05-01-02C

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PTO/SB/05 (2/98)
Approved for use through 09/30/2000. OMB 0651-0032
Patent and Trademark Office: U S DEPARTMENT OF COMMERCE

Please type a plus sign (+) inside this box → +

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37C F R §1 53(b))

Attorney Docket No.	PC11872A
First Named Inventor or Application Identifier	D Bogle et al
Title	TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1 $0^{2,11}.0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF
Express Mail Label No.	EL 768 265 645 US

ADDRESS TO: Commissioner for Patents, Box Patent Application, Washington, DC 20231

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents

1. ☒ *Fee Transmittal Form (e.g., *PTO/SB/17*) *(Submit an original, and a duplicate for fee processing)*
2. ☒ Specification [Total Pages 45]
   (preferred arrangement set forth below)
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R&D
   - Reference in Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. ☒ Drawing(s) *(35 U.S.C 11.3)*[Total sheets 20]
4. ☐ Oath or Declaration [Total pages]
   a ☐ Newly executed (original or copy)
   b. ☐ Copy from a prior application (37 CFR §1.63(d)) *(for continuation/divisional with Box 17 completed)* ***[Note Box 5 below]***
   i. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§1.63(d)(2) and 1.33(b).
5. ☐ Incorporation By Reference *(useable if Box 4b is checked)* The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. ☐ Microfiche Computer Program *(Appendix)*
7. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. ☐ Computer Readable Copy
   b. ☐ Paper Copy (identical to computer copy)
   c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. ☐ Assignment Papers (cover sheet & document(s))
9. ☐ 37 C.F.R. §3 73(b) Statement ☐ Power of Attorney *(when there is an assignee)*
10. ☐ English Translation Document *(if applicable)*
11. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
12. ☒ Preliminary Amendment
13. ☒ Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
14. ☐ *Small Entity Statement(s) *(PTO/SB/09-12)* ☐ Statement filed in prior application, Status still proper and desired
15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
16. ☒ Other: This application claims the benefit of U S Provisional Ser. No. 60/290,861, filed May 14, 2001.

NOTE FOR ITEMS 1 & 14: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

17. **If a CONTINUING APPLICATION,** *check appropriate box, and supply the requisite information below and in a preliminary amendment*
☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No. __/_____

Prior application information: Examiner_____ *Group/Art Unit:* _____

18. CORRESPONDENCE ADDRESS

☐ *Customer Number or Bar Code Label* ***(Insert Customer No. or Attach bar code label here)*** *or* ☒ *Correspondence address below*

Name	Paul H. Ginsburg				
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City	New York	State	New York	Zip Code	10017-5612
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NAME (Print/type)	Roy F. Waldron	*Registration No. (Attorney/Agent)*	42,208
Signature		*Date*	May 6, 2002

UTILITY TRANSMITTAL PTO SB 05, 3/99, (1/1)

EXPRESS MAIL NO. EL 768 265 645 US

Apotex Exhibit 1004.001

PTO/SB/17(2/98)
Approved for use through 09/30/2000
OMB 0651-0032 Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL

Patent fees are subject to annual revision on October 1. These are the fees effective October 1, 2001.

*Small Entity payments **must** be supported by a small entity statement, otherwise large entity fees must be paid. See Forms PTO/SB/09-12.*

See 37 C.F.R. §§ 1.27 and 1.28.

Total Amount of Payment ($)2448.00

Complete if Known	
Application Number	NOT YET ASSIGNED
Filing Date	CONCURRENTLY HEREWITH
First Named Inventor	D. Bogle et al.
Examiner Name	NOT YET ASSIGNED
Group/Art Unit	NOT YET ASSIGNED
Attorney Docket No.	PC11872A

METHOD OF PAYMENT (check one)

1. ☒ The commissioner is hereby authorized to charge indicated fees and credit any over payments to:

Deposit Account Number: 16-1445

Deposit Account Name: PFIZER INC

☒ Charge Any Additional Fee Required Under 37 C.F.R. §§ 1.16 and 1.17.

☐ Charge the Issue Fee Set in 37 C.F.R. § 1.18 at the Mailing of the Notice of Allowance.

2. ☐ Payment Enclosed:

☐ Check ☐ Money Order ☐ Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	740	201	370	Utility filing fee	740.00
106	330	206	165	Design filing fee	
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	160	214	80	Provisional filing fee	

SUBTOTAL (1) ($)740.00

2. EXTRA CLAIM FEES

			Extra Claims		Fee from below		Fee Paid
Total Claims	90	-20**=	70	X	18	=	1260.00
Independent Claims	5	- 3**=	2	X	84	=	168.00
Multiple Dependent					280.00	=	280.00

*** or number previously paid, if greater; For Reissues, see below*

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	84	202	42	Independent claims in excess of 3
104	280	204	140	Multiple dependent claim, if not paid
109	84	209	42	**Reissue independent claims over original patent
110	18	210	9	**Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 1708.00

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge – late fee or oath	
127	50	227	25	Surcharge–late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	
117	920	217	460	Extension for reply within third month	
118	1,440	218	720	Extension for reply within fourth month	
128	1,960	228	980	Extension for reply within fifth month	
119	320	219	160	Notice of Appeal	
120	320	220	160	Filing a brief in support of an appeal	
121	280	221	140	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,280	241	640	Petition to revive - unintentional	
142	1,280	242	640	Utility issue fee (or reissue)	
143	460	243	230	Design issue fee	
144	620	244	310	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	180	126	180	Submission of Information Disclosure Statement	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	740	246	370	Filing a submission after final rejection (37 CFR 1.129(a))	
149	740	249	370	For each additional invention to be examined (37 CFR 1.129(b))	
Other Fee (specify)					
Other Fee (specify)					

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($)0.00

SUBMITTED BY				Complete (if Applicable)	
Type or Printed Name	Roy F. Waldron			Reg. Number	42,208
Signature		Date	May 6, 2002	Deposit Account User ID	16-1445/PFIZER INC

EXPRESS MAIL NO. EL 768 265 645 US

"EXPRESS MAIL" LABEL NO. EL 768 265 645 US, Date of Deposit: May 6, 2002. I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C F R 1.10 on the date indicated above and is addressed to Commissioner for Patents, Box Patent Application, Washington, D.C. 20231.
By

(Signature of person mailing)
ROY F. WALDRON
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: D. Bogle et al. :
Examiner: Not Yet Assigned

SER. NO.: Not Yet Assigned :
Group Art Unit: Not Assigned

FILING DATE: Concurrently Herewith :

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF :

Commissioner for Patents
Box Patent Application
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

Prior to examination on the merits and calculation of filing fees, please enter the following amendments to the abstract, specification and claims. Marked up versions of the amendments to the abstract, specification and claims are found in the Appendix attached hereto.

IN THE SPECIFICATION

at page 1, line 3, insert the following new paragraph:

This application claims the benefit of U.S. Provisional Application Ser. No. 60/290,861, filed May 14, 2001.

REMARKS

Applicants have inserted a statement on page 1 of the application to indicate the priority required by 37 C.F.R. § 1.78. This amendment adds no new matter to the application.

Applicants believe the set of pending claims are condition for allowance and request the issuance of a Notice of Allowance.

If a telephone interview would assist the furtherance of the prosecution of this application, the Examiner is invited to contact the undersigned.

Respectfully submitted,

Date: 5/6/2002

Roy F. Waldron
Registration No. 42,208
Attorney for Applicant(s)

Pfizer, Inc
Patent Department
150 East 42nd Street (150/05/49)
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APPENDIX TO PRELIMINARY AMENDMENT

MARKED-UP VERSIONS OF AMENDED SPECIFICATION AND CLAIMS

IN THE SPECIFICATION

at page 1, line 7, insert the following new paragraph:

This application claims the benefit of U.S. Provisional Application Ser. No. 60/290,861, filed May 14, 2001.

EXPRESS MAIL CERTIFICATION

"Express Mail" Label No. EL 768 265 645 US, Date of Deposit: May 6, 2002. I hereby certify that the accompanying Specification: 37 pages; Claims: 7 pages; Abstract 1 page; Drawings: 20 pages; Utility Patent Application Transmittal; Fee Transmittal (2 copies) and Preliminary Amendment; is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to: Commissioner for Patents, Box Patent Application, Washington, D.C. 20031.

By 

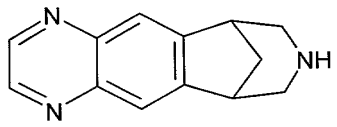
(Signature of person transmitting and mailing)

ROY F. WALDRON

(Typed or printed name of person)

TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

The present invention is directed to the tartrate salts of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene:



and pharmaceutical compositions thereof. The present invention in particular is directed to the L-tartrate salt, and further to the various polymorphs of the L-tartrate salt, including two distinct anhydrous polymorphs (referred to herein as Forms A and B) and a hydrate polymorph (referred to herein as Form C). In addition, the present invention is also directed to the D-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene and the various polymorphs thereof; as well as the D,L-tartrate salt thereof and its polymorphs, and the meso-tartrate salt thereof and its polymorphs.

The compound, 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, binds to neuronal nicotinic acetylcholine specific receptor sites and is useful in modulating cholinergic function. This compound is useful in the treatment of inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, drug/toxin-induced cognitive impairment (*e.g.*, from alcohol, barbiturates, vitamin deficiencies, recreational drugs, lead, arsenic, mercury), disease-induced cognitive impairment (*e.g.*, arising from Alzheimer's disease (senile dementia), vascular dementia, Parkinson's disease, multiple sclerosis, AIDS, encephalitis, trauma, renal and hepatic encephalopathy, hypothyroidism, Pick's disease, Korsakoff's syndrome and frontal and subcortical dementia), hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (*e.g.*, dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, migraine, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, attention deficit hyperactivity disorder (ADHD), Tourette's Syndrome, particularly, nicotine dependency, addiction and withdrawal; including use in smoking cessation therapy.

The tartrate salts of this invention may also be used in a pharmaceutical composition in combination with an antidepressant such as, for example, a tricyclic antidepressant or a

serotonin reuptake inhibiting antidepressant (SRI), in order to treat both the cognitive decline and depression associated with AD, PD, stroke, Huntington's chorea or traumatic brain injury (TBI); in combination with muscarinic agonists in order to stimulate both central muscarinic and nicotinic receptors for the treatment, for example, of ALS, cognitive dysfunction, age-related cognitive decline, AD, PD, stroke, Huntington's chorea and TBI; in combination with neurotrophic factors such as NGF in order to maximize cholinergic enhancement for the treatment, for example, of ALS, cognitive dysfunction, age-related cognitive decline, AD, PD stroke, Huntington's chorea and TBI; or in combination with agents that slow or arrest AD such as cognition enhancers, amyloid aggregation inhibitors, secretase inhibitors, tau kinase inhibitors, neuronal anti-inflammatory agents and estrogen-like therapy.

