidly dividing cancer cells, and doranidazole, a sensitizer of hypoxic cells). We are also advancing pre-clinical stage dual functional ATM-DNA targeting candidate drugs that protect normal cells by activating the ATM gene product and the DNA damage response pathway.

Ropidoxuridine

Ropidoxuridine, our lead clinical product, is an orally available halogenated pyrimidine with strong cancer radiation sensitizing properties. Halogenated pyrimidines are incorporated into DNA by rapidly growing cancer cells and become more sensitive to the effects of radiation therapy. We propose to evaluate this drug in combination with conventionally fractionated radiation therapy. Together with our collaborators at the Lifespan/Rhode Island Hospital, we will evaluate ropidoxuridine in a Phase I clinical trial to determine safety and the maximum tolerated dose in patients with advanced gastrointestinal (GI) cancers. Funding for this Phase I clinical trial has been secured by the award of a "fast track" small business (SBST) contract from the National Institutes of Health (NIH) to Shuttle Pharma, The Cancer Therapy Evaluation Program (CTEP) of the NCI has approved the Phase I clinical protocol and provides drug and clinical data management support to the Rhode Island Hospital. A positive signal from this clinical trial will allow Shuttle to advance to Phase II and if clinical trials, to be conducted through a Clinical Research Organization (CRO).

Upon positive results from the Phase I clinical trial, we plan to perform initial Phase II clinical trials of ropidoxuridine and radiation therapy in patients with brain tumors and soft tissue sarcomas. Ropidoxuridine (RUP) is a prodrug that is converted to the radiation sensitizing agent, RUPP by metabolic processes following oral administration. We believe that the oral delivery of RUPP provides a significant drug delivery advantage for clinical applications with radiation therapy. RUPP is then

Ropidoxuridine

Doranidazole

ATMHDAC

Pipeline

ROPIDOXURIDINE – STILL GOING AFTER ALL THESE YEARS

European Cancer Organization (Dublin, Ireland, November 14, 2018)

"A new drug designed to make radiotherapy more effective in treating cancer has been given to patients while they are receiving radiation and shown to be safe, according to research presented today."

(Wednesday) at the 30th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Dublin, Ireland.

FROM IBOGAINE TO "IBOGANOIDS"

United States Patent [19]
Efange et al.

US005616575A
[11] Patent Number: 5,616,575
[45] Date of Patent: Apr. 1, 1997

[54] BIOACTIVE TRICYCLIC IBOGAINE ANALOGS
[75] Inventors: S. Mhuu N. Efange, Plymouth, Minn.; Deborah C. Mash, North Bay Village, Fla.
[73] Assignees: Regents of the University of Minnesota, Minneapolis, Minn.; University of Miami, Miami, Fla.

[21] Appl. No.: 567,374
[22] Filed: Dec. 4, 1995
[51] Int. Cl.⁶: A61K 31/095
[52] U.S. Cl.: 514/215; 540/586; 514/012
[58] Field of Search: 514/215; 812; 540/586

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Primary Examiner—James H. Reamer
Attorney, Agent, or Firm—Schwegman, Lundberg, Woessner & Kohn, P.A.

ABSTRACT
Ibogaine analogs are provided, which are phenyl-substituted-hexahydroazepino[4,5-b]indoles useful to treat cocaine addiction and the use of other addictive substances.

21 Claims, 3 Drawing Sheets

FROM NICOTINE TO CHROMAPROLINE

(15) United States Patent
Efange

US 6,846,817 B2
(15) Date of Patent: Jan. 25, 2005

(54) NICOTINE RECEPTOR LIGANDS
(75) Inventors: S. Mhuu N. Efange, Plymouth, MN (US)
(73) Assignees: Regents of the University of Minnesota, Minneapolis, MN (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.: 08/997,718
(22) Filed: Nov. 30, 2001
(30) Prior Publication Data
US 2003/007560 A1 Feb. 6, 2003

Related U.S. Application Data
(43) Continuation of application No. PCT/US00/11508, filed on Jan. 2, 2000.
(40) Provisional application No. 60/137,099, filed on Jan. 2, 2000.

