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Bathe et al.

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(54) **POLYMORPHIC FORMS OF 1-[4-(5-CYANOINDOL-3-YL)BUTYL]-4-(2-CARBAMOYL BENZOFURAN-5-YL) PIPERAZINE HYDROCHLORIDE**

5,977,112	A	11/1999	Bathe et al.
7,381,726	B2	6/2008	Bathe et al.
7,834,020	B2	11/2010	Bathe et al.
7,981,894	B2	7/2011	Bathe et al.
8,193,195	B2	6/2012	Bathe et al.
8,236,804	B2	8/2012	Bathe et al.
8,318,744	B2	11/2012	Bathe et al.
8,673,921	B2	3/2014	Bathe et al.
2011/0183994	A1	7/2011	Bathe et al.
2011/0294824	A1	12/2011	Bathe et al.
2013/0102616	A1	4/2013	Bathe et al.

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Related U.S. Application Data

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C07D 403/14 (2006.01)
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(52) **U.S. Cl.**
CPC **C07D 405/14** (2013.01)
USPC **514/254.09; 544/373**

(58) **Field of Classification Search**
USPC 514/254.09; 544/373
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,521,241 A 5/1996 Wu

FOREIGN PATENT DOCUMENTS

EP	0648767	A1	4/1995
EP	0738722	A1	10/1996
WO	00/72832	A2	12/2000
WO	02/102794	A2	12/2002

OTHER PUBLICATIONS

Summary of Facts Regarding US Clinical Trials Prior to Jun. 5, 2001. Sorbera, L.A. et al. "Vilazodone Hydrochloride. Antidepressant 5-HT_{2A} Partial Agonist 5-HT Reuptake Inhibitor" *Drugs of the Future* 2001, 26(3):247-252. (Mar. 2001).
Remington Farmacia Tomo 2 19. sup. a edicion. (1998).
Farmacotecnia Teorica Y Practica Tomo iV, Dr. Jose Helman. (1980).
Hungarian Search Report of May 10, 2010, citing HU P0201275 which corresponds to WO 00/72832.
Office Action for U.S. Appl. No. 12/945,260, date of mailing Aug. 17, 2011.
Office Action for U.S. Appl. No. 12/945,272, date of mailing Aug. 17, 2011.
Office Action for U.S. Appl. No. 13/100,911, date of mailing Nov. 9, 2011.
Office Action for U.S. Appl. No. 13/085,117, date of mailing Jan. 13, 2012.
Notice of Allowance for U.S. Appl. No. 12/945,272, date of mailing Mar. 19, 2012.

(Continued)

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(57) **ABSTRACT**

The invention relates to new crystalline modifications of the hydrochloride of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine, crystalline modification of the dihydrochloride of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine and amorphous 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride which are suitable in particular for the preparation of solid medicaments for the treatment or prevention of depressive disorders, anxiety disorders, bipolar disorders, mania, dementia, substance-related disorders, sexual dysfunctions, eating disorders, obesity, fibromyalgia, sleeping disorders, psychiatric disorders, cerebral infarct, tension, for the therapy of side-effects in the treatment of hypertension, cerebral disorders, chronic pain, acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome and undesired puerperal lactation.



(56)

References Cited

OTHER PUBLICATIONS

Corrected Notice of Allowance for U.S. Appl. No. 12/945,272, date of mailing Apr. 3, 2012.
Office Action for U.S. Appl. No. 13/100,911, date of mailing Mar. 23, 2012.
Office Action for U.S. Appl. No. 13/100,911, date of mailing Aug. 17, 2012.
Office Action for U.S. Appl. No. 13/085,117, date of mailing Apr. 3, 2012.
Notice of Allowance for U.S. Appl. No. 13/085,117, date of mailing Aug. 17, 2012.

Office Action for U.S. Appl. No. 13/100,948, date of mailing Nov. 18, 2011.
Office Action for U.S. Appl. No. 13/100,948, date of mailing Mar. 27, 2012.
Notice of Allowance for U.S. Appl. No. 13/100,948, date of mailing Jun. 4, 2012.
Morissette et al. Advanced Drug Delivery Reviews, 2004, 56:275-300.
Notice of Allowance for U.S. Appl. No. 14/032,183, date of mailing Dec. 13, 2013.
Office Action for U.S. Appl. No. 13/658,088, date of mailing May 23, 2013.
Office Action for U.S. Appl. No. 13/658,088, date of mailing Dec. 2, 2013.

