



US007772199B2

(12) United States Patent
Ionescu et al.**(10) Patent No.: US 7,772,199 B2**
(45) Date of Patent: Aug. 10, 2010**(54) FORMS OF 5-AZACYTIDINE****(75) Inventors:** **Dumitru Ionescu**, Ann Arbor, MI (US);
Peter Blumbergs, Royal Oak, MI (US);
Gary L Silvey, Overland Park, KS (US)**(73) Assignee:** **Celgene Corporation**, Summit, NJ (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.:** **11/458,365****(22) Filed:** **Jul. 18, 2006****(65) Prior Publication Data**

US 2006/0247189 A1 Nov. 2, 2006

Related U.S. Application Data**(60)** Continuation of application No. 11/052,615, filed on Feb. 7, 2005, now Pat. No. 7,078,518, which is a division of application No. 10/390,578, filed on Mar. 17, 2003, now Pat. No. 6,887,855.**(51) Int. Cl.****A61K 31/706** (2006.01)**C07H 19/12** (2006.01)**(52) U.S. Cl.** **514/43; 536/28.3****(58) Field of Classification Search** 536/28.3,
536/124, 28.5, 23.1, 24.31, 24.33, 22.1;
514/49, 85, 269; 424/45, 450

See application file for complete search history.

(56) References Cited

U.S. PATENT DOCUMENTS

3,350,388	A	10/1967	Sorm et al.	
3,817,980	A	6/1974	Vorbrüggen et al.	
3,891,623	A	6/1975	Vorbrüggen et al.	
4,082,911	A	4/1978	Vorbrüggen	
4,209,613	A	6/1980	Vorbrüggen	
5,700,640	A *	12/1997	Voss et al.	435/6
6,723,728	B2	4/2004	Hu et al.	
6,753,426	B2	6/2004	Zhang et al.	
6,887,855	B2 *	5/2005	Ionescu et al.	514/43
6,943,249	B2	9/2005	Ionescu et al.	
7,038,038	B2	5/2006	Ionescu et al.	
7,078,518	B2 *	7/2006	Ionescu et al.	536/28.3
7,132,552	B2	11/2006	Dolitzky et al.	
2004/0186284	A1	9/2004	Ionescu et al.	

FOREIGN PATENT DOCUMENTS

CZ	114716	11/1964
CZ	116297	4/1965
DE	1922702	4/1971
DE	2012888	9/1971
FR	2 123 632	9/1972
GB	1 227 692	4/1971
GB	1227691	4/1971

OTHER PUBLICATIONS

Braga et al., "Making crystals from crystals: a green route to crystal

Pharmaceutical Dosage Forms: Tablets, vol. 2, Published by Marcel Dekker, Inc., ed. by Lieberman, Lachman, and Schwartz, pp. 462-472.*

Dean, J., Analytical Chemistry Handbook, Published by McGraw-Hill, Inc., pp. 10.23-10.26.*

Jain et al., "Polymorphism in Pharmacy" Indian Drugs (1986) vol. 23, No. 6, pp. 315-329.*

Kritz et al., "Pilot study of 5-azacytidine (5-AZA) and carboplatin (CBDCA) in patients with relapsed/refractory leukemia" American Journal of Hematology (1996) vol. 51, No. 2, pp. 117-121.*

Cabri et al., "Polymorphisms and Patent, Market, and Legal Battles: Cefdinir Case Study" Organic Process Research and Development (2007) vol. 11, pp. 64-72.*

Niedballa et al. "A General Synthesis of N-Glycosides. V. Synthesis of 5-azacytidine" J. Org. Chem. (1974) vol. 39 No. 25, pp. 3672-3674.*

Beisler et al., "Chemistry of Antitumor Triazine Nucleosides. An improved Synthesis of Dihydro-5-Azacytidine" Journal of Carbohydrates, Nucleosides, and Nucleotides (1977) vol. 4 No. 5, pp. 281-299.*

Pharmaceutical Dosage Forms: Tablets, vol. 2, Published by Marcel Dekker, Inc., (1990) ed. by Lieberman, Lachman, and Schwartz, pp. 462-472.*

Dean, J., Analytical Chemistry Handbook, Published by McGraw-Hill, Inc., (1995) pp. 10.23-10.26.*

Beisler, Journal of Medicinal Chemistry, 21(2):204 (1978).

Niedballa & Vorbrüggen, Journal of Organic Chemistry, 39(25):3672 (1974).

Kornblith et al., J. Clin Oncol. 20: 2441 (2002).

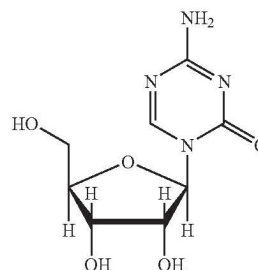
Piskala & Sorm, Collect. Czech. Chem. Commun. 29:2060 (1964).

Piskala & Sorm, Nucleic Acid Chemistry 1: 435 (1978).

