

ANDREAS J. KESEL

**THE POTENTIAL
HEALING OF
CANCER WITH P53
(RE)ACTIVATORS**

**TWO NEW DRUGS
EXPLOITING CANCER'S
WARBURG EFFECT**



tredition

© 2023 Andreas Johannes Kesel

ISBN Softcover: 978-3-384-00311-9

ISBN Hardcover: 978-3-384-00312-6

Druck und Distribution im Auftrag des Autors:
tredition GmbH, Heinz-Beusen-Stieg 5, 22926 Ahrensburg,
Germany

Das Werk, einschließlich seiner Teile, ist urheberrechtlich geschützt. Für die Inhalte ist der Autor verantwortlich. Jede Verwertung ist ohne Zustimmung des Autors unzulässig. Die Publikation und Verbreitung erfolgen im Auftrag des Autors, zu erreichen unter: tredition GmbH, Abteilung "Impressumservice", Heinz-Beusen-Stieg 5, 22926 Ahrensburg, Deutschland.

TABLE OF CONTENTS

TABLE OF CONTENTS	I
BIOGRAPHY OF THE AUTHOR	X
PUBLICATIONS OF THE AUTHOR	XII
PATENTS OF THE AUTHOR	XVI
ACKNOWLEDGEMENTS	XXIII
DEDICATION	XXV
PREFACE AND ABSTRACT	XXVI
INTRODUCTION	XXX
 CHAPTER ONE	
THE DRUG PT162 (NSC 796018)	1

1. PT162 (NSC 796018)	1
1.1. The synthesis of salt-containing PT162 (PENTA)	1
1.2. The synthesis of pure PT162 (NSC 796018)	2
1.3. Structure elucidation of PT162	2
2. References	15

CHAPTER TWO

THE DRUG PT166 (NSC 750423)	17
1. PT166 (NSC 750423)	17
1.1. The synthesis of drug PT166 (NSC 750423)	17
1.2. The nuclear magnetic resonance spectra of PT166	19

1.3. The X-ray crystallographic crystal and molecular structure determination of compound 2 (PT166)_____	26
--	----

2. References _____	33
----------------------------	----

CHAPTER THREE

THE DRUG PT167 (NSC 799315) _____	38
--	----

1. PT167 (NSC 799315) _____	38
------------------------------------	----

1.1. The synthesis of drug PT167 (NSC 799315) ____	40
---	----

1.2. The proton nuclear magnetic resonance spectrum (¹ H-NMR) of PT167 (NSC 799315) _____	42
--	----

1.3. The liquid chromatographic (HPLC) investigation of PT167 (NSC 799315) _____	48
---	----

1.4. The electrospray ionization (ESI) mass spectrometric investigation of PT167 (NSC 799315) after HPLC separation_____	52
---	----

2. References	53
----------------------	-----------

CHAPTER FOUR

ANTINEOPLASTIC ACTIVITIES OF PT162, PT166 AND PT167	55
--	-----------

1. NCI 60 Cell Five-Dose Screen with the Drugs PT162, PT166 and PT167	55
--	-----------

1.1. National Cancer Institute (NCI) Developmental Therapeutics Program (DTP) 60-cancer cell 5-dose testing	55
--	-----------

1.2. Overall NCI 60 cell five-dose screen results with the drugs PT162, PT166 and PT167	57
--	-----------

2. National Cancer Institute (NCI) Developmental Therapeutics Program (DTP) 60-Cancer Cell 5- Dose Testing Results with the Drugs PT162, PT166 and PT167	58
---	-----------

2.1. National Cancer Institute (NCI) Developmental Therapeutics Program (DTP) 60-cancer cell 5-dose testing results with compound **1 (PT162, NSC 796018)**_____ 59

2.2. National Cancer Institute (NCI) Developmental Therapeutics Program (DTP) 60-cancer cell 5-dose testing results with compound **2 (PT166, NSC 750423)**_____ 69