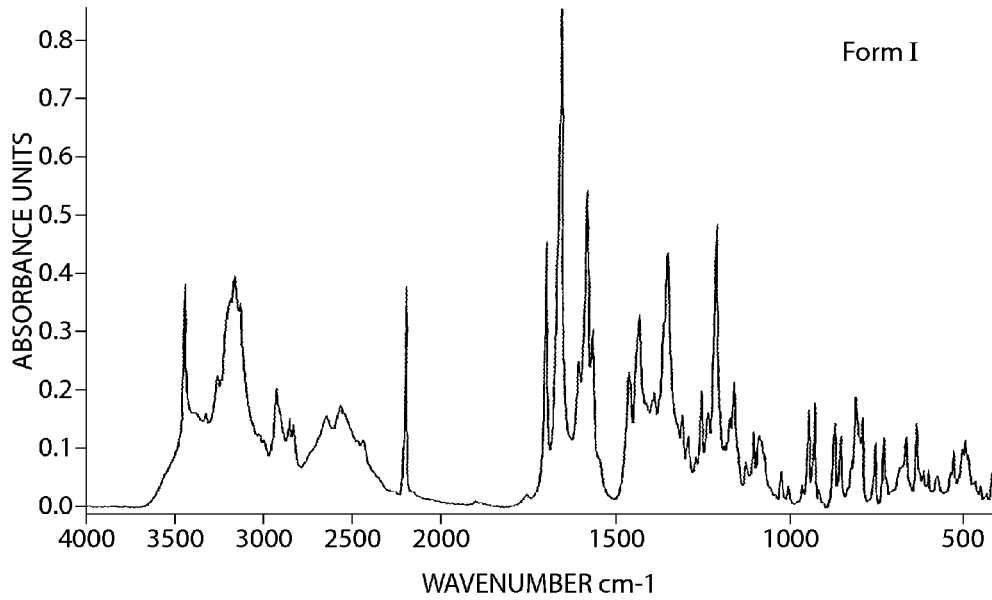


Fig. 1

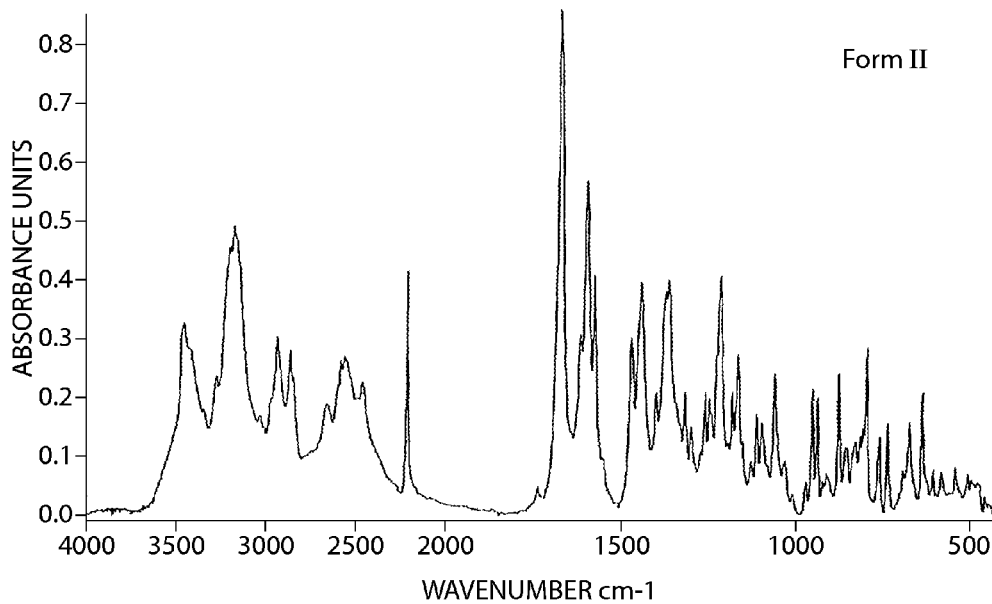


Fig. 2

