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Ionescu et al.

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(54) **FORMS OF 5-AZACYTIDINE**

DE 2012888 9/1971
GB 1227691 4/1971

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OTHER PUBLICATIONS

Winkley et al. J. Org. Chem., 35 (2), 491-495, 1970.*
Beisler, Journal of Medicinal Chemistry, 21(2):204 (1978).
Niedballa & Vorbrüggen, Journal of Organic Chemistry, 39(25):3672 (1974).

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(Continued)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 45 days.

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(51) **Int. Cl.**⁷ **A61K 31/4436**; C07D 411/04

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514/547; 514/575; 536/23.1; 536/24.5;
536/24.31; 536/24.33; 536/28.1; 536/28.3;
435/6; 424/93.7

(58) **Field of Search** 514/43, 274, 50,
514/547, 575; 536/23.1, 24.5, 24.31, 24.33,
28.1, 28.3; 435/6; 424/93.7

(56) **References Cited**

U.S. PATENT DOCUMENTS

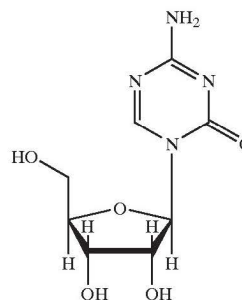
3,350,388 A 10/1967 Sorm et al.
3,817,980 A 6/1974 Vorbrüggen et al.
3,891,623 A 6/1975 Vorbrüggen et al.
4,082,911 A 4/1978 Vorbrüggen
4,209,613 A 6/1980 Vorbrüggen
6,723,728 B2 * 4/2004 Hu et al. 514/274

FOREIGN PATENT DOCUMENTS

DE 1922702 4/1971

(57) **ABSTRACT**

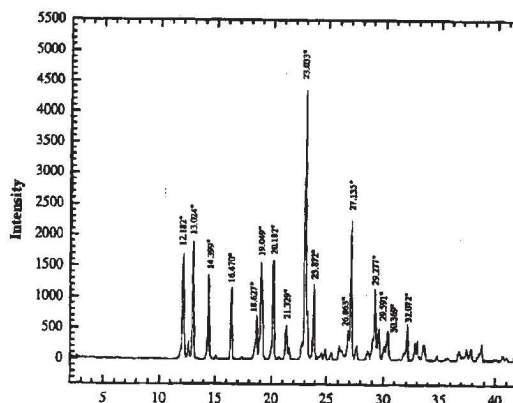
The invention provides novel polymorphic and pseudopolymorphic crystalline forms of 5-azacytidine, along with methods for preparing said forms, wherein 5-azacytidine is represented by the formula:



The invention also includes pharmaceutical compositions comprising said forms.

8 Claims, 8 Drawing Sheets

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



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OTHER PUBLICATIONS

Komblith 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).
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 & Bennua, Chem Ber. 114: 1279 (1981).
Vorbrüggen & Ruh-Pohlenz in Organic Reactions, vol. 55, p100 (L. A. Paquette Ed., John Wiley & Sons, New York, 2000).
Winkley & Robins, Journal of Organic Chemistry, 35(2):491 (1970).
Wittenburg, Z. Chem. 4:303 (1964).

* cited by examiner

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

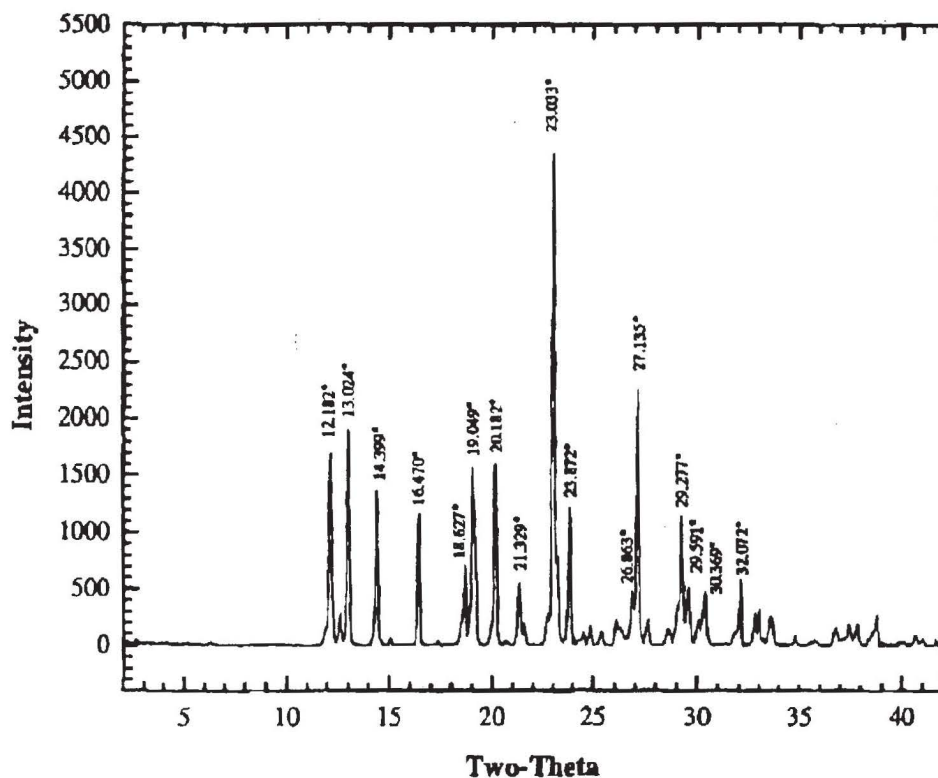


Figure 2 X-ray Powder Diffraction Pattern of Azacitidine, Mixed Phase Forms I and II, Labeled with the more Prominent 2θ Angles (Cu Kα Radiation)