2.3. National Cancer Institute (NCI) Developmental Therapeutics Program (DTP) 60-cancer cell 5-dose testing results with compound **3 (PT167, NSC 799315)**_____ 74

3. Cytochrome *c* Assay (Mitochondrial and Cytosolic) with the Drugs PT162, PT166 and PT167 in the Human Prostate Cancer Cell Lines PC-3 and DU-145_____ 79

4. HIV-1_{LAI} Replication Reverse Transcriptase Assay with the Drug PT162 in Primary PBL Cells 81

5. References	82
----------------------	----

APPENDIX

MATERIALS AND METHODS, CHEMICAL SYNTHESIS, EXPERIMENTAL INSTRUCTIONS AND SUPPLEMENTARY DATA	85
--	----

1. Materials and Methods	85
---------------------------------	----

1.1. Materials	85
----------------	----

1.2. Methods	86
--------------	----

1.3. Software	88
---------------	----

2. Chemical Synthesis	88
------------------------------	----

2.1. Salt-containing tetrakis{3-[(tricyclo[3.3.1.1 ^{3,7}]decan-1-ammonio)methyl]benzyl}ammonium pentachloride (compound 1 × 1.5 NaCl, PT162 × 1.5 NaCl)	88
---	----

2.2. Pure (salt-free) tetrakis{3-[(tricyclo[3.3.1.1^{3,7}]decan-1-ammonio)methyl]benzyl}ammonium pentachloride (**PT162, NSC 796018**)_____ 90

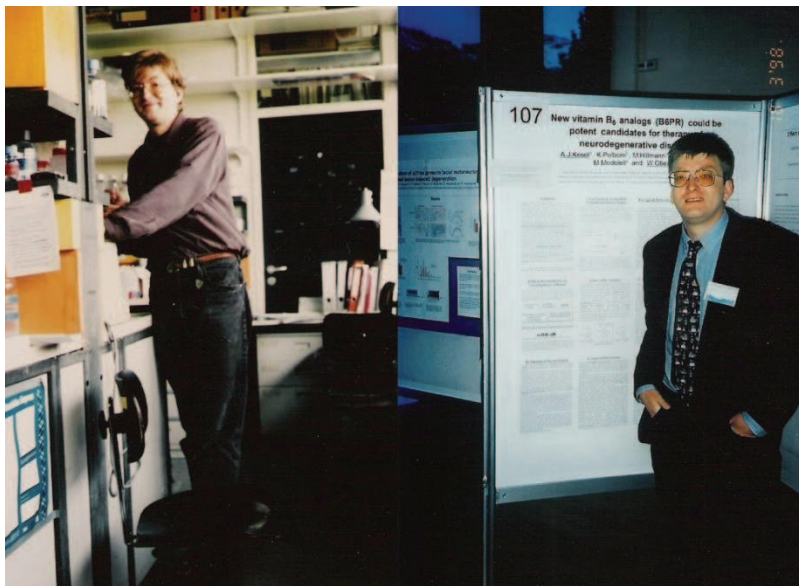
2.3. (*M*)-10-(2-Carbamothioylhydrazinyl)-10-demethoxycolchicine monohydrate $\times \frac{2}{3}$ (ethyl acetate) = *N*-[(a*S*,7*S*)-10-(2-carbamothioylhydrazinyl)-1,2,3-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-7-yl]acetamide monohydrate $\times \frac{2}{3}$ (ethyl acetate) (**PT166, NSC 750423**)_____ 92

2.4. [(Bis{3-[(tricyclo[3.3.1.1^{3,7}]decan-1-ylamino)methyl]benzyl}ammonio)bis(methanediylbenzene-3,1-diylmethanediyl)]di-2-[(a*S*,7*S*)-7-(acetylamino)-1,2,3-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[*a*]heptalen-10-yl]-*N*-(tricyclo[3.3.1.1^{3,7}]decan-1-yl)hydrazinecarbothioamide chloride pentahydrate (**PT167, NSC 799315**)_____ 95