(Continued)

Primary Examiner—Eric S Olson*(74) Attorney, Agent, or Firm*—Jones Day**(57) ABSTRACT**

The invention provides novel polymorphic and pseudopolymorphic crystalline forms of 5-azacytidine, along with methods for preparing said forms, wherein 5-azacytidine is represented by the formula:



The invention also includes pharmaceutical compositions comprising said forms.

OTHER PUBLICATIONS

Piskala & Sorm, *Nucleic Acids Research*, Special Publication No. 1: s17 (1975).

Silverman et al., *J. Clin Oncol.* 20: 2429 (2002).

Vorbrüggen et al, *Chem. Ber.* 114: 1234 (1981).

Vorbrüggen & Benna, *Chem Ber.* 114: 1279 (1981).

Vorbrüggen & Ruh-Pohlenz in *Organic Reactions*, vol. 55, p. 100 (L. A. Paquette Ed., John Wiley & Sons, New York, 2000).

Winkley & Robins, *Journal of Organic Chemistry*, 35(2):491-495 (1970).

Wittenburg, *Z. Chem.* 4:303 (1964).

Beisler et al. (1977) "Chemistry of antitumor triazine nucleosides. An improved synthesis of Dihydro-5-AZacytidine" *Journal of Carbohydrates, Nucleosides Nucleotides*, Marcel Dekker, Basel, CH, 4:(5):281-299.

Zaitseva et al. (1995) "Convergent synthesis and cytostatic properties of 2-chloro-2'-deoxy-2'-fluoroadenosine and its N7-isomer." *Bioorganic & Medicinal Chemistry Letters*, 5(24), 2999-3002.

Database HCAPLUS on CAS (Columbus, OH, USA), No. 1995:448387, Zaitseva, et al. "Convergent synthesis and cytostatic

properties of 2-chloro-2'-deoxy-2'-fluoroadenosine and its N7-isomer," abstract, *Bioorganic & Medicinal Chemistry Letters*, 5(24), 2999-3002.

Vogler et al., "5-Azacytidine (NSC 102816): A New Drug for the Treatment of Myeloblastic Leukemia," *Blood*, Sep. 1976, 48(3):331-337.

Opposition Brief dated Sep. 3, 2007 in Chile Application No. 2267-2005 (with English translation).

Hanka, L.J., et al., "Microbiological Production of 5-Azacytidine: I. Production and Biological Activity," *Antimicrobial Agents and Chemotherapy*, 1966, pp. 619-624.

Bergy and Herr, "Microbiological Production of 5-Azacytidine: II. Isolation and Chemical Structure," *Antimicrobial Agents and Chemotherapy*, 1966, pp. 625-630.

Office Action dated Aug. 1, 2007 in U.S. Appl. No. 11/198,550.

Office Action dated May 12, 2008 in U.S. Appl. No. 11/198,550.

Notice of Allowance dated Dec. 2, 2009 in U.S. Appl. No. 11/198,550.

* cited by examiner

Figure 1. X-ray Powder Diffraction Pattern of Azacitidine, Form I, Labeled with the more Prominent 2θ Angles (Cu Kα Radiation)

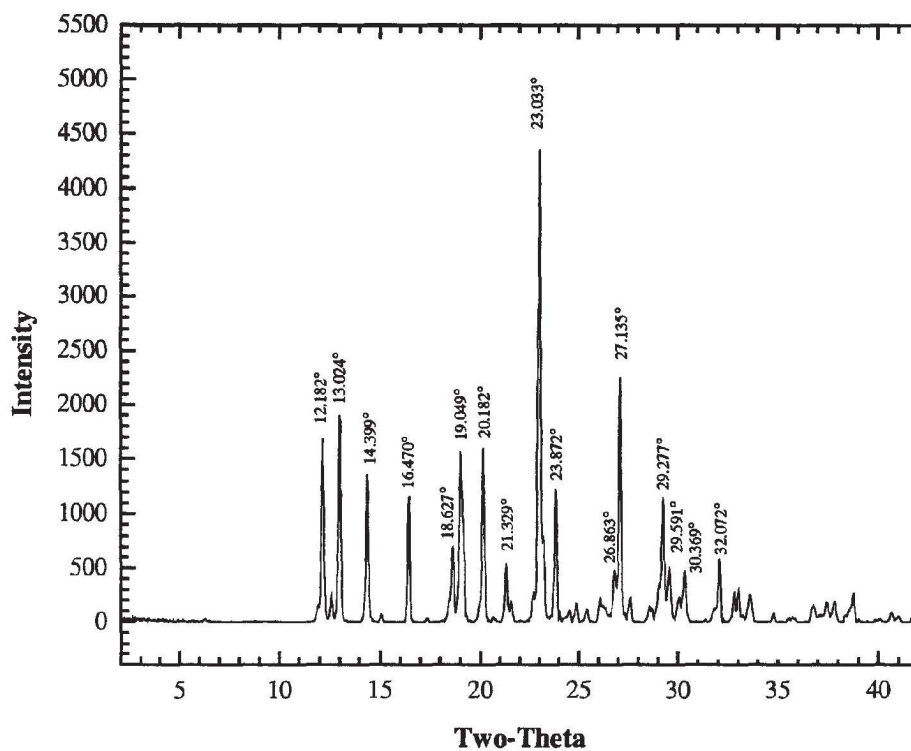


Figure 2 X-ray Powder Diffraction Pattern of Azacitidine, Mixed Phase Forms I and II, Labeled with the more Prominent 2θ Angles (Cu Kα Radiation)