Compounds that bind to neuronal nicotinic receptor sites, including 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, and its hydrochloride salt, are referred to in WO 99/35131, published July 15, 1999 (corresponding to U.S Ser. No. 09/402,010, filed September 28, 1999 and 09/514,002, filed February 25, 2000). The foregoing applications, owned in common with the present application and incorporated herein by reference in their entirety, generically recite pharmaceutically acceptable acid addition salts for the compounds referred to therein.

The L-tartrate salt of the present invention exhibits properties, including those of high solid-state stability and compatibility with certain drug product formulation excipients, that render it superior to previously known salts of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene. Further, the D-tartrate and D,L-tartrate salts exhibit properties that also make them appropriate for drug product formulation use.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a powder X-ray diffraction of the anhydrous L-tartrate salt Form A of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta).

Figure 2 is the powder X-ray diffraction of the anhydrous L-tartrate salt Form B of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta).

Figure 3 is the powder X-ray diffraction of the L-tartrate salt hydrate Form C of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta).

Figure 4A is the calculated powder X-ray diffraction pattern of the anhydrous Form B L-tartrate salt of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta). **Figure 4B** is the calculated powder X-ray diffraction pattern of the Form C L-tartrate salt hydrate of 5,8,14-triazatetra-

cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta).

Figure 5A is the calculated powder X-ray diffraction pattern (lower trace) laid over the observed X-ray diffraction pattern (upper trace) for the anhydrous Form B L-tartrate salt of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta). **Figure 5B** is the calculated powder X-ray diffraction pattern (lower trace) laid over the observed X-ray diffraction pattern (upper trace) for the Form C L-tartrate salt hydrate of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta).

Figure 6 is the overlay of the powder X-ray diffraction patterns of the Form A (lower trace), Form B (middle trace) and Form C (upper trace) L-tartrate salts of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta).

Figures 7A, 7B and **7C** are the solid state ^{13}C NMR spectra of the L-tartrate salts of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene Forms A, B and C, respectively, as measured by cross-polarization magic angle spinning (CPMAS) at 295 K on a Bruker 7mm wide-bore magic angle spinning (WB MAS) probe positioned in a Bruker Avance DRX 500 MHz NMR Spectrometer. Peaks marked with asterisks (*) are spinning sidebands which are displaced at multiples of the spinning frequencies along both sides of the real peaks (centerbands).

Figure 8A is the X-ray crystal structure (absolute configuration) for the anhydrous Form B L-tartrate salt of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene. **Figure 8B** is the X-ray crystal structure (absolute configuration) for the Form C L-tartrate salt hydrate of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

Figure 9A, 9B and 9C are the differential scanning calorimetric traces for the L-tartrate salts Forms A, B and C, respectively, of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

Figure 10A and 10B are the powder X-ray diffraction patterns of the D,L-tartrate salt Forms X and Y, respectively, of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta).

Figure 11A and 11B are the differential scanning calorimetric traces for the D,L-tartrate salts Forms X and Y, respectively, of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

SUMMARY OF THE INVENTION

The present invention relates to the tartrate salts of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene. The tartrate salts of the invention include the L-tartrate, D-tartrate, D,L-tartrate and meso-tartrate salts.

In particular, the present invention relates to the L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

In one embodiment of the invention, the L-tartrate of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene is the anhydrous L-tartrate salt, referred to herein as Form A. The L-tartrate Form A is characterized by the principal x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation (within the margins of error indicated):

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
6.1	14.5
12.2	7.2
13.0	6.8
14.7	6.0
16.8	5.3
19.4	4.6
21.9	4.1
24.6	3.6

The L-tartrate crystal Form A is characterized in that it has a onset of melt at about 223 °C as measured by differential scanning calorimetry at a heating rate of 5 degrees per minute. The L-tartrate Form A is also characterized in that when examined by solid state ^{13}C NMR cross-polarization magic angle spinning techniques, it exhibits the following principal resonance peaks (± 0.1ppm) downfield from 100 ppm (adamantane standard 29.5 ppm): 178.4, 149.3, 147.4, 145.1, and 122.9 ppm.

In another embodiment of the invention, the L-tartrate of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene is another anhydrous L-tartrate salt polymorph, referred to herein as Form B. The L-tartrate salt Form B is characterized by the principal x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation (within the margins of error indicated):

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
5.9	15.0
12.8	6.9
14.4	6.1
15.3	5.8
16.9	5.2
17.2	5.2
21.8	4.1
23.8	3.7
25.1	3.5

The L-tartrate salt Form B has a single crystal x-ray structure (absolute configuration) as set forth in Figure 8A. Further, the Form B forms orthorhombic crystals belonging to the P2(1)2(1)2(1) space group. Form B is further characterized in having an onset of melting at about 215 °C as measured by differential scanning calorimetry at a heating rate of 5 degrees per minute. Further, Form B of the invention is also characterized in having an aqueous solubility of about 156 mg/ml and a native pH of about 3.3 in aqueous solution. In addition, Form B has a hygroscopicity of approximately 0.2% at 90% relative humidity.

The L-tartrate Form B is also characterized in that when examined by solid state ^{13}C NMR cross-polarization magic angle spinning techniques, it exhibits the following principal resonance peaks (± 0.1ppm) downfield from 100 ppm (adamantane standard 29.5 ppm): 179.2, 178.0, 147.4, 145.2, 144.4, 124.8 and 122.5 ppm.

In another embodiment of the invention, the L-tartrate of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene is the hydrate L-tartrate salt, referred to herein as Form C. The L-tartrate Form C is characterized by the principal x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation (within the margins of error indicated):

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
5.9	15.1
11.8	7.5
16.5	5.4
21.2	4.2
23.1	3.8
23.8	3.7
26.5	3.4

The hydrate L-tartrate crystal Form C has a single crystal structure as set forth in Figure 8B. Further, the hydrate Form C forms monoclinic crystals belonging to the P2(1) space group. Form C is further characterized in having an onset of a solid-solid transition at

about 72 °C and an onset of melting transition at about 220 °C. Because Form B converts to the hydrate Form C upon contact with 100% relative humidity, Form C has the same aqueous solubility as Form B.

The L-tartrate Form C is also characterized in that when examined by solid state ^{13}C NMR cross-polarization magic angle spinning techniques, it exhibits the following principal resonance peaks (± 0.1ppm) downfield from 100 ppm (adamantane standard 29.5 ppm): 179.0, 176.1, 147.5, 144.5 and 124.6 ppm.

A further embodiment of the invention is directed to the D-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene. In particular, the present invention is directed to the three D-tartrate salt polymorphs (referred to here as Forms A', B' and C') which exhibit the same x-ray diffraction characteristics, hygroscopicity, water content and thermal characteristics as Forms A, B and C of the L-tartrate salt.

In another embodiment, the present invention relates to the D,L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, and in particular, two polymorphs, an anhydrous form (herein referred to as Form X) and a hydrate form (herein referred to as Form Y).

The D,L-tartrate Form X is characterized by the principal x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation (within the margins of error indicated):

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
6.0	14.6
11.9	7.4
15.0	5.9
17.1	5.2
22.1	4.0
24.5	3.6

The D,L-tartrate Form X is further characterized in having an onset of a melting transition at about 212 °C.

The D,L-tartrate Form Y is characterized by the principal x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation (within the margins of error indicated):

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
6.2	14.2
12.0	7.4
15.2	5.8
18.1	4.9
24.0	3.7
25.1	3.5

The D,L-tartrate Form Y is further characterized in having an onset of a solid-solid transition at about 131 °C and an onset of melting transition at about 217 °C.

Another embodiment of the invention relates to a pharmaceutical composition comprising at least one of polymorphic Forms A, B or C, preferably Form B, of the L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene and a pharmaceutically acceptable carrier or excipient, for use in the treatment of inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, drug/toxin-induced cognitive impairment (*e.g.*, from alcohol, barbiturates, vitamin deficiencies, recreational drugs, lead, arsenic, mercury), disease-induced cognitive impairment (*e.g.*, arising from Alzheimer's disease (senile dementia), vascular dementia, Parkinson's disease, multiple sclerosis, AIDS, encephalitis, trauma, renal and hepatic encephalopathy, hypothyroidism, Pick's disease, Korsakoff's syndrome and frontal and subcortical dementia), hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (*e.g.*, dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, migraine, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, attention deficit hyperactivity disorder (ADHD), and Tourette's Syndrome. Another more preferred embodiment of the invention is wherein the pharmaceutical composition is useful in the treatment of nicotine dependency, addiction and withdrawal; most preferably, for use in smoking cessation therapy.

The present invention further relates to pharmaceutical compositions for the uses described in the foregoing paragraph comprising any one of the D-tartrate salt of, the D,L-tartrate salt of, or the meso-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

The present invention further relates to a method of treating inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, drug/toxin-induced cognitive impairment (*e.g.*, from alcohol, barbiturates, vitamin deficiencies, recreational drugs, lead, arsenic, mercury), disease-induced cognitive impairment (*e.g.*, arising from Alzheimer's disease (senile dementia), vascular dementia, Parkinson's disease, multiple sclerosis, AIDS, encephalitis, trauma, renal and hepatic encephalopathy, hypothyroidism, Pick's disease, Korsakoff's syndrome and frontal and subcortical dementia), hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (*e.g.*, dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, migraine, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, attention deficit hyperactivity disorder (ADHD), and Tourette's Syndrome comprises administering to a subject in need of treatment a therapeutically effective amount of any of Forms A, B or C of the L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, preferably Form B. Another more preferred embodiment of the invention relates to a method of treatment for nicotine dependency, addiction and withdrawal, in particular for use in smoking cessation therapy activity, comprising the administration of any of Forms A, B or C of the L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, preferably Form B, to a subject in need thereof.

The present invention further relates to methods of treatment described in the foregoing paragraph comprising the administration of any of the D-tartrate salt, the D,L-tartrate salt or the meso-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene to a subject in need thereof.

The term "treating" as used herein, refers to, and includes, reversing, alleviating, inhibiting the progress of, or preventing a disease, disorder or condition, or one or more symptoms thereof; and the term "treatment" refers to the act of treating, as defined above.

The invention also relates to a process for the preparation of the Form A of L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with between 1 and 2 equivalents of L-tartaric acid; and

(ii) collecting the crystals formed.