3. X-Ray Crystallographic Determination of the Crystal and Molecular Structure of (<i>M</i>)-10-(2-Carbamothioylhydrazinyl)-10-demethoxy-colchicine Sesquihydrate $\times \frac{1}{2}$ (Ethyl Acetate) = <i>N</i>-[(<i>aS</i>,7<i>S</i>)-10-(2-Carbamothioylhydrazinyl)-1,2,3-trimethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[<i>a</i>]heptalen-7-yl]acetamide Sesquihydrate $\times \frac{1}{2}$ (Ethyl Acetate) (Crystalline PT166)	97
3.1. Crystallization of PT166 single crystals	97
3.2. Crystal data of PT166 single crystals	97
3.3. Crystallographic information file (cif-file) of PT166	97
3.4. Deposition of the X-ray crystallographic structure determination of PT166	122
4. Experimental Instructions	122

4.1. Cytotoxicity and HIV-1 _{LAI} replication reverse transcriptase assays with PT162	122
4.2. Cytochrome <i>c</i> assay (mitochondrial and cytosolic)	123
4.3. National Cancer Institute (NCI) Developmental Therapeutics Program (DTP) 60-cancer cell 5-dose testing	124
5. Supplementary Data	126
5.1. Table of contents	126
5.2. Supplementary References	143

BIOGRAPHY OF THE AUTHOR



1990 ABITUR. 1991–1993 CHEMISTRY SCHOOL DR. ERWIN ELHARDT, STUDY OF CHEMICAL-TECHNICAL ASSISTANT (CTA). 1993 PRACTICAL TRAINING, MAX-PLANCK-INSTITUTE FOR BIOCHEMISTRY, MARTINSRIED, GERMANY, DEPARTMENT OF PROTEIN CHEMISTRY OF DR. FRIEDRICH LOTTSPEICH, IN THE FORMER LABORATORY OF DR. PEHR VICTOR EDMAN (ADVISOR: KERSTIN ANDERSSON, GENERAL TRAINING IN PROTEIN CHEMISTRY, ELECTROPHORESIS, AND PROTEIN SEQUENCING BY THE *EDMAN* METHOD). 1993 PRACTICAL TRAINING, MAX-PLANCK-INSTITUTE FOR NEUROBIOLOGY, MARTINSRIED, GERMANY, DEPARTMENT OF NEUROIMMUNOLOGY OF PROF. DR. DR. H.C. HARTMUT WEKERLE (ADVISOR: DR. ANTONIO IGLESIAS, TRAINING IN MOLECULAR BIOLOGY AND DNA SEQUENCING). 1993–1995 WORK AS CHEMICAL-TECHNICAL ASSISTANT AT MAX-PLANCK-INSTITUTE FOR BIOCHEMISTRY IN THE DEPARTMENT

OF VIRUS RESEARCH OF PROF. DR. DR. DR. H.C. PETER HANS HOFSCHEIDER, WITH SPECIAL TRAINING IN THE MOLECULAR BIOLOGY OF HUMAN HEPATITIS B VIRUS. 1995–2000 STUDY OF PHARMACY AT LUDWIG-MAXIMILIANS-UNIVERSITY, MUNICH, GERMANY. 2004–2005 STUDY OF PHARMACY AT JULIUS-MAXIMILIANS UNIVERSITY OF WÜRZBURG, GERMANY. 2006–2011 DOCTORAL STUDY AT JULIUS-MAXIMILIANS UNIVERSITY OF WÜRZBURG, GERMANY, IN THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY OF PROF. DR. ULRIKE HOLZGRABE. 2011–2015 PUBLICATION WORK AS PRIVATE RESEARCHER IN MUNICH, GERMANY. 2015–2017 WORK AS CHIEF MEDICINAL CHEMIST FOR POP TEST ONCOLOGY LLC OF RANDICE LISA ALTSCHUL, CLIFFSIDE PARK, NJ, USA. 1998 ELECTION AS AN EXTERNAL MEMBER OF THE NEW YORK ACADEMY OF SCIENCES, NEW YORK, USA. 2005 MEMBER OF THE AMERICAN CHEMICAL SOCIETY, DIVISION OF MEDICINAL CHEMISTRY. 18 PUBLICATIONS AND/OR CONGRESS ABSTRACTS IN PEER-REVIEWED JOURNALS. 2 BOOKS PUBLISHED. 31 CO-AUTHORED PATENTS.