(51) Int. Cl.⁷: C07D 405/04; A61K 31/353; A61K 31/025; A61P 25/34
(52) U.S. Cl.: 514/215; 514/254; 514/307; 514/326; 514/337; 514/342; 540/586; 540/591; 540/593; 540/594; 540/595; 540/596; 540/597; 540/598; 540/599; 540/600; 540/601; 540/602; 540/603; 540/604; 540/605; 540/606; 540/607; 540/608; 540/609; 540/610; 540/611; 540/612; 540/613; 540/614; 540/615; 540/616; 540/617; 540/618; 540/619; 540/620; 540/621; 540/622; 540/623; 540/624; 540/625; 540/626; 540/627; 540/628; 540/629; 540/630; 540/631; 540/632; 540/633; 540/634; 540/635; 540/636; 540/637; 540/638; 540/639; 540/640; 540/641; 540/642; 540/643; 540/644; 540/645; 540/646; 540/647; 540/648; 540/649; 540/650; 540/651; 540/652; 540/653; 540/654; 540/655; 540/656; 540/657; 540/658; 540/659; 540/660; 540/661; 540/662; 540/663; 540/664; 540/665; 540/666; 540/667; 540/668; 540/669; 540/670; 540/671; 540/672; 540/673; 540/674; 540/675; 540/676; 540/677; 540/678; 540/679; 540/680; 540/681; 540/682; 540/683; 540/684; 540/685; 540/686; 540/687; 540/688; 540/689; 540/690; 540/691; 540/692; 540/693; 540/694; 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March 08, 2019

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To: Simon Mbusa Ngale Efangé
c/o University of Bura
P. O. Box 63
Bura, SW Region
CAMEROON

RE: UNITED STATES provisional patent application nr. 62/815,660
Receipt Date: March 08, 2019 - official Filing Date: Not yet determined
For: Dihydro-spiro[indoline-3:1'-isoquinoline]-2-ones and their analogues and derivatives
Applicants/Inventors: Simon Mbusa Ngale Efangé & Lobe Maloba Mesembe Mabanyi
Our Reference: E23-001PROV


Dear Dr. Efangé:

We are pleased to report that we have filed today the above-referenced patent application in the United States Patent and Trademark Office. We are enclosing herewith a copy of the application as filed. The application has been assigned Application Number **62/815,660** and Receipt Date March 08, 2019. We will forward to you a copy of an official Filing Receipt when we receive one.

Please note that we have one year from the official Filing Date of this application in which to file a PCT or US non-provisional application which claims priority from the present application. This deadline is projected to be **March 08, 2020**. Kindly inform us approximately 2-3 months in advance of the deadline as to whether or not you wish to have us file such an additional application.

If you have any question, please do not hesitate to contact us.

With kind regards,

Very truly yours,

Henry D. Coleman

HDC:h
Enclosure

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Patent Electronic Filing Page 1 of 2

Acknowledgement Receipt
The USPTO has received your submission at **15:34:06** Eastern Time on **08-MAR-2019**.

\$ 140 fee paid by e-File via **RAM** with Confirmation Number: 031119NTEFSPW00002119040838.

Filed Application Information

EFS ID	35368675
Application Number	62815660
Confirmation Number	6539
Title	DIHYDRO-SPIRO [INDOLINE-3:1'- ISOQUINOLINE]-2-ONES AND THEIR ANALOGUES AND DERIVATIVES
First Named Inventor	SIMON MBUSA NGALE EFANGÉ
Customer Number or Correspondence Address	28156
Filed By	Henry D. Coleman/Harold Hull
Attorney Docket Number	E23-001PROV
Filing Date	
Receipt Date	08-MAR-2019
Application Type	Provisional

Application Details

Sequence	Submitted Files	Page Count	Document Description	File Size	Warnings
1	E23-001PROV-- PROV-CS.pdf	3	Provisional Cover Sheet (5816)	2032309 bytes	◆ PASS
No validation errors found.					
2	E23-001PROV-- ADS.pdf	8	Application Data Sheet	1255902 bytes	◆ PASS
No validation errors found.					
3	E23-001Prov-- SPEC--Part1.pdf	40	Specification	14386575 bytes	◆ PASS
No validation errors found.					
4	E23-001Prov-- SPEC--Part2.pdf	34		11373396 bytes	◆ PASS
No validation errors found.					
	Document Description		Page Start	Page End	
	Specification		1	15	
	Claims		16	33	
	Abstract		34	34	
5	E23-001Prov-- FIGURES.pdf	5	Drawings-only black and white line drawings	641521 bytes	◆ PASS

<https://efw-my.uspto.gov/EFWebUI/Registered/EFSAckReceipt?receipt-y&transID=201903...> 3/8/2019

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- Yes, we can, but we must re-shape our attitude to research and innovation.
- We must be prepared to work even harder. Otherwise, we shall be condemned to live with *“....trop de chercheurs, pas de trouveurs”*.

PARTING MESSAGE

Your ideas may be worth more than the paper they are written on,
but you must be prepared to work harder.

ACKNOWLEDGEMENTS

- Thomas J. Bardos (deceased), formerly Professor of Medicinal Chemistry & Biochemical Pharmacology, SUNY Buffalo.
- Hank F. Kung (emeritus), Professor of Radiology & Pharmacology, University of Pennsylvania.
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- US SBIR (NovoNeuron)
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- MINESUP/Research Modernization Scheme