A preferred embodiment of this invention relates to the above process wherein 1.1 equivalents of L-tartaric acid is employed and the tartaric acid is added to a solution containing the free base. A preferred mode of practicing this process is wherein the contact step is allowed to proceed for less than 2 hours. A more preferred embodiment of this invention relates to the above process wherein the contact step (*i.e.*, step "(i)" above) is allowed to proceed above 45 °C. Another preferred embodiment of this invention relates to the above process wherein the suitable solvent is selected from the group consisting of a (C_1-C_6)alkyl alcohol, a (C_1-C_6)alkyl ketone or a (C_1-C_6)alkyl ether, acetonitrile and (C_1-C_6)alkyl esters (e.g., ethyl acetate, isopropyl acetate, etc.). More preferably, the suitable solvent is ethanol or methanol.

The invention further relates to a process for the preparation of Form A' of the D-tartrate salt comprising steps (i) and (ii) referred to above for making Form A of the L-tartrate salt, but using D-tartaric acid in step (i) in place of L-tartaric acid.

The invention also relates to a process for the preparation of Form B of L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene comprising the steps of:

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of L-tartaric acid; and

(ii) collecting the crystals formed.

A preferred embodiment of this invention relates to the above process wherein about 1.1 to about 2.2 equivalents, more preferably 1.1 equivalents, of L-tartaric acid is employed and the free base in solution is added to a solution containing L-tartaric acid. A preferred mode of practicing this process is wherein the contact step is allowed to proceed for a minimum of 1 hours; more preferably, for at least 2 hours; most preferably, longer than 12 hours. A preferred embodiment is wherein the suitable solvent is selected from the group consisting of a (C_1-C_6)alkyl alcohol, a (C_1-C_6)alkyl ketone or a (C_1-C_6)alkyl ether, acetonitrile and (C_1-C_6)alkyl esters (e.g., ethyl acetate, isopropyl acetate, etc.). More preferably, the suitable solvent is methanol or ethanol, most preferably methanol.

The invention further relates to a process for the preparation of Form B' of the D-tartrate salt comprising steps (i) and (ii) referred to above for making Form B of the L-tartrate salt, but using D-tartaric acid in step (i) in place of L-tartaric acid.

Another aspect of the present invention relates to a process for the preparation of the Form C of the L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene comprising the steps of:

(i) contacting either of Form A or Form B of the L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene with water; and

(ii) collecting the crystals formed.

A preferred embodiment of this invention relates to the above process wherein the contacting of step (i) comprises slurrying either of Forms A or B with water with subsequent addition of an organic solvent to promote precipitation of the Form C product. A more preferred embodiment of the process is wherein the organic solvent use to promote precipitation is methanol, ethanol or acetonitrile.

The invention further relates to a process for the preparation of Form C' of the D-tartrate salt comprising steps (i) and (ii) referred to above for making Form C of the L-tartrate salt but using Forms A' or B' of the D-tartrate salt in step (i) in place of Forms A or B of the L-tartrate salt.

The present invention further relates to a process for the preparation of Form X of the D,L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene comprising the steps of:

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of D,L-tartaric acid; and

(ii) collecting the crystals formed.

A preferred embodiment of this invention relates to the above process wherein about 2.2 equivalents of D,L-tartaric acid is employed and the free base in solution is added to a solution containing D,L-tartaric acid. A preferred mode of practicing this process involves allowing the contact step to proceed for a minimum of 2 hours; more preferably, for at least 12 hours; and most preferably, at least 24 hours.

Another preferred embodiment of this invention relates to the above process for preparing Form X wherein the suitable solvent is anhydrous or nearly anhydrous and is selected from the group consisting of a (C_1-C_6)alkyl alcohol, a (C_1-C_6)alkyl ketone or a (C_1-C_6)alkyl ether, acetonitrile and (C_1-C_6)alkyl esters (e.g., ethyl acetate, isopropyl acetate, etc.). More preferably, the suitable solvent is ethanol.

The present invention further relates to a process for the preparation of Form Y of the D,L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene comprising the steps of:

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of D,L-tartaric acid; and

(ii) collecting the crystals formed.

A preferred embodiment of this invention relates to the above process wherein about 2.2 equivalents of D,L-tartaric acid is employed and the free base in solution is added to a solution containing D,L-tartaric acid. A preferred mode of practicing this process involves allowing the contact step to proceed for a minimum of 2 hours; more preferably, for at least 12 hours; most preferably, for at least 24 hours.

Another preferred embodiment of this invention relates to the above process for preparing Form Y wherein the suitable solvent is selected from the group consisting of a (C_1-C_6)alkyl alcohol, a (C_1-C_6)alkyl ketone or a (C_1-C_6)alkyl ether, acetonitrile and (C_1-C_6)alkyl esters (e.g., ethyl acetate, isopropyl acetate, etc.) admixed with water. More preferably, the suitable solvent is ethanol admixed with water; most preferably, 20% aqueous ethanol.

DETAILED DESCRIPTION OF THE INVENTION

The compound, 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene is a nicotinic partial agonist for the treatment of a number of CNS diseases, disorders and conditions including, in particular, nicotine dependency, addiction and withdrawal.

Although in general the salts of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene are all crystalline, the majority of such salts are so significantly hygroscopic as to render them poor candidates for pharmaceutical formulation use. The L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene is very slightly hygroscopic, has high aqueous solubility and is high melting. These characteristics, combined with its relative inertness towards common excipients, make it highly suitable for pharmaceutical formulation use. The D-tartrate salt, the D,L-tartrate salt and the meso-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene also exhibit favorable characteristics.

The L-tartrate salt exists as three possible forms: two anhydrous forms and one hydrate form. Of the two anhydrous forms, Form A and Form B, Form A is the kinetic polymorph, which will convert under appropriate conditions to the thermodynamically favored Form B. The hydrate L-tartrate salt Form C is a monohydrate and is relatively stable under ambient conditions. It will maintain its one equivalent of water under vacuum at moderate temperatures for at least a day (*e.g.*, for 24 hours in a 45 °C vacuum oven), but eventually over time (*i.e.*, 48 hours or more) will lose water and convert to the anhydrous Form B. Form B is the most stable of the polymorphs at low humidity. Accordingly, Form B would appear to be the most appropriate and most stable polymorph of the L-tartrate salts of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene for pharmaceutical formulation use.

As noted above, Form A is the anhydrous kinetic polymorph, which converts under appropriate conditions to the thermodynamically-favored Form B. Form A is obtainable from a synthesis involving, e.g., contacting the free base of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene with approximately one equivalent of L-tartaric acid in methanol or ethanol, allowing little or no time for equilibration. Form A is observed as the resulting product initially from the combination of the 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene free base and L-tartaric acid, but Form B begins to form on

continued or prolonged agitation of the reaction mixture. The rate of formation of Form B may be accelerated by using at least a two-fold or more stoichiometric excess of L-tartaric acid (*i.e.*, faster with 2.2 equivalents of L-tartaric acid present than with only 1.1 equivalents) and allowing the reaction to proceed for longer than two hours, preferably for at least a day or more. Conversion to Form B is ordinarily complete after about 5 hours using 2.2 equivalents. In contrast, the conversion may require more than 20 hours using 1.1 equivalents. In any case, conversion to Form B is usually complete under most conditions after 48 hours at 20-25 °C.

The temperature of the L-tartrate salt formation reaction also influences whether Form A or Form B is isolated, since Forms A and B appear to be thermally interconvertable. Running the salt formation reaction above 45 °C give Form A. Conversely, formation of the salt below 45 °C results in the formation of predominantly Form B. Also, stirring Form A in methanol below 40 °C results in the formation of Form B.

Although any number of solvents may be used, including most lower alcohols, Form B is obtained in high yield preferably using methanol, which permits a high filtration rate of the crystalline material and allows the formation of Form B directly. The solubility of both the free base and L-tartaric acid are higher in methanol than in other lower alkyl alcohols.

The rate of formation of Form B may also be accelerated by employing the specific order of addition wherein the 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene free base is added to the solution of L-tartaric acid. To maximize the virtual concentration of L-tartaric acid present in the reaction, the methanolic solution of free base may be added to a solution containing either 1.1 or more equivalents of L-tartaric acid at 20 °C . The desired anhydrous Form B may then be isolated directly and the polymorph conversion completed in less than 2 hours.

One optimized procedure for making the anhydrous Form B comprises charging a speck-free vessel with between 1.1 and 2.2 equivalents of L-tartaric acid and methanol (4 to 50 volumes), and stirring this mixture until dissolved and speck-free filtering the resulting solution into a crystallization vessel. 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene free base (1.0 equivalents) and methanol (4 to 50 volumes) are stirred in a vessel until dissolved at 0 to 50 °C, more preferably at 20 to 25 °C. The resulting solution of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene free base is then added over about a period of time ranging from 1 minute to 2 hours, more preferably over about 30 minutes, to the L-tartaric acid solution. The product was allowed to stir at 0 to 40 °C, more preferably at 20 to 25 °C, for between 1 and 48 hours, more preferably for about 1 hour, and then isolated by filtration. The product is dried generally under vacuum at 20 to 60 °C, more preferably at 35 to 45 °C, to give Form B of the L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

Both anhydrous Forms A and B can be converted to the monohydrate Form C by exposing either to a relative humidity (RH) of 100% or slurrying either of them in water. Form C is most readily obtained from either of Forms A or B by dissolving either in water at 20 to 50 °C followed by addition of an organic solvent in which the salt is not soluble, preferably methanol, ethanol or acetonitrile, and allowing the mixture to stir for between 1 and 30 minutes, preferably about 10 minutes. Upon filtering off the Form C which precipitates out as a white salt, the Form C salt may be air dried.

Noteworthy is that when exposed to conditions of 100% RH, Form B will convert to Form C within 2 days. Conversely, however, Form C readily converts to Form B upon exposure to 0% relative humidity conditions in roughly the same period of time. Hydrate Form C will however more slowly dehydrate upon exposure to conditions of less than 50% RH. Experiments at 23% and 43% RH have verified this phenomena. Nonetheless, both Forms B and C appear to be relatively stable over a several month period at RH greater than 60%, as experiments at 75% and 87% relative humidity have shown.

Further, Form A can be obtained from Form C by dissolving Form C in a hot organic solvent, preferably ethanol, at or near its reflux point, preferably at about 75 °C, and allowing it to stir for from 10 minutes to 3 hours, preferably 30 minutes. Hot filtering the mixture allows the collection of crystals which upon drying in a vacuum oven at 45 °C yields Form A.