PUBLICATIONS OF THE AUTHOR

- [1] Eberhard Hildt, Stephan Urban, Andreas Kesel, Peter Hans Hofschneider. *Functional characterization of baculovirus-derived MHBs^t*, Molecular Biology of Hepatitis B Viruses, October 3–6 **1994**, Institut Pasteur, Paris, France (Chair: Marie Annick Buendia, Alan McLachlan).
- [2] Stephan Urban, Eberhard Hildt, Christoph Eckerskorn, Andreas Kesel, Peter Hans Hofschneider. *Mass Spectrometric Analysis of Baculovirus-Derived HBX*, Molecular Biology of Hepatitis B Viruses, October 3–6 **1994**, Institut Pasteur, Paris, France (Chair: Marie Annick Buendia, Alan McLachlan).
- [3] Andreas J. Kesel, Stephan Urban, Walter Oberthür. *Interconvertible (Z/E)-Stereoisomers of a Vitamin B₆ Coenzyme Analog Derived from Pyridoxal 5'-Phosphate and Rhodanine*, Tetrahedron **1996**, 52, 14787–14800.
- [4] Andreas J. Kesel, Isolde Sonnenbichler, Kurt Polborn, Lutz Gürtler, Wolfgang E. F. Klinkert, Manuel Modolell, Andreas K. Nüssler, Walter Oberthür. *A New Antioxidative Vitamin B₆ Analogue Modulates Pathophysiological Cell Proliferation and Damage*, Bioorg. Med. Chem. **1999**, 7, 359–367.

- [5] Andreas J. Kesel. *A System of Protein Target Sequences for Anti-RNA-viral Chemotherapy by a Vitamin B₆-Derived Zinc-Chelating Trioxa-adamantane-triol*, Bioorg. Med. Chem. **2003**, 11, 4599–4613.
- [6] Andreas J. Kesel. *Synthesis of retinoid vitamin A–vitamin B₆ conjugate analogues for antiviral chemotherapy*, Biochem. Biophys. Res. Commun. **2003**, 300, 793–799.
- [7] Julian A. Tanner, Bo-Jian Zheng, Jie Zhou, Rory M. Watt, Jie-Qing Jiang, Kin-Ling Wong, Yong-Ping Lin, Lin-Yu Lu, Ming-Liang He, Hsiang-Fu Kung, Andreas J. Kesel, Jian-Dong Huang. *The Adamantane-Derived Bananins Are Potent Inhibitors of the Helicase Activities and Replication of SARS Coronavirus*, Chem. Biol. (Cell Chem. Biol.) **2005**, 12, 303–311.
- [8] Andreas J. Kesel. *Synthesis of Novel Test Compounds for Antiviral Chemotherapy of Severe Acute Respiratory Syndrome (SARS)*, Curr. Med. Chem. **2005**, 12, 2095–2162.
- [9] Andreas J. Kesel. *The Bananins: New Anticorona-RNA-Viral Agents with Unique Structural Signature*, Anti-Infective Agents Med. Chem. **2006**, 5, 161–174.