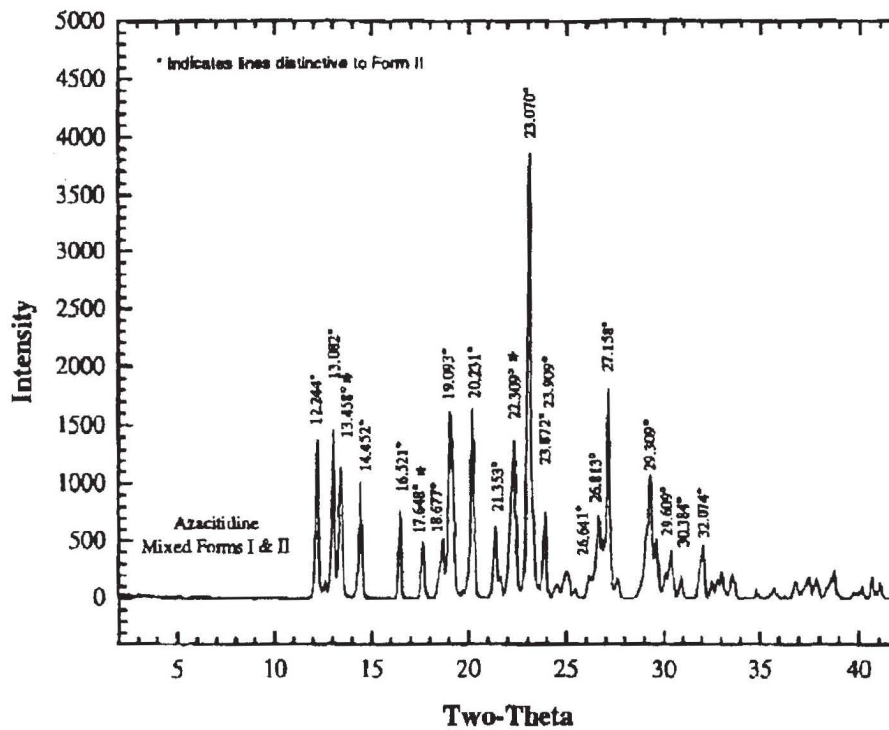
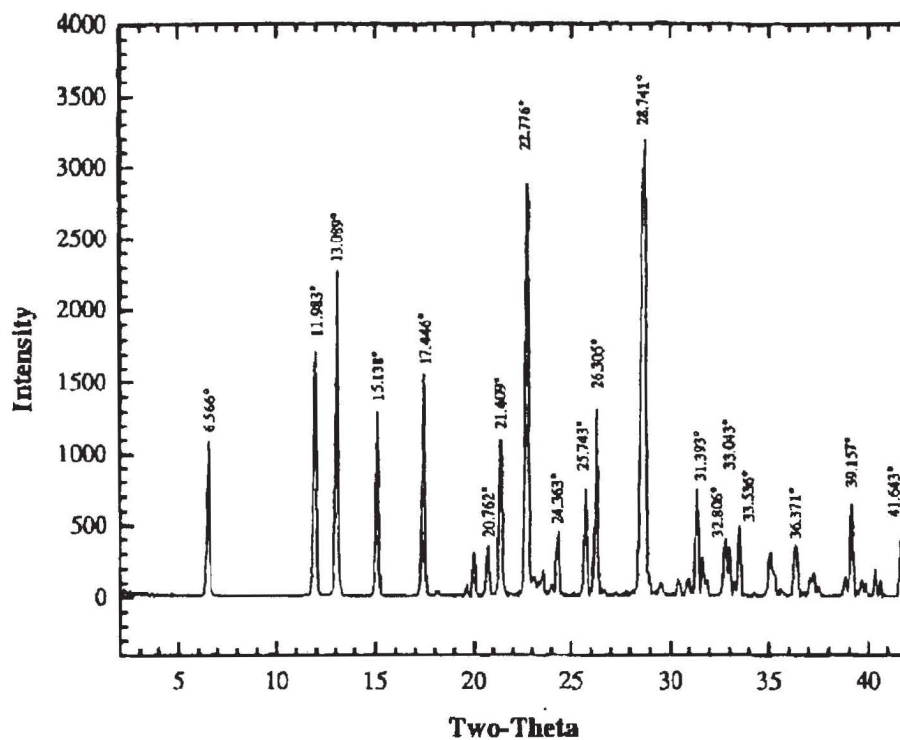


Figure 3 X-ray Powder Diffraction Pattern of Azacitidine, Form III, Labeled with the more Prominent 2 θ Angles (Cu K α Radiation)



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