The D-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene has three polymorphs (Forms A', B' and C'), which exhibit the same x-ray diffraction characteristics, hygroscopicity, water content and thermal characteristics as the corresponding Forms A, B and C, respectively, of the L-tartrate salt; and are made in an identical manner as the corresponding L-tartrate salt polymorphs, with the exception that D-tartaric acid is employed in those procedures in place of L-tartaric acid.

The preparation of the anhydrous polymorph (Form X) of the D,L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene involves the steps of dissolving 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent, preferably anhydrous ethanol, with about 1 to about 2.3 equivalents of D,L-tartaric acid, preferably 2.2 equivalents, at 20 °C to solvent reflux temperature for at least 2 hours, more preferably for at least 12 hours, most preferably at least 24 hours; collecting the crystals formed, washing the product with solvent and air drying it. The hydrate polymorph (Form Y) of the D,L-tartrate salt may be made in an analogous fashion but with the use of a solvent admixed with water, preferably an ethanol and water mixture, more preferably 20% aqueous ethanol. In addition, the meso-tartrate may be made in an analogous fashion to the D,L-tartrate.

Differential Scanning Calorimetry

The solid state thermal behavior of Forms A, B and C of the L-tartrate salt of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene were investigated by differential scanning calorimetry (DSC). The traces for Forms A, B and C are shown in Figures 9A, 9B and 9C, respectively. The DSC thermograms were obtained on a Mettler Toledo DSC 821^e ($STAR^e$ System). Generally, samples between 1 and 10 mg were prepared in crimped aluminum pans with a small pinhole. The measurements were run at a heating rate of 5 °C per minute in the range of 30 to 300 °C.

As seen in Figure 9A, the L-tartrate salt Form A exhibits an onset of melt transition at 223 °C with a melting peak accompanied by decomposition at 225 °C measured at a rate of 5 °C per minute. As seen in Figure 9B, the L-tartrate salt Form B exhibited an onset of melt transition at 215 °C with a melting peak accompanied by decomposition at 218 °C measured at a rate of 5 °C per minute. As seen in Figure 9C, the L-tartrate salt hydrate Form C exhibits a solid-solid transition onset at 73 °C with a peak at 76 °C. This solid-solid transition is believed to correspond to the loss of water from the crystal lattice. A melt transition onset is also observed at 220 °C, with a peak at 223 °C accompanied by decomposition.

The solid state thermal behavior of Forms X and Y of the D,L-tartrate salt of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene were also investigated by DSC. As seen in Figure 11A, the D,L-tartrate salt Form X (anhydrous) exhibits an onset of melting transition at 212 °C. In Figure 11B, the differential scanning calorimetric trace for the D,L-tartrate salt Form Y indicates an exhibits a solid-solid transition onset at 131 °C with a peak at 137 °C. This solid-solid transition is believed to correspond to or to be associated with the loss of water from the crystal lattice. A melt transition onset for Form Y is also observed at 217 °C and is accompanied by decomposition.

One of skill in the art will however note that in DSC measurements there is a certain degree of variability in actual measured onset and peak temperatures which is dependant on rate of heating, crystal shape and purity, and a number of measurement parameters.

Powder X-ray Diffraction Patterns

The powder x-ray diffraction patterns for both Forms A, B and C of the L-tartrate salt were collected using a Bruker D5000 diffractometer (Bruker AXS, Madison, Wisconsin) equipped with copper radiation (CuK_{α}), fixed slits (1.0, 1.0, 0.6 mm), and a Kevex solid state detector. Data was collected from 3.0 to 40.0 degrees in two theta (2θ) using a step size of 0.04 degrees and a step time of 1.0 seconds.

The x-ray powder diffraction pattern of the L-tartrate salt Form A was conducted with a copper anode with wavelength 1 at 1.54056 and wavelength 2 at 1.54439 (relative intensity: 0.500). The range for 2θ was between 3.0 to 40.0 degrees with a step size of 0.04 degrees, a step time of 1.00, a smoothing width of 0.300 and a threshold of 1.0.

The diffraction peaks at diffraction angles (2θ) in a measured powder X-ray diffraction analysis for the Form A are shown in Table I. The relative intensities, however, may change depending on the crystal size and morphology. The actual measured powder diffractogram is displayed in Figure 1.

Table I. Powder X-ray Diffraction Pattern for L-Tartrate Form A with Intensities and Peak Locations of Diffraction Lines.

Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)
6.1	14.5	73.3	20.6	4.3	16.8	30.8	2.9	5.6
11.8	7.5	6.1	21.9	4.1	100.0	32.0	2.8	5.8
12.2	7.2	15.8	22.6	3.9	9.1	32.5	2.8	8.9
13.0	6.8	23.9	23.9	3.7	13.4	34.0	2.6	6.0
14.7	6.0	14.6	24.6	3.6	29.2	34.8	2.6	6.9
16.8	5.3	99.5	27.2	3.3	10.5	35.2	2.5	8.8
17.6	5.0	11.7	27.7	3.2	6.1	37.0	2.4	6.9
18.3	4.8	7.0	28.8	3.1	8.0	37.5	2.4	8.6
19.0	4.7	14.4	29.4	3.0	5.3	38.2	2.4	6.5
19.4	4.6	28.4	29.8	3.0	15.9	-	-	-

Table II sets forth the 2θ, d-spacings and relative intensities representative of Form A. The numbers as listed are computer-generated.

Table II. Intensities and Peak Locations Representative of L-Tartrate Form A.

Angle 2θ	d-value (Å)	I (rel.)
6.1	14.5	73.3
12.2	7.2	15.8
13.0	6.8	23.9
14.7	6.0	14.6
16.8	5.3	99.5
19.4	4.6	28.4
21.9	4.1	100.0
24.6	3.6	29.2

The x-ray powder diffraction pattern of the salt Form B was measured with the same equipment and under that same parameters used above for the measurement of Form A. The diffraction peaks at diffraction angles (2θ) in a measured powder X-ray diffraction analysis for the Form B are shown in Table III. Again, the relative intensities, however, may

change depending on the crystal size and morphology. The actual measured powder diffractogram is displayed in Figure 2.

Table III. Powder X-ray Diffraction Pattern for L-Tartrate Form B with Intensities and Peak Locations of Diffraction Lines.

Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)
5.9	15.0	57.0	19.1	4.6	11.1	29.1	3.1	8.6
11.7	7.5	8.2	20.7	4.3	6.3	29.7	3.0	4.9
12.8	6.9	27.2	21.1	4.2	6.0	31.9	2.8	11.9
14.4	6.1	23.2	21.8	4.1	100.0	34.6	2.6	7.2
15.3	5.8	4.9	23.8	3.7	26.9	34.9	2.6	5.5
16.4	5.4	23.0	24.3	3.7	10.5	35.6	2.5	5.0
16.9	5.2	41.8	25.1	3.5	15.8	37.3	2.4	5.4
17.2	5.2	49.3	25.8	3.4	11.4	38.8	2.3	5.4
17.8	5.0	6.8	26.9	3.3	6.6	-	-	-
18.7	4.7	5.6	27.8	3.2	8.7	-	-	-

Table IV sets forth the 2θ, d-spacings, and relative intensities representative of Form B. The numbers as listed are computer-generated.

Table IV. Intensities and Peak Locations Representative of L-Tartrate Form B.

Angle 2θ	d-value (Å)	I (rel.)
5.9	15.0	57.0
12.8	6.9	27.2
14.4	6.1	23.2
15.3	5.8	4.9
16.9	5.2	41.8
17.2	5.2	49.3
21.8	4.1	100.0
23.8	3.7	26.9
25.1	3.5	15.8

The x-ray powder diffraction pattern of the salt Form C was measured with the same equipment and under that same parameters used above for the measurement of Form A. The diffraction peaks at diffraction angles (2θ) in a measured powder X-ray diffraction analysis for the Form C are shown in Table V. Again, the relative intensities, however, may change depending on the crystal size and morphology. The actual measured powder diffractogram is displayed in Figure 3.

Table V. Powder X-ray Diffraction Pattern for L-Tartrate Form C with Intensities and Peak Locations of Diffraction Lines.

Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)
5.9	15.1	85.5	23.8	3.7	78.5	32.1	2.8	8.7
11.8	7.5	49.4	26.1	3.4	11.6	33.5	2.7	5.9
13.1	6.8	14.4	26.5	3.4	65.8	35.8	2.5	10.0
14.5	6.1	9.2	27.0	3.3	9.6	36.0	2.5	13.0
16.5	5.4	97.4	27.9	3.2	5.8	37.0	2.4	5.7
17.5	5.1	10.0	28.9	3.1	9.5	37.9	2.4	11.5
18.8	4.7	7.0	29.3	3.0	27.3	-	-	-
20.3	4.4	8.2	29.9	3.0	33.0	-	-	-
21.2	4.2	100.0	31.3	2.9	6.7	-	-	-
23.1	3.8	35.0	31.6	2.8	9.0	-	-	-

Table VI sets forth the 2θ, d-spacings, and relative intensities representative of Form C. The numbers as listed are computer-generated.

Table VI. Intensities and Peak Locations Representative of L-Tartrate Form C.

Angle 2θ	d-value (Å)	I (rel.)
5.9	15.1	85.5
11.8	7.5	49.4
16.5	5.4	97.4
21.2	4.2	100.0
23.1	3.8	35.0
23.8	3.7	78.5
26.5	3.4	65.8

As shown in Figure 6, the overlay of the observed x-ray powder diffraction patterns for L-tartrate salt Forms A, B and C shows some x-ray powder diffraction peak shifting and that each Form has a distinctive powder pattern fingerprint.

The x-ray powder diffraction pattern of the D,L-tartrate salt Form X (anhydrous) was measured with the same equipment and under that same parameters used above for the measurement of Form A, L-tartrate salt. The diffraction peaks at diffraction angles (2θ) in a measured powder X-ray diffraction analysis for the Form X are shown in Table VII. Again, the relative intensities, however, may change depending on the crystal size and morphology. The actual measured powder diffractogram is displayed in Figure 10A.

Table VII. Powder X-ray Diffraction Pattern for D,L-Tartrate Form X with Intensities and Peak Locations of Diffraction Lines.

Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)
6.0	14.6	100.0	18.3	4.8	10.3	27.5	3.2	3.7
10.9	8.1	3.8	18.7	4.8	4.8	28.2	3.2	4.4
11.5	7.7	13.0	19.6	4.5	6.0	31.8	2.8	11.7
11.9	7.4	38.0	22.1	4.0	49.5	37.2	2.4	4.0
13.6	6.5	18.4	24.5	3.6	24.5	37.3	2.4	3.7
14.1	6.3	8.8	25.3	3.5	4.3			
15.0	5.9	27.6	25.6	3.5	3.9			
17.1	5.2	49.2	26.4	3.4	11.8			

Table VIII sets forth the 2θ, d-spacings, and relative intensities representative of Form X. The numbers as listed are computer-generated.