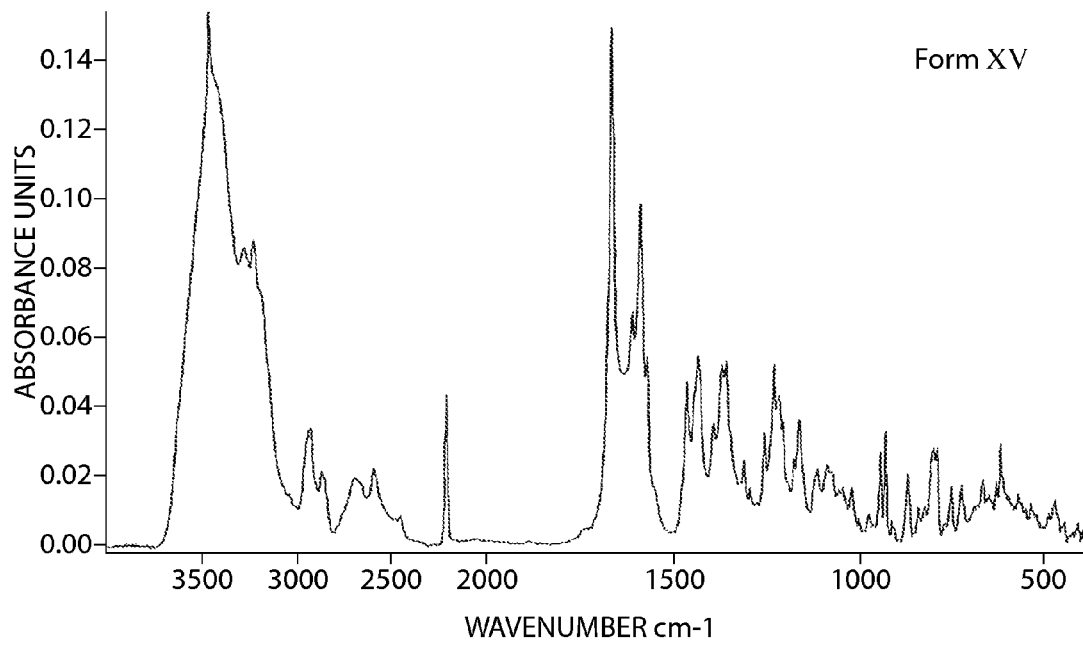


Fig. 3

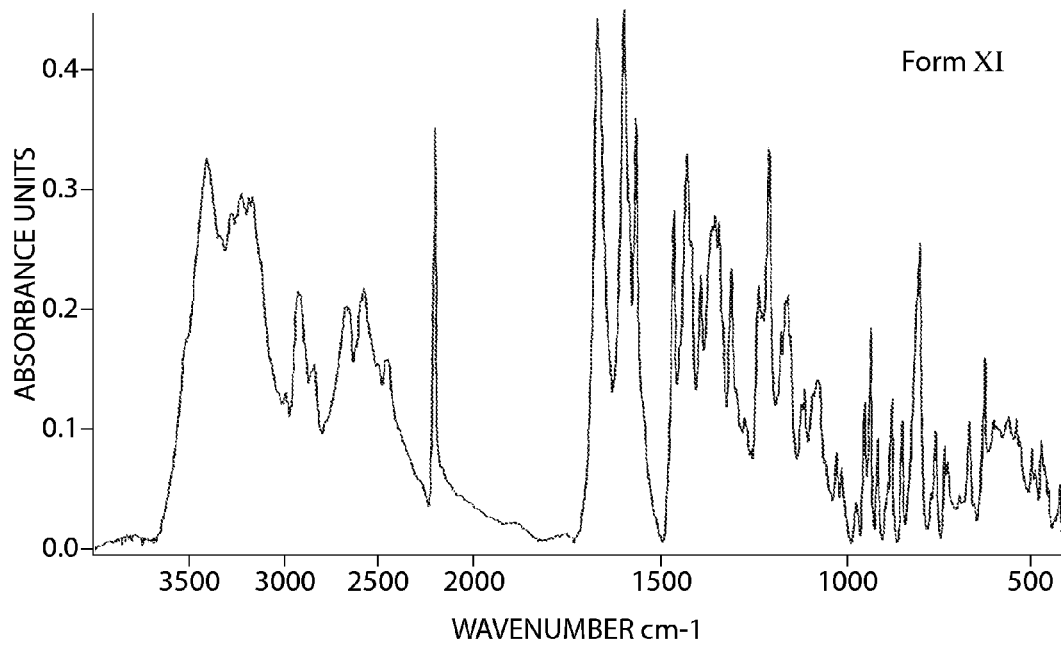


Fig. 4

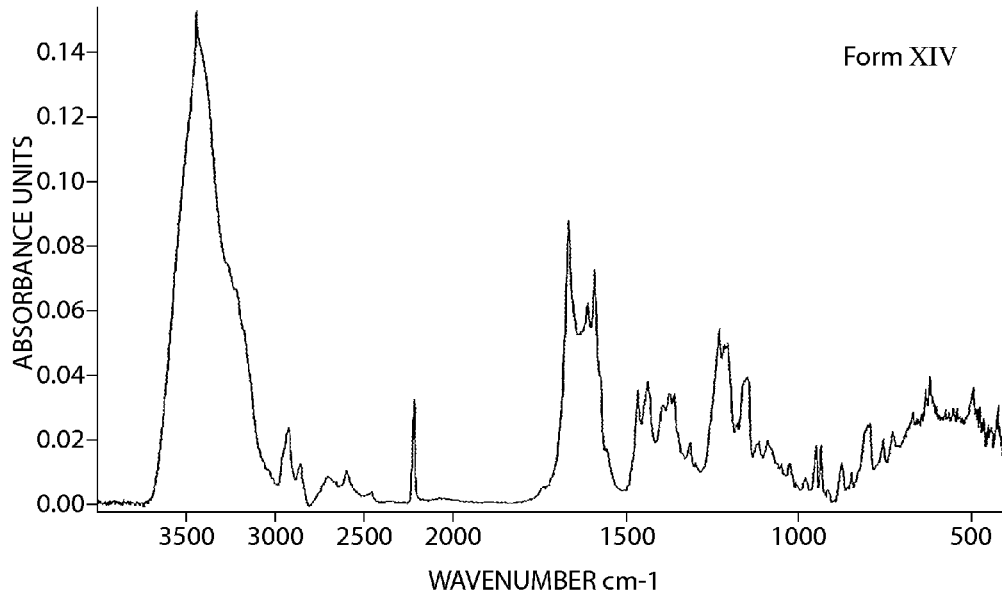