- [10] Andreas J. Kesel. *Broad-spectrum antiviral activity including human immunodeficiency and hepatitis C viruses mediated by a novel retinoid thiosemicarbazone derivative*, Eur. J. Med. Chem. **2011**, 46, 1656–1664.
- [11] Andreas J. Kesel. *An Update on the Bananins: Anti-RNA-Viral Agents with Unique Structural Signature*, Anti-Infective Agents **2013**, 11, 1–21.
- [12] Andreas J. Kesel, Hans-Christoph Weiss, Andreas Schönleber, Craig W. Day, Dale L. Barnard, Mervi A. Detorio, Raymond F. Schinazi. *Antiviral agents derived from novel 1-adamantyl singlet nitrenes*, Antivir. Chem. Chemother. **2013**, 23, 113–128.
- [13] Andreas J. Kesel, Zhuhui Huang, Michael G. Murray, Mark N. Prichard, Laura Caboni, Daniel K. Nevin, Darren Fayne, David G. Lloyd, Mervi A. Detorio, Raymond F. Schinazi. *Retinazone inhibits certain blood-borne human viruses including Ebola virus Zaire*, Antivir. Chem. Chemother. **2014**, 23, 197–215.
- [14] Andreas Schönleber, Sander van Smaalen, Hans-Christoph Weiss, Andreas J. Kesel. *N—H...O and C—H...F hydrogen bonds in the incommensurately modulated crystal structure of adamantan-1-ammonium*

- 4-fluorobenzoate*, Acta Crystallogr. B Struct. Sci. Cryst. Eng. Mater. **2014**, 70, 652–659.
- [15] Francesco Saettini, Matteo F. Olivieri, Andreas J. Kesel, Laura Bonalume, Francesca Marzari. *Dermatology in ancient Greece: The myth of Melampus and the use of Helleborus*, Vth Congresso Nazionale SiDerP (Società Italiana di Dermatologia Pediatrica – Italian Society of Pediatric Dermatology), April 16–18 **2015**, Florio Park Hotel, Palermo, Italy.
- [16] Andreas J. Kesel, Craig W. Day, Catherine M. Montero, Raymond F. Schinazi. *A new oxygen modification cyclooctaoxygen binds to nucleic acids as sodium crown complex*, Biochim. Biophys. Acta **2016**, 1860, 785–794.
- [17] Matteo F. Olivieri, Francesca Marzari, Andreas J. Kesel, Laura Bonalume, Francesco Saettini. *Pharmacology and psychiatry at the origins of Greek medicine: The myth of Melampus and the madness of the Proetides*, J. Hist. Neurosci. **2017**, 26, 193–215.
- [18] Andreas J. Kesel. *The Spermine Phosphate-Bound Cyclooctaoxygen Sodium Epigenetic Shell of Euchromatin DNA Is Destroyed by the Epigenetic Poison Glyphosate*, Preprints **2017**, 2017010086, <https://doi.org/10.20944/preprints201701.0086.v4>.

- [19] Andreas J. Kesel. *The Spermine Phosphate-Bound Cyclooctaoxygen Sodium Epigenetic Shell of Euchromatin DNA Is Destroyed by the Epigenetic Poison Glyphosate*, Arch. Clin. Biomed. Res. **2023**, 7, 171–190, <https://doi.org/10.26502/acbr.50170331>.
- [20] Andreas J. Kesel. *The Epigenetic Protection Shell of Euchromatin DNA. Selenium Content — Detoriation by Glyphosate*, 1st ed., tredition GmbH, Ahrensburg, Germany, 2023, ISBN 978-3347944442.

PATENTS OF THE AUTHOR

- [1] Andreas J. Kesel, Walter Oberthür. (Z)-5-[[3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridinyl]methylen]-2-thioxo-4-thiazolidinon, Verfahren zu dessen Herstellung und Verwendung. **Ger. Pat.** DE 196 45 974 C1 (1998). Filed 1996/11/07.
- [2] Andreas J. Kesel, Walter Oberthür. Mono-, oligo-, and polymeric Knoevenagel condensation products useful e.g. in pharmaceuticals, cosmetics and assay procedures. **Ger. Pat.** DE 198 19 820 A1 (2000). Filed 1998/05/04.
- [3] Andreas J. Kesel, Walter Oberthür. NEW KNOEVENAGEL CONDENSATION PRODUCTS, METHOD FOR THEIR PRODUCTION AND THEIR