Table VIII. Intensities and Peak Locations Representative of D,L-Tartrate Form X.

Angle 2θ	d-value (Å)	I (rel.)
6.0	14.6	100.0
11.9	7.4	38.0
15.0	5.9	27.6
17.1	5.2	49.2
22.1	4.0	49.5
24.5	3.6	24.5

The x-ray powder diffraction pattern of the D,L-tartrate salt Form Y (hydrate) was measured with the same equipment and under that same parameters used above for the measurement of Form A, L-tartrate salt. The diffraction peaks at diffraction angles (2θ) in a measured powder X-ray diffraction analysis for the Form Y are shown in Table IX. Again, the relative intensities, however, may change depending on the crystal size and morphology. The actual measured powder diffractogram is displayed in Figure 10B.

Table IX. Powder X-ray Diffraction Pattern for D,L-Tartrate Form Y with Intensities and Peak Locations of Diffraction Lines.

Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)
4.1	21.4	5.2	17.3	5.1	18.6	26.1	3.4	8.5
6.2	14.2	100.0	18.1	4.9	32.2	27.5	3.2	17.9
10.9	8.1	7.8	18.7	4.7	7.1	29.3	3.0	7.4
11.5	7.7	23.1	19.9	4.5	24.7	29.7	3.0	8.4
12.0	7.4	39.1	21.1	4.2	7.0	30.3	2.9	11.7
12.5	7.1	4.6	21.7	4.1	11.0	31.5	2.8	17.4
13.5	6.5	16.6	22.5	4.0	5.4	35.8	2.5	6.4
14.4	6.1	14.7	23.2	3.8	12.2	36.7	2.4	4.5
15.0	5.9	16.4	24.0	3.7	52.7	37.3	2.4	4.6
15.2	5.8	32.7	25.1	3.5	75.1	39.1	2.3	5.4
15.6	5.7	9.6	25.5	3.5	10.3			

Table X sets forth the 2θ, d-spacings and relative intensities of Form Y. The numbers as listed are computer-generated.

Table X. Intensities and Peak Locations Representative of D,L-Tartrate Form Y.

Angle 2θ	d-value (Å)	I (rel.)
6.2	14.2	100.0
12.0	7.4	39.1
15.2	5.8	32.7
18.1	4.9	32.2
24.0	3.7	52.7
25.1	3.5	75.1

Single Crystal X-ray Analysis

Single crystals for the L-tartrate salt Forms B and C were obtained and investigated by X-ray diffraction. For each form, a representative crystal was surveyed and a 1Å data set (maximum sin Θ/λ=0.5) was collected on a Siemens R4RA/v diffractometer. Atomic scattering factors were taken from the International Tables for X-Ray Crystallography, Vol. IV, pp. 55, 99 and 149 (Birmingham: Kynoch Press, 1974). Single crystal X-ray data were collected at room temperature. All crystallographic calculations were facilitated by the SHELXTL™ system (SHELXTL™ Reference Manual, Version 5.1, Bruker AXS, Madison, WI 1997). The pertinent crystal data collection and refinement are summarized in Table XI below for Form B and in Table XII below for Form C.

For both Forms, the trial structure was obtained by direct methods and was then refined routinely. A difference map revealed two waters of crystallization – one for each salt molecule. Hydrogen positions were calculated wherever possible. The hydrogens on nitrogen and oxygen were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycles of least squares refinement were all less than 0.1 of the corresponding standard deviations. For Form B, the final R-index was 3.25%. For Form C, the final R-index was 3.47%. A final difference Fourier revealed no missing or misplaced electron density. The refined structure was plotted using the SHELXTL plotting package and is shown in Figure 8A (Form B) and 8B (Form C). The absolute configuration was based on the use of L(+)-tartaric acid.

Table XIII sets forth the atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x\ 10^3$) for Form B. Table XIV lists the observed bond lengths [Å] and angles [°] for Form B. In Table XV, the anisotropic displacement parameters ($Å^2x\ 10^3$) for Form B are set forth to allow calculation of the anisotropic displacement factor exponent which has the form: $-2\pi^2[\ h^2\ a^{*2}U_{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$. Finally, in Table XVI, below, hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2x\ 10^3$) for Form B are listed.

Table XVII sets forth the atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x\ 10^3$) for Form C. Table XVIII lists the observed bond lengths [Å] and angles [°] for Form C. In Table XIX, the anisotropic displacement parameters ($Å^2x\ 10^3$) for Form C are set forth to allow calculation of the anisotropic displacement factor exponent which has the form: $-2\pi^2[\ h^2\ a^{*2}U_{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$. Finally, in Table XX, below, hydrogen Coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2x\ 10^3$) for Form C are listed.

Table XI. Crystal Structure Data and Measurement Parameters: L-Tartrate Salt Form B

Parameter	L-Tartrate Form B
Empirical formula	$C_{13}H_{14}N_3^+C_4H_5O_6^-$
Formula weight	361.35
Crystal System	Orthorhombic
Space Group	P2(1)2(1)2(1)
Crystal Size, mm^3	0.01 x 0.08 x 0.10
a	7.0753(5) Å
b	7.7846(5) Å
c	29.870(2) Å
α	90°
γ	90°
β	90°
Volume	1645.21(19) $Å^3$
Density calc'd, ρ	1.459 g/cm^3
Z	4
Temperature	298(2) K
Wavelength	1.54178 Å
Absorption coefficient	0.944 mm^{-1}
F(000)	760
Reflections collected	3490
Independent reflections	1318 [R(int) = 0.0542]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1318 / 0 / 251
Goodness-of-fit on F^2	0.856
Final R indices [I>2sigma(I)]	R1 = 0.0325, wR2 = 0.0638
Absolute structure parameter	0.0031(3)
Largest diff. peak and hole	0.115 and -0.150 $e.Å^{-3}$

Table XII. Crystal Structure Data and Measurement Parameters: L-Tartrate Salt Form C

Parameter	L-Tartrate Hydrate Form C
Empirical formula	$C_{13}H_{14}N_3^+C_4H_5O_6^-\cdot H_2O$
Formula weight	379.37
Crystal System	Monoclinic
Space Group	P2(1)
Crystal Size, mm^3	0.04 x 0.38 x 0.30
X-ray Code	F611
a	7.5120Å
b	29.854Å
c	7.671Å
α	90°
γ	90°
β	90.40°
Volume	1720.3$Å^3$
Density calc'd, ρ	1.465g/cm^3
Z	4
Temperature	298(2) K
Wavelength	1.54178 Å
Absorption coefficient	0.974 mm^{-1}
F(000)	800
Reflections collected	1983
Independent reflections	1817 [R(int) = 0.0224]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1817 / 0 / 528
Goodness-of-fit on F^2	1.028
Final R indices [I>2sigma(I)]	R1 = 0.0347, wR2 = 0.0834
Absolute structure parameter	0.0(3)
Largest diff. peak and hole	0.168 and -0.230 e.$Å^{-3}$

Table XIII. Atomic Coordinates ($x10^4$) And Equivalent Isotropic Displacement Parameters ($Å^2x10^3$) For Form B. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
N(1)	8211(8)	10638(7)	12233(1)	61(1)
C(2)	8968(8)	9093(11)	12235(2)	72(2)
C(3)	8093(11)	7629(9)	12047(2)	75(2)
N(4)	6431(8)	7715(6)	11853(1)	64(1)
C(5)	5624(9)	9313(8)	11834(2)	50(1)
C(6)	6502(8)	10752(9)	12025(2)	49(1)
C(7)	5676(8)	12396(7)	11985(1)	48(1)
C(8)	4007(8)	12557(6)	11762(2)	41(1)
C(9)	3107(7)	11097(7)	11572(1)	42(1)
C(10)	3890(8)	9495(7)	11605(1)	49(1)
C(11)	2865(7)	14122(6)	11634(1)	44(1)
C(12)	891(6)	13347(6)	11573(1)	53(1)
C(13)	1397(7)	11686(6)	11315(1)	46(1)
C(14)	3510(6)	14823(6)	11182(1)	43(1)
N(15)	3597(5)	13405(5)	10838(1)	39(1)
C(16)	1962(6)	12183(5)	10838(1)	46(1)
C(20)	7858(9)	6393(6)	10523(1)	37(1)
O(21)	9522(5)	6116(4)	10603(1)	47(1)
O(22)	6680(4)	5324(4)	10349(1)	47(1)
C(23)	7033(6)	8162(5)	10623(1)	32(1)
O(24)	5062(4)	8318(4)	10542(1)	44(1)
C(25)	8063(6)	9486(5)	10339(1)	31(1)
O(26)	7763(4)	9176(4)	9873(1)	35(1)
C(27)	7520(6)	11321(6)	10465(2)	35(1)
O(28)	7065(4)	11655(4)	10852(1)	43(1)
O(29)	7681(4)	12417(4)	10148(1)	47(1)

Table XIV. Bond lengths [Å] and angles [°] for L-Tartrate Form B.