Fig. 5

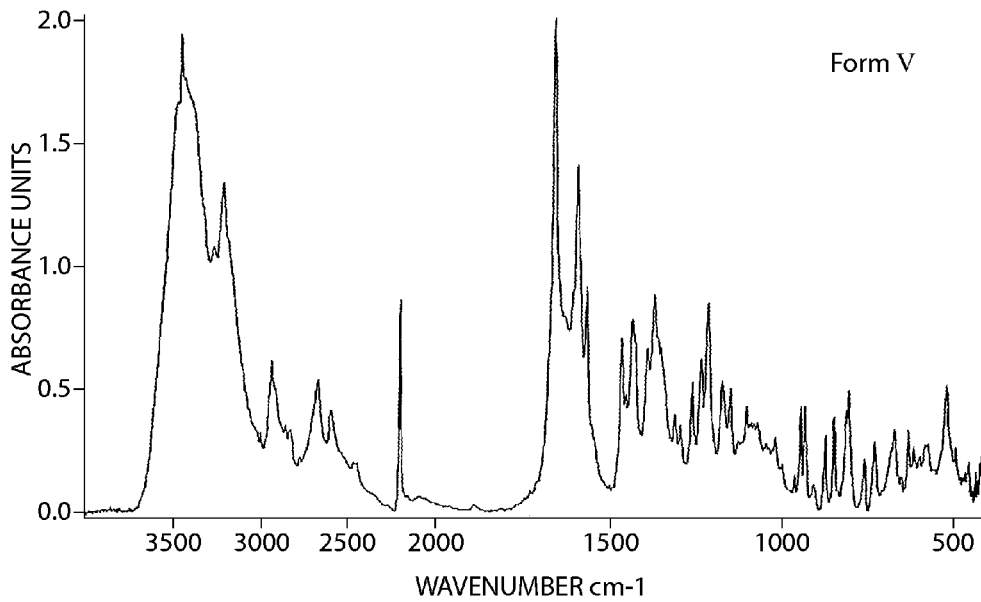


Fig. 6

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