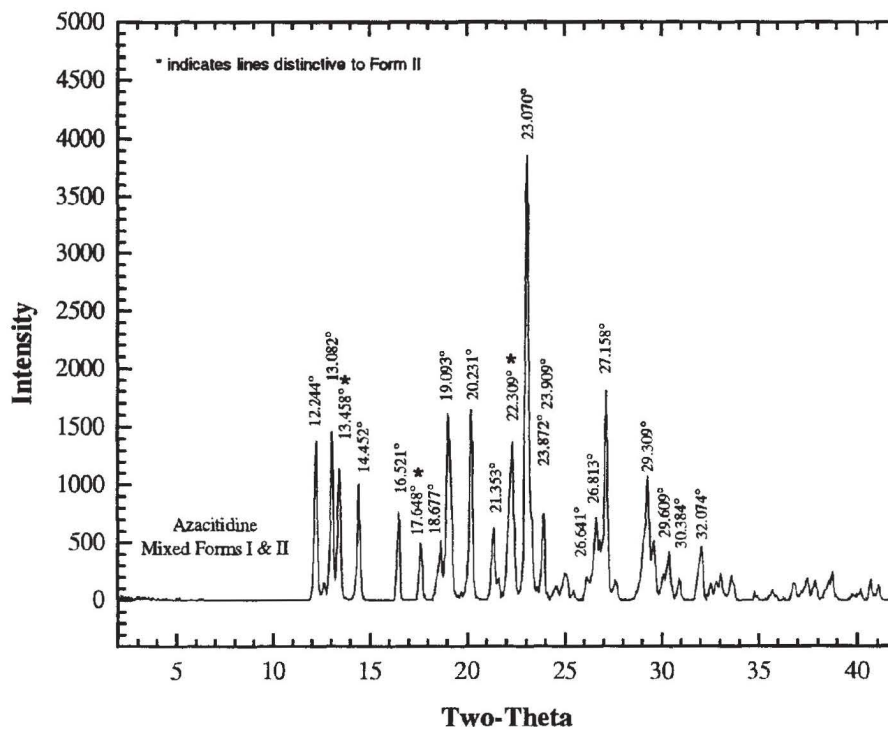
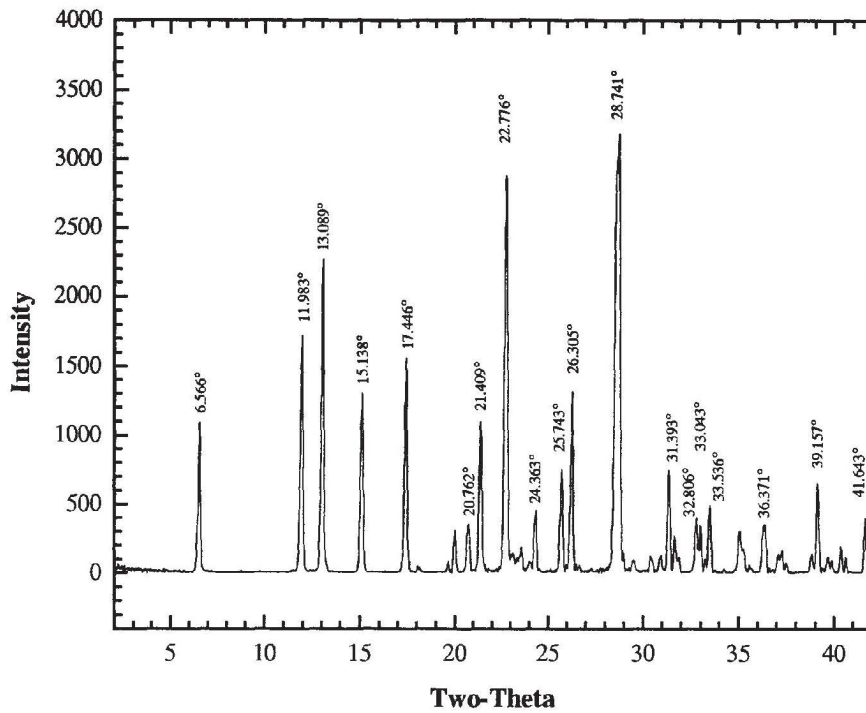


Figure 3 X-ray Powder Diffraction Pattern of Azacitidine, Form III, Labeled with the more Prominent 2θ Angles (Cu Kα Radiation)



Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.