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Bathe et al.

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

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.
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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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

(73) Assignee: **Merck Patentgesellschaft**, Darmstadt (DE)

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Related U.S. Application Data

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Summary of Facts Regarding US Clinical Trials Prior to Jun. 5, 2001. Sorbera, L.A. et al. "Vilazodone Hydrochloride. Antidepressant 5-HT_{1A} 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.
Corrected Notice of Allowance for U.S. Appl. No. 12/945,272, date of mailing Apr. 3, 2012.

(Continued)

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(30) Foreign Application Priority Data

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A61K 31/496 (2006.01)
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(52) **U.S. Cl.**
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
5,532,241	A	7/1996	Bottcher et al.
5,723,614	A	3/1998	Bathe et al.

(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

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.

Office Action for U.S. Appl. No. 13/658,088, date of mailing May 23, 2012.

Morissette, et al. Advanced Drug Delivery Reviews, 56, 2004, p. 275-300.

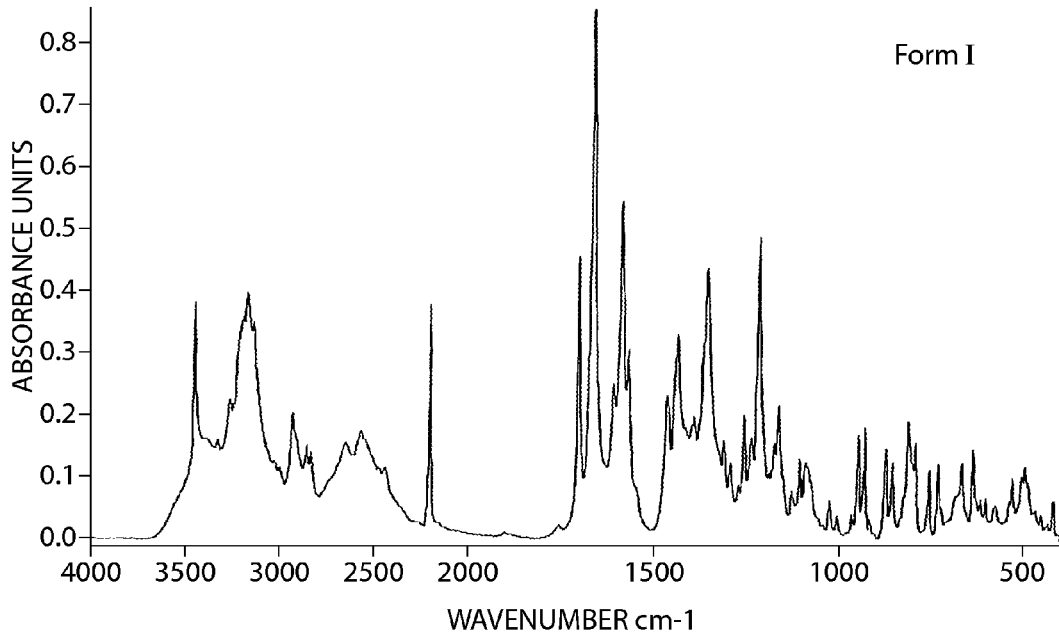


Fig. 1

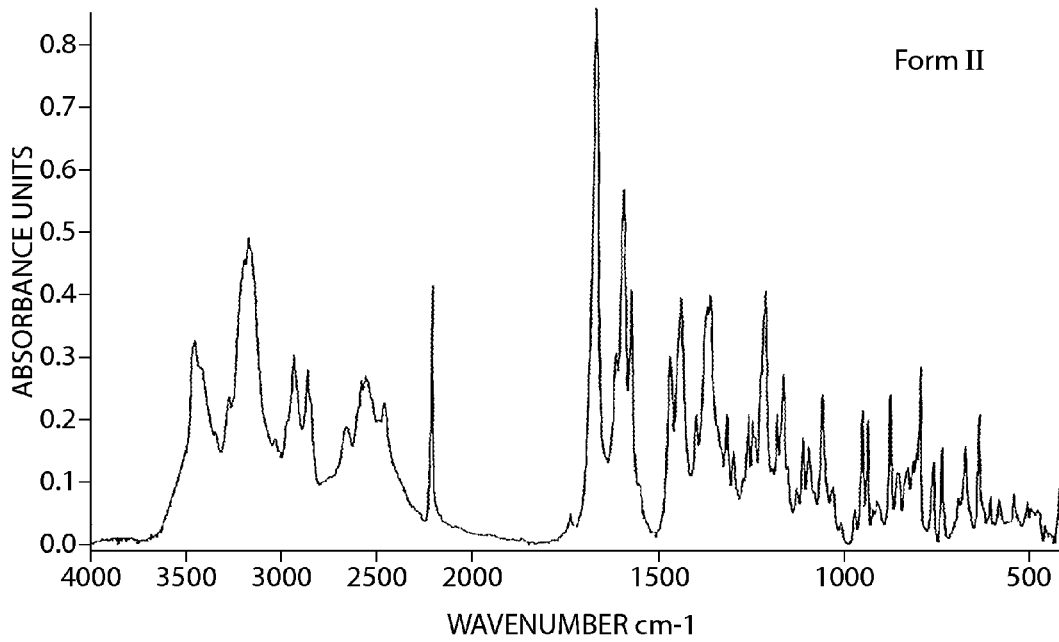


Fig. 2

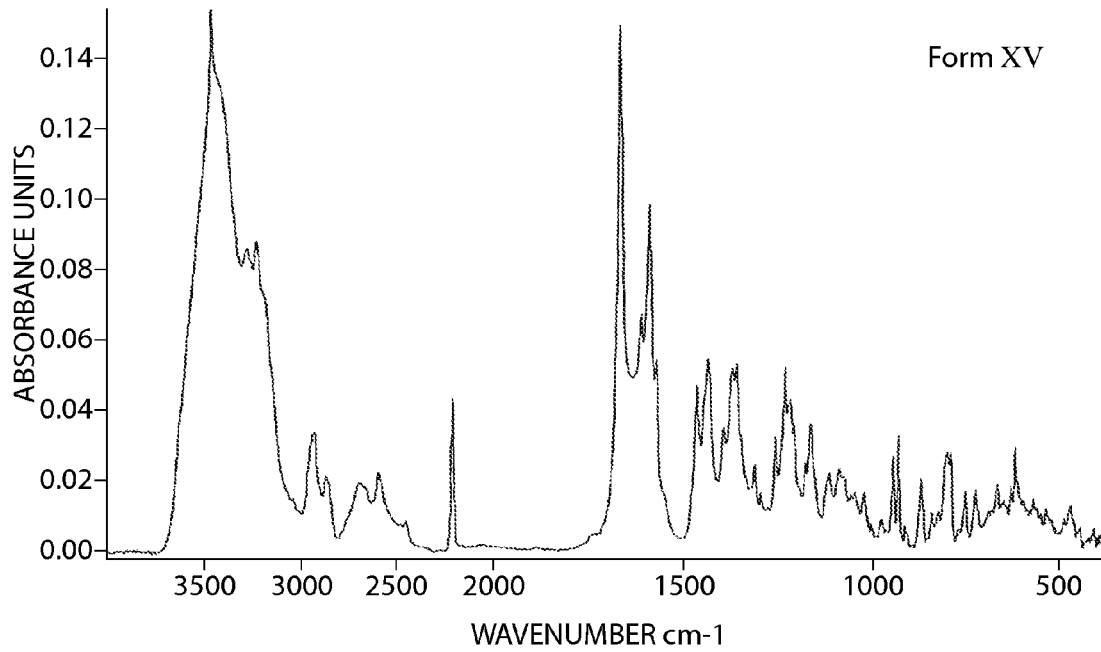


Fig. 3

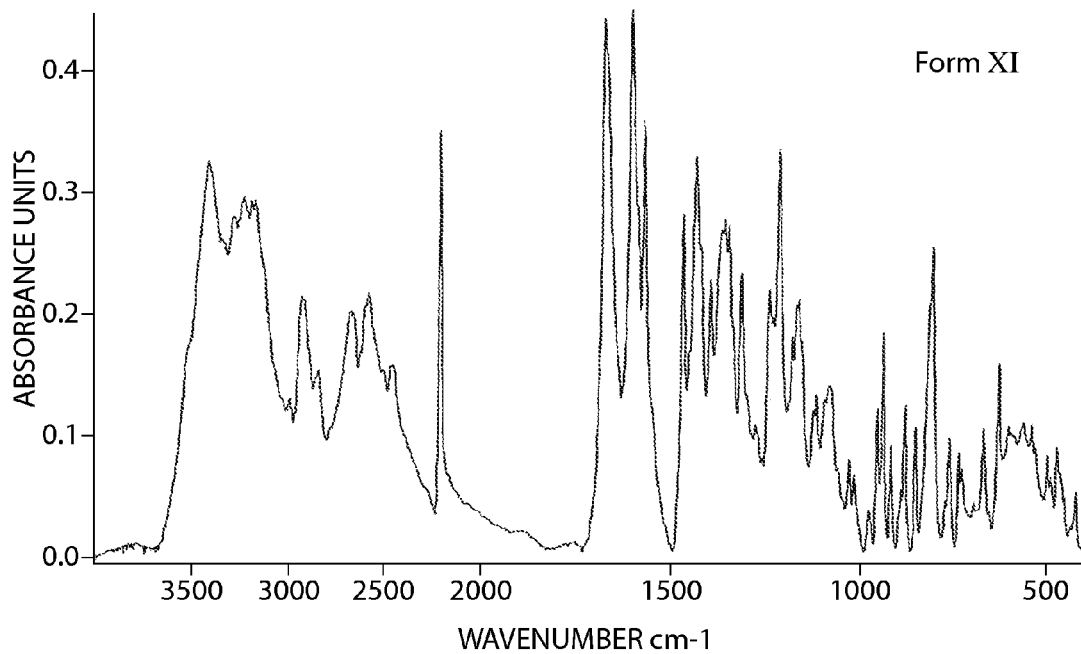


Fig. 4

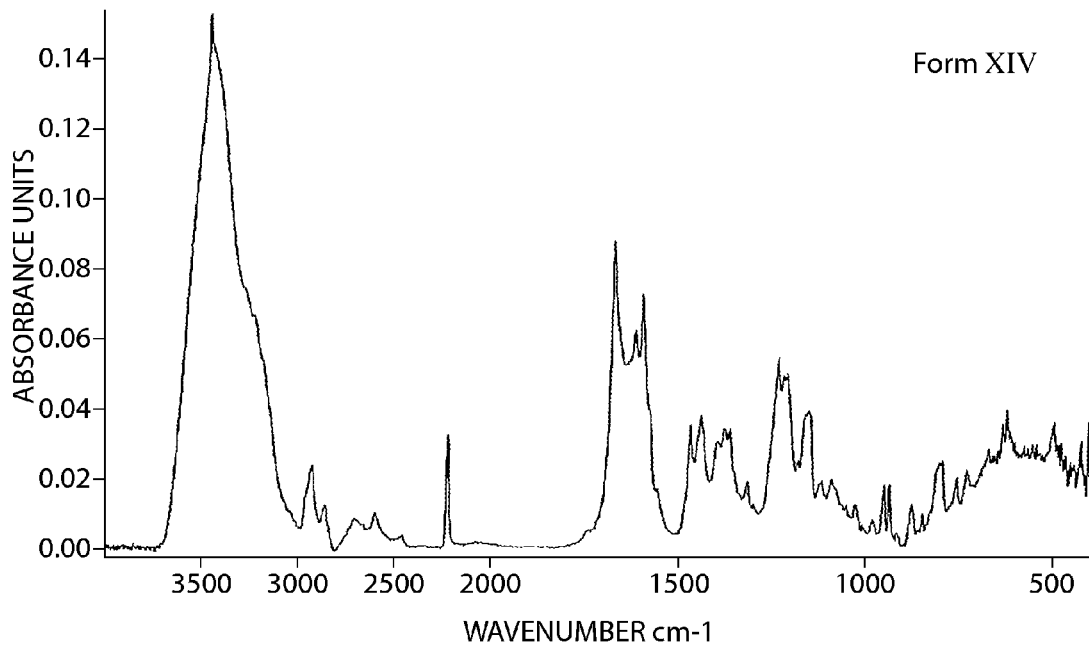


Fig. 5

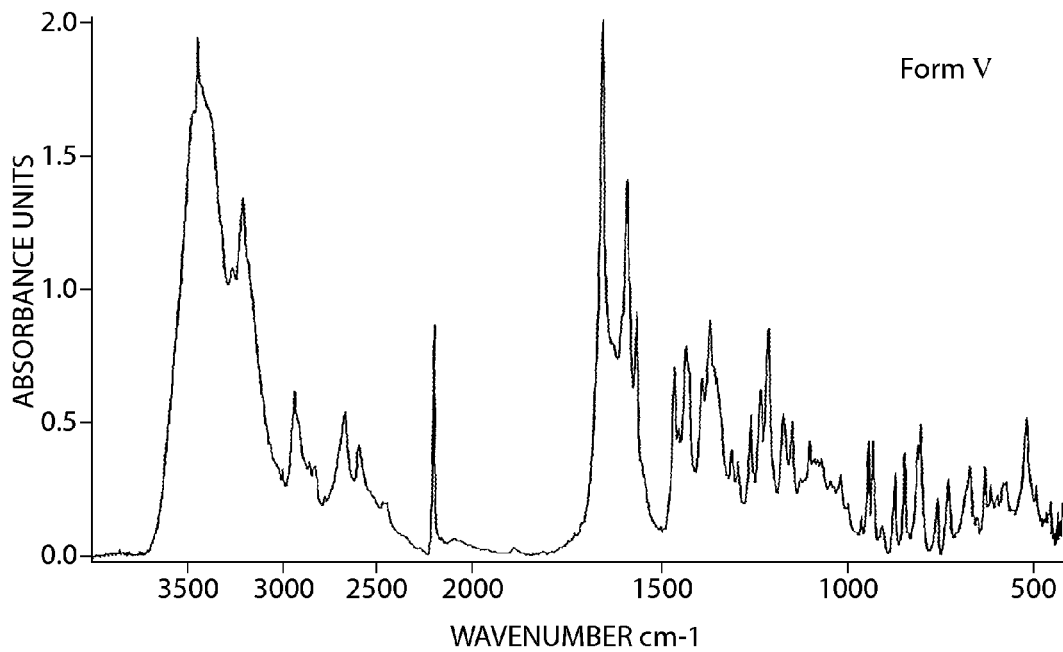


Fig. 6

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