Bond Lengths			
N(1)-C(2)	1.316(6)	C(11)-C(12)	1.532(6)
N(1)-C(6)	1.362(6)	C(12)-C(13)	1.547(6)
C(2)-C(3)	1.413(7)	C(13)-C(16)	1.531(5)
C(3)-N(4)	1.314(7)	C(14)-N(15)	1.510(5)
N(4)-C(5)	1.370(6)	N(15)-C(16)	1.498(5)
C(5)-C(10)	1.411(6)	C(20)-O(21)	1.221(5)
C(5)-C(6)	1.403(7)	C(20)-O(22)	1.288(5)
C(6)-C(7)	1.412(6)	C(20)-C(23)	1.525(6)
C(7)-C(8)	1.361(6)	C(23)-O(24)	1.420(5)
C(8)-C(9)	1.421(6)	C(23)-C(25)	1.521(5)
C(8)-C(11)	1.511(6)	C(25)-O(26)	1.428(5)
C(9)-C(10)	1.368(6)	C(25)-C(27)	1.526(6)
C(9)-C(13)	1.504(6)	C(27)-O(28)	1.227(5)
C(11)-C(14)	1.526(5)	C(27)-O(29)	1.281(5)

Bond Angles			
C(2)-N(1)-C(6)	115.0(5)	C(14)-C(11)-C(12)	107.9(3)
N(1)-C(2)-C(3)	123.9(5)	C(11)-C(12)-C(13)	100.2(3)
N(4)-C(3)-C(2)	121.8(5)	C(9)-C(13)-C(16)	110.0(4)
C(3)-N(4)-C(5)	116.0(5)	C(9)-C(13)-C(12)	100.8(4)
N(4)-C(5)-C(10)	118.3(6)	C(16)-C(13)-C(12)	108.2(4)
N(4)-C(5)-C(6)	121.5(6)	N(15)-C(14)-C(11)	110.6(4)
C(10)-C(5)-C(6)	120.2(6)	C(16)-N(15)-C(14)	115.7(3)
N(1)-C(6)-C(5)	121.8(6)	N(15)-C(16)-C(13)	111.2(3)
N(1)-C(6)-C(7)	117.8(6)	O(21)-C(20)-O(22)	126.1(5)
C(5)-C(6)-C(7)	120.3(5)	O(21)-C(20)-C(23)	119.4(5)
C(8)-C(7)-C(6)	119.0(5)	O(22)-C(20)-C(23)	114.5(5)
C(7)-C(8)-C(9)	120.7(5)	O(24)-C(23)-C(25)	108.5(3)
C(7)-C(8)-C(11)	131.5(5)	O(24)-C(23)-C(20)	114.8(4)
C(9)-C(8)-C(11)	107.7(4)	C(25)-C(23)-C(20)	108.6(3)
C(10)-C(9)-C(8)	121.2(5)	O(26)-C(25)-C(23)	111.0(3)
C(10)-C(9)-C(13)	129.8(5)	O(26)-C(25)-C(27)	111.2(3)
C(8)-C(9)-C(13)	108.7(5)	C(23)-C(25)-C(27)	112.0(4)
C(9)-C(10)-C(5)	118.6(5)	O(28)-C(27)-O(29)	125.4(4)
C(8)-C(11)-C(14)	110.7(4)	O(28)-C(27)-C(25)	119.8(4)
C(8)-C(11)-C(12)	101.6(4)	O(29)-C(27)-C(25)	114.7(4)

Table XV. Anisotropic Displacement Parameters ($Å^2 x\ 10^3$) For Form B. (The Anisotropic displacement factor exponent takes the form: $-2\pi 2[\ h^2\ a^{*2} U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$).

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N(1)	63(4)	70(4)	50(3)	12(2)	-2(3)	8(3)
C(2)	54(4)	114(6)	49(4)	20(4)	-3(3)	8(5)
C(3)	79(5)	78(5)	66(4)	14(4)	-6(4)	30(5)
N(4)	78(4)	54(4)	60(3)	8(3)	-9(3)	13(3)
C(5)	65(4)	45(4)	39(3)	5(3)	-3(3)	6(4)
C(6)	41(4)	69(5)	36(3)	8(3)	-9(3)	1(4)
C(7)	51(4)	56(5)	38(3)	3(3)	-2(3)	-5(4)
C(8)	45(4)	41(4)	38(3)	4(3)	1(3)	-3(4)
C(9)	46(4)	40(4)	40(3)	12(3)	9(3)	-4(4)
C(10)	54(4)	52(5)	41(3)	8(3)	-5(3)	-14(4)
C(11)	49(3)	43(3)	38(3)	-1(3)	1(3)	-1(3)
C(12)	45(4)	63(4)	50(3)	6(3)	7(3)	3(3)
C(13)	42(3)	49(3)	48(3)	11(3)	-3(3)	-4(3)
C(14)	43(3)	39(3)	46(3)	-3(3)	2(2)	-1(3)
N(15)	35(3)	41(3)	40(2)	7(2)	3(2)	-2(2)
C(16)	42(3)	51(3)	44(3)	6(3)	-4(3)	-2(3)
C(20)	48(4)	30(4)	33(3)	9(3)	10(3)	-6(4)
O(21)	30(2)	41(2)	68(2)	3(2)	-5(2)	7(2)
O(22)	44(2)	22(2)	73(2)	-5(2)	-2(2)	2(2)
C(23)	26(3)	28(3)	42(3)	0(2)	7(2)	0(3)
O(24)	33(2)	33(2)	68(2)	-10(2)	4(2)	1(2)
C(25)	35(3)	25(3)	32(3)	-7(2)	-1(2)	4(3)
O(26)	35(2)	32(2)	38(2)	-5(1)	3(2)	-1(2)
C(27)	22(3)	40(4)	42(4)	-7(3)	-8(3)	1(3)
O(28)	53(2)	36(2)	41(2)	-7(2)	2(2)	2(2)
O(29)	74(2)	27(2)	41(2)	5(2)	7(2)	4(2)

Table XVI. Hydrogen Coordinates ($x10^4$) And Isotropic Displacement Parameters ($Å^2x10^3$) For Form B.

	x	y	z	U(eq)
H(2A)	10149	8958	12367	80
H(3A)	8710	6576	12062	80
H(7A)	6264	13354	12108	80
H(10A)	3292	8546	11480	80
H(11A)	2887	15004	11868	80
H(12A)	76	14092	11398	80
H(12B)	295	13097	11858	80
H(13A)	372	10840	11321	80
H(14A)	2636	15704	11082	80
H(14B)	4748	15344	11213	80
H(15A)	3600(70)	14000(60)	10578(14)	80
H(15B)	4860(70)	12850(60)	10867(14)	80
H(16A)	2302	11156	10672	80
H(16B)	894	12713	10688	80
H(23A)	7270	8427	10939	80
H(24A)	4680(70)	7400(60)	10401(15)	80
H(25A)	9419	9355	10397	80
H(26A)	6710(70)	9120(70)	9841(17)	80
H(29A)	7180(60)	13930(80)	10298(14)	80

Table XVII. Atomic Coordinates ($x10^4$) And Equivalent Isotropic Displacement Parameters ($Å^2x10^3$) For Form C. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
N(1)	-159(7)	10186(3)	-1642(7)	45(1)
C(2)	-239(10)	10333(3)	-58(10)	52(2)
C(3)	1241(10)	10446(3)	959(9)	50(2)
N(4)	2878(7)	10415(3)	368(6)	42(1)
C(5)	3033(8)	10257(3)	-1310(8)	33(2)
C(6)	1520(7)	10141(3)	-2302(8)	30(2)
C(7)	1723(7)	9967	-4007(7)	32(2)
C(8)	3381(7)	9902(3)	-4622(7)	25(1)
C(9)	4905(7)	10018(3)	-3648(7)	25(1)
C(10)	4759(8)	10194(3)	-2016(8)	36(2)
C(11)	6537(7)	9881(3)	-4655(7)	31(2)
C(12)	7003(7)	9395(3)	-4191(7)	33(2)
N(13)	5380(6)	9102(3)	-4292(6)	27(1)
C(14)	4292(7)	9171(3)	-5922(7)	29(1)
C(15)	4011(7)	9668(3)	-6277(7)	28(1)
C(16)	5826(8)	9887(3)	-6550(8)	41(2)
C(1X)	1541(7)	7444(3)	-5634(8)	23(1)
O(2X)	1182(4)	7444(2)	-7182(5)	36(1)
O(3X)	361(5)	7474(2)	-4418(5)	38(1)
C(4X)	3457(6)	7425(3)	-4997(7)	24(1)
O(5X)	3649(5)	7280(2)	-3247(5)	32(1)
C(6X)	4282(7)	7881(3)	-5336(7)	25(1)
O(7X)	3348(4)	8230(2)	-4482(5)	28(1)
C(8X)	6296(7)	7900(3)	-4948(7)	22(1)
O(9X)	7172(5)	7560(2)	-5428(5)	37(1)
O(10X)	6935(5)	8241(2)	-4266(5)	35(1)
O(1W)	3226(6)	7996(2)	-924(5)	37(1)
N(51)	3493(6)	6295(3)	3311(7)	43(1)
C(52)	3598(9)	6141(3)	4922(9)	47(2)
C(53)	2144(9)	6031(3)	5890(8)	45(2)
N(54)	494(7)	6065(3)	5313(7)	43(1)
C(55)	289(8)	6228(3)	3651(7)	30(1)
C(56)	1799(7)	6340(3)	2642(8)	30(2)
C(57)	1574(8)	6528(2)	950(8)	32(2)
C(58)	-95(8)	6593(3)	320(7)	27(1)
C(59)	-1609(7)	6472(2)	1339(7)	25(1)
C(60)	-1436(7)	6295(3)	2965(9)	35(2)
C(61)	-3249(8)	6621(3)	334(8)	32(2)
C(62)	-3717(7)	7097(3)	850(7)	33(2)
N(63)	-2088(6)	7392(3)	720(6)	26(1)
C(64)	-1014(7)	7329(3)	-916(6)	29(1)
C(65)	-765(7)	6828(3)	-1308(7)	30(1)
C(66)	-2599(8)	6612(3)	-1564(7)	36(2)
C(1Y)	-2999(7)	8598(3)	27(7)	26(1)
O(2Y)	-3633(5)	8257(2)	745(5)	35(1)
O(3Y)	-3884(5)	8934(2)	-462(5)	34(1)
C(4Y)	-986(6)	8611(3)	-356(7)	20(1)
O(5Y)	-53(4)	8261(2)	523(5)	28(1)
C(6Y)	-163(7)	9070(3)	-16(7)	23(1)
O(7Y)	-328(5)	9219(2)	1725(5)	33(1)
C(8Y)	1746(7)	9048(3)	-658(8)	24(1)
O(9Y)	2954(5)	9023(2)	572(5)	36(1)
O(10Y)	2085(5)	9039(2)	-2209(5)	37(1)
O(2W)	54(6)	8500(2)	4066(5)	39(1)

Table XVIII. Bond lengths [Å] and angles [°] for L-Tartrate Form C.

Bond Lengths (Form C)			
N(1)-C(2)	1.294(8)	N(51)-C(52)	1.320(8)
N(1)-C(6)	1.369(7)	N(51)-C(56)	1.375(7)
C(2)-C(3)	1.396(10)	C(52)-C(53)	1.365(9)
C(3)-N(4)	1.316(8)	C(53)-N(54)	1.317(8)
N(4)-C(5)	1.377(8)	N(54)-C(55)	1.373(8)
C(5)-C(6)	1.407(8)	C(55)-C(60)	1.410(8)
C(5)-C(10)	1.421(9)	C(55)-C(56)	1.417(8)
C(6)-C(7)	1.417(8)	C(56)-C(57)	1.424(8)
C(7)-C(8)	1.349(8)	C(57)-C(58)	1.355(8)
C(8)-C(9)	1.407(8)	C(58)-C(59)	1.431(8)
C(8)-C(15)	1.526(8)	C(58)-C(65)	1.514(8)
C(9)-C(10)	1.362(8)	C(59)-C(60)	1.360(8)
C(9)-C(11)	1.511(8)	C(59)-C(61)	1.515(8)
C(11)-C(12)	1.534(8)	C(61)-C(62)	1.518(9)
C(11)-C(16)	1.545(8)	C(61)-C(66)	1.539(8)
C(12)-N(13)	1.501(7)	C(62)-N(63)	1.511(7)
N(13)-C(14)	1.504(6)	N(63)-C(64)	1.508(6)
C(14)-C(15)	1.525(8)	C(64)-C(65)	1.537(8)
C(15)-C(16)	1.528(8)	C(65)-C(66)	1.533(8)
C(1X)-O(2X)	1.216(6)	C(1Y)-O(3Y)	1.259(7)
C(1X)-O(3X)	1.295(6)	C(1Y)-O(2Y)	1.254(7)
C(1X)-C(4X)	1.518(7)	C(1Y)-C(4Y)	1.543(8)
C(4X)-O(5X)	1.417(6)	C(4Y)-O(5Y)	1.424(6)
C(4X)-C(6X)	1.517(8)	C(4Y)-C(6Y)	1.526(8)
C(6X)-O(7X)	1.419(7)	C(6Y)-O(7Y)	1.413(7)
C(6X)-C(8X)	1.541(7)	C(6Y)-C(8Y)	1.521(8)
C(8X)-O(10X)	1.240(7)	C(8Y)-O(10Y)	1.219(6)
C(8X)-O(9X)	1.267(7)	C(8Y)-O(9Y)	1.306(7)
Bond Angles (Form C)			
C(2)-N(1)-C(6)	115.5(6)	C(52)-N(51)-C(56)	115.6(5)
N(1)-C(2)-C(3)	124.4(7)	N(51)-C(52)-C(53)	123.4(6)
N(4)-C(3)-C(2)	122.2(6)	N(54)-C(53)-C(52)	123.6(6)
C(3)-N(4)-C(5)	115.6(5)	C(53)-N(54)-C(55)	116.0(5)
N(4)-C(5)-C(6)	121.1(6)	N(54)-C(55)-C(60)	119.6(5)
N(4)-C(5)-C(10)	119.0(5)	N(54)-C(55)-C(56)	120.4(5)
C(6)-C(5)-C(10)	119.8(6)	C(60)-C(55)-C(56)	120.0(5)
N(1)-C(6)-C(5)	121.3(6)	N(51)-C(56)-C(55)	121.0(6)
N(1)-C(6)-C(7)	118.9(5)	N(51)-C(56)-C(57)	118.8(5)
C(5)-C(6)-C(7)	119.9(5)	C(55)-C(56)-C(57)	120.1(5)
C(8)-C(7)-C(6)	118.8(5)	C(58)-C(57)-C(56)	119.0(5)
C(7)-C(8)-C(9)	121.9(5)	C(57)-C(58)-C(59)	120.4(5)
C(7)-C(8)-C(15)	130.5(5)	C(57)-C(58)-C(65)	131.4(5)
C(9)-C(8)-C(15)	107.4(5)	C(59)-C(58)-C(65)	107.9(5)
C(10)-C(9)-C(8)	120.9(5)	C(60)-C(59)-C(58)	121.9(5)
C(10)-C(9)-C(11)	130.2(5)	C(60)-C(59)-C(61)	130.8(5)
C(8)-C(9)-C(11)	108.7(5)	C(58)-C(59)-C(61)	107.1(5)
C(9)-C(10)-C(5)	118.7(5)	C(59)-C(60)-C(55)	118.7(5)
C(9)-C(11)-C(12)	108.9(5)	C(59)-C(61)-C(62)	109.2(5)
C(9)-C(11)-C(16)	101.6(5)	C(59)-C(61)-C(66)	102.4(5)
C(12)-C(11)-C(16)	107.9(5)	C(62)-C(61)-C(66)	109.8(5)
N(13)-C(12)-C(11)	110.8(5)	N(63)-C(62)-C(61)	109.8(5)
C(14)-N(13)-C(12)	113.6(4)	C(64)-N(63)-C(62)	114.9(4)
Bond Angles (Form C)			

N(13)-C(14)-C(15)	110.8(4)	N(63)-C(64)-C(65)	110.6(4)
C(16)-C(15)-C(14)	108.6(5)	C(58)-C(65)-C(66)	101.8(4)
C(16)-C(15)-C(8)	101.6(4)	C(58)-C(65)-C(64)	109.1(4)
C(14)-C(15)-C(8)	109.8(4)	C(66)-C(65)-C(64)	108.9(5)
C(15)-C(16)-C(11)	99.7(4)	C(65)-C(66)-C(61)	99.3(4)
O(2X)-C(1X)-O(3X)	123.7(5)	O(3Y)-C(1Y)-O(2Y)	125.2(5)
O(2X)-C(1X)-C(4X)	121.2(5)	O(3Y)-C(1Y)-C(4Y)	116.1(5)
O(3X)-C(1X)-C(4X)	115.1(5)	O(2Y)-C(1Y)-C(4Y)	118.7(5)
O(5X)-C(4X)-C(6X)	113.4(4)	O(5Y)-C(4Y)-C(6Y)	112.3(4)
O(5X)-C(4X)-C(1X)	114.0(4)	O(5Y)-C(4Y)-C(1Y)	111.8(4)
C(6X)-C(4X)-C(1X)	107.5(4)	C(6Y)-C(4Y)-C(1Y)	112.7(4)
O(7X)-C(6X)-C(4X)	112.0(4)	O(7Y)-C(6Y)-C(8Y)	114.1(4)
O(7X)-C(6X)-C(8X)	111.8(4)	O(7Y)-C(6Y)-C(4Y)	113.9(4)
C(4X)-C(6X)-C(8X)	113.7(4)	C(8Y)-C(6Y)-C(4Y)	106.7(4)
O(10X)-C(8X)-O(9X)	125.6(5)	O(10Y)-C(8Y)-O(9Y)	123.7(5)
O(10X)-C(8X)-C(6X)	119.3(5)	O(10Y)-C(8Y)-C(6Y)	121.4(5)
O(9X)-C(8X)-C(6X)	115.1(5)	O(9Y)-C(8Y)-C(6Y)	114.9(5)

Table XIX. Anisotropic Displacement Parameters ($Å^2 x\ 10^3$) For Form C. (The Anisotropic displacement factor exponent takes the form: $-2\pi 2[\ h^2\ a^{*2}U_{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$).

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N(1)	42(4)	46(4)	46(4)	-8(3)	4(3)	0(3)
C(2)	53(5)	51(5)	52(5)	-5(4)	9(4)	3(4)
C(3)	63(5)	40(4)	49(4)	-2(4)	19(4)	11(4)
N(4)	59(4)	30(3)	37(3)	-8(3)	-7(3)	11(3)
C(5)	44(4)	19(3)	35(4)	1(3)	-8(3)	9(3)
C(6)	27(3)	25(4)	39(4)	1(3)	3(3)	3(3)
C(7)	30(4)	36(4)	30(4)	-1(3)	-10(3)	4(3)
C(8)	28(4)	27(3)	19(3)	1(2)	-4(3)	3(3)
C(9)	27(3)	20(3)	29(4)	4(3)	-9(3)	0(3)
C(10)	33(4)	32(4)	44(4)	-8(3)	-14(3)	-4(3)
C(11)	30(3)	26(4)	38(4)	0(3)	-1(3)	-6(3)
C(12)	22(3)	44(4)	34(3)	0(3)	0(3)	0(3)
N(13)	27(3)	32(3)	21(3)	1(2)	0(2)	1(2)
C(14)	26(3)	34(4)	27(3)	-4(3)	-11(3)	-1(3)
C(15)	24(3)	29(4)	30(3)	7(3)	-5(3)	-2(3)
C(16)	42(4)	41(4)	39(4)	5(3)	7(3)	-2(3)
C(1X)	23(3)	19(3)	28(4)	-1(3)	8(3)	1(3)
O(2X)	28(2)	56(3)	25(2)	-7(2)	-2(2)	-1(2)
O(3X)	19(2)	69(3)	26(2)	8(2)	5(2)	2(2)
C(4X)	19(3)	30(3)	24(3)	5(3)	-1(2)	1(3)
O(5X)	29(2)	34(2)	33(2)	5(2)	-5(2)	8(2)
C(6X)	20(3)	28(3)	26(3)	-1(3)	2(2)	1(3)
O(7X)	21(2)	25(2)	36(2)	-3(2)	5(2)	4(2)
C(8X)	21(3)	30(4)	16(3)	-2(3)	1(2)	5(3)
O(9X)	19(2)	43(3)	49(3)	-10(2)	-1(2)	4(2)
O(10X)	26(2)	35(3)	45(2)	-10(2)	-7(2)	-1(2)
O(1W)	28(2)	47(3)	35(2)	-9(2)	1(2)	-1(2)
N(51)	29(3)	47(4)	54(4)	7(3)	-3(3)	8(3)
C(52)	44(4)	46(4)	51(5)	11(4)	-9(4)	4(3)
C(53)	50(5)	48(4)	35(4)	2(3)	-4(3)	10(4)
N(54)	53(4)	40(3)	37(3)	4(3)	5(3)	8(3)
C(55)	34(4)	28(3)	27(3)	5(3)	4(3)	3(3)
C(56)	28(4)	25(3)	36(4)	-5(3)	2(3)	2(3)
C(57)	30(4)	34(4)	32(4)	4(3)	7(3)	3(3)
C(58)	32(4)	24(4)	24(3)	-1(3)	5(3)	-1(3)
C(59)	22(3)	21(3)	33(4)	0(3)	1(3)	-2(3)
C(60)	25(3)	32(4)	49(4)	3(3)	10(3)	-3(3)
C(61)	26(3)	30(4)	40(4)	2(3)	-6(3)	-6(3)
C(62)	25(3)	35(4)	38(4)	4(3)	0(3)	-2(3)
N(63)	25(3)	27(3)	27(3)	-2(2)	5(2)	1(2)
C(64)	36(3)	33(4)	18(3)	2(3)	8(3)	1(3)
C(65)	35(3)	33(4)	21(3)	-5(3)	3(3)	6(3)
C(66)	42(4)	32(4)	33(4)	-6(3)	-6(3)	2(3)
C(1Y)	23(3)	38(4)	17(3)	-1(3)	-6(2)	0(3)
O(2Y)	21(2)	42(3)	43(2)	11(2)	5(2)	-2(2)
O(3Y)	19(2)	41(3)	44(3)	11(2)	3(2)	8(2)
C(4Y)	18(3)	22(3)	21(3)	3(2)	-1(2)	4(3)
O(5Y)	21(2)	31(2)	30(2)	3(2)	-2(2)	4(2)
C(6Y)	23(3)	30(3)	17(3)	4(3)	1(2)	7(3)
O(7Y)	32(2)	37(3)	31(3)	-3(2)	6(2)	7(2)
C(8Y)	23(3)	16(3)	33(4)	3(3)	-2(3)	-4(2)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(9Y)	19(2)	61(3)	27(2)	-9(2)	-6(2)	5(2)
O(10Y)	28(2)	57(3)	24(2)	4(2)	6(2)	1(2)
O(2W)	32(2)	50(3)	35(3)	7(2)	-2(2)	3(2)

Table XX. Hydrogen Coordinates ($x10^4$) And Isotropic Displacement Parameters ($Å^2x10^3$) For Form C.

	x	y	z	U(eq)
H(2)	-1359	10366	435	80
H(3)	1066	10546	2094	80
H(7)	732	9899	-4690	80
H(10)	5770	10272	-1377	80
H(11)	7541	10086	-4476	80
H(12A)	7896	9284	-4990	80
H(12B)	7499	9383	-3021	80
H(13X)	5710(100)	8750(30)	-4290(90)	80
H(13Y)	4660(100)	9130(30)	-3380(100)	80
H(14A)	3147	9025	-5797	80
H(14B)	4897	9035	-6903	80
H(15)	3202	9720	-7264	80
H(16A)	5715	10190	-6996	80
H(16B)	6570	9712	-7324	80
H(3XX)	-980(110)	7490(30)	-4900(90)	80
H(4X)	4082	7208	-5730	80
H(5XX)	3350(100)	7550(30)	-2600(100)	80
H(6X)	4144	7936	-6589	80
H(7XX)	3230(100)	8210(30)	-3240(100)	80
H(1WX)	2060(110)	8070(30)	-390(90)	80
H(1WY)	4280(110)	8050(30)	-270(100)	80
H(52)	4720	6106	5423	80
H(53)	2329	5927	7019	80
H(57)	2559	6605	286	80
H(60)	-2435	6220	3610	80
H(61)	-4250	6416	511	80
H(62A)	-4647	7211	87	80
H(62B)	-4158	7101	2035	80
H(63X)	-2480(100)	7730(30)	650(90)	80
H(63Y)	-1300(100)	7360(30)	1730(100)	80
H(64A)	141	7470	-772	80
H(64B)	-1620	7471	-1889	80
H(65)	16	6777	-2307	80
H(66A)	-2509	6308	-2010	80
H(66B)	-3358	6788	-2329	80
H(4Y)	-860	8553	-1607	80
H(5YX)	-140(100)	8240(30)	1670(100)	80
H(6Y)	-797	9286	-757	80
H(7YX)	-100(110)	9020(30)	2280(100)	80
H(9YX)	4230(110)	8990(30)	40(90)	80
H(2WX)	1040(110)	8370(30)	4630(100)	80
H(2WY)	-990(110)	8380(30)	4830(100)	80

The powder X-ray diffraction patterns for Forms B and C were calculated from the respective single crystal data gathered for each L-tartrate salt form via the use of the XFOG and XPOW computer programs provided as part of the SHELXTL™ computer library. The calculated powder pattern for Form B is shown in Figure 4A. The calculated powder pattern for Form C is shown in Figure 4B.

A comparison of the observed Form B powder pattern and the calculated pattern results are displayed in the overlaid powder X-ray diffraction pattern of Figure 5A. The lower pattern trace corresponds to the calculated powder pattern (from single crystal results) and the upper pattern corresponds to a representative experimental powder pattern. The general match between the two patterns indicates the agreement between powder sample and the corresponding single crystal structure.

A comparison of the observed Form C powder pattern and the calculated pattern results are displayed in the overlaid powder X-ray diffraction pattern of Figure 5B. The lower pattern trace corresponds to the calculated powder pattern (from single crystal results) and the upper pattern corresponds to a representative experimental powder pattern. The general match between the two patterns indicates the agreement between powder sample and the corresponding single crystal structure.

Solid State NMR

Forms A, B and C of the L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene were characterized by solid state NMR techniques. Approximately 300 mg of a sample was tightly packed into 7mm ZrO spinner. The ^{13}C spectra were collected using cross-polarization magic angle spinning (CPMAS) at 295 K on Bruker 7mm WB MAS probe positioned into a wide-bore Bruker Avance DRX 500 MHz NMR spectrometer. The samples were spun at 7 kHz. The cross-polarization contact time was set to 1 ms. The total of 512 scans were acquired for most of the samples resulting in approximately 30 minute acquisition times. The spectra were referenced using external sample of adamantane with the most upfield methyl signal set to 29.5 ppm.

The resulting ^{13}C CPMAS spectra of Forms A, B and C are shown in Figures 7A, 7B and 7C, respectively. The samples behaved reasonably well from the point of view of solid state spectra quality. The resolution was good and the sensitivity was acceptable. The spectra features of all the compounds differ substantially from each other suggesting that solid state NMR can easily resolve the minor physical/chemical differences between the samples.

All the peaks marked with asterisks (*) are spinning sidebands in Figure 7A, 7B and 7C. The spinning sidebands are displaced at multiple of the spinning frequencies along both sides of the real peaks (centerbands). The spinning speed was set to 7 kHz which at the 500 MHz magnet translates into 55.7 ppm. The sideband intensities depend on the spinning

speed (the higher the speed the lower the sideband intensity) and on the size of the anisotropic contribution of the chemical shielding for the given carbon. They can be easily distinguished from centerbands by variable spinning speed experiments. Carbonyl and aromatic sites tend to have very intense sidebands due to their large chemical shielding anisotropies. CH and CH_2 type of carbons give origin to relatively small spinning sidebands. Methyl groups (CH_3) usually don't generate any sidebands.

The major resonance peaks (those downfield from 100 ppm; ± 0.1ppm) for the solid state carbon spectrum of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene L-tartrate salt Forms A, B and C are listed in Table XXI.

Table XXI. Major Solid State ^{13}C-NMR Resonance Peaks For 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene L-Tartrate Salt Forms A, B and C (Only Peaks Downfield from 100 ppm Listed) (Adamantane 29.5 ppm Standard).

FORM A ^{13}C (ppm) Solid	FORM B ^{13}C (ppm) Solid	FORM C ^{13}C (ppm) Solid
178.4	179.2	179.0
149.3	178.0	176.1
147.4	147.4	147.5
145.1	145.2	144.5
122.9	144.4	124.6
	124.8	
	122.5	

The L-tartrate, the D-tartrate, the D,L-tartrate and the meso-tartrate salts of the invention (hereafter "the active salts") can be administered via either the oral, transdermal (e.g., through the use of a patch), intranasal, sublingual, rectal, parenteral or topical routes. Transdermal and oral administration are preferred. These salts are, most desirably, administered in dosages ranging from about 0.01 mg up to about 1500 mg per day, preferably from about 0.1 to about 300 mg per day in single or divided doses, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.001 mg to about 10 mg per kg of body weight per day is most desirably employed. Variations may nevertheless occur depending upon the weight and condition of the persons being treated and their individual responses to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval during which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such larger doses are first divided into several small doses for administration throughout the day.

The active salts can be administered alone or in combination with pharmaceutically acceptable carriers or diluents by any of the several routes previously indicated. More

particularly, the active salts can be administered in a wide variety of different dosage forms, *e.g.*, they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, transdermal patches, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents. In addition, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compound is present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc can be used for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar, as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration the active ingredient may be combined with various sweetening or flavoring agents, coloring matter and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

For parenteral administration, a solution of an active salt in either sesame or peanut oil or in aqueous propylene glycol can be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8), if necessary, and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

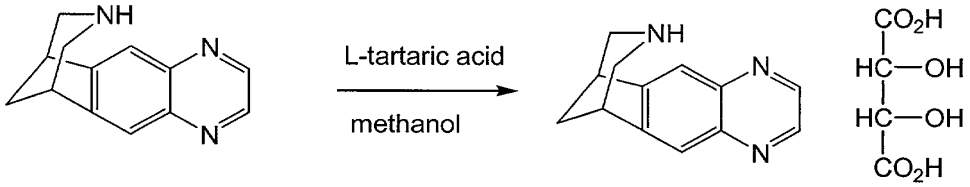
It is also possible to administer the active salts topically and this can be done by way of creams, a patch, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

EXAMPLES

The following examples illustrate the methods and compounds of the present invention. It will be understood, however, that the invention is not limited to the specific Examples.

Example 1

L-Tartrate Salt of 5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (Anhydrous Polymorph, Form B)



CP-526,555
MW 211.27

CP-526,555-18
MW 361.36

A speck-free vessel was charged with L-tartaric acid (780 grams, 1.1 equiv.) and methanol (7.5 L). The contents of the vessel were stirred until solution and speck free filtered into the crystallization vessel. 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene free base (992 grams) and methanol (7.5 L) were dissolved in the vessel; the mixture was maintained at between 20 to 25 °C. The solution of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene free base was added over about 45 minutes to the L-tartaric acid solution through a filter to render the solution speck and fiber free. The product was allowed to stir at 20 to 25 °C overnight and isolated by filtration. The product was dried under vacuum at 35 to 45 °C to give 1618.4 grams (95.4%) of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene L-tartrate salt Form B (MW 361.36). M.p. 210.5 °C; verified as Form B by powder x-ray diffraction.

Example 2

L-Tartrate Salt of 5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (Anhydrous Polymorph, Form A)

A reactor was charged with 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene free base (2 g; 0.0095 mole, 1.0 equiv.) and methanol (60 mL, 30 mL/g). The mixture was stirred at 20 to 25 °C until completely dissolved. A second reactor containing a solution of L-tartaric acid (1.55 g, 0.0103 mole, 1.1 equiv.) dissolved in methanol (60 mL, 30 mL/g) was heated to reflux in methanol (*i.e.*, 60 to 66 °C). The free base solution was added to the L-tartaric acid solution at methanolic reflux temperature over 20 minutes. The resulting slurry was cooled to 20 to 25 °C over a 1 hour period. The reaction mixture was allowed to stir for approximately 2 hours followed by isolation of the product by filtration. The solid product was washed with methanol (10 mL), then dried under vacuum at 30 to 35 °C to

give 3.3 grams (97%) of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene L-tartrate Form A. The identity as Form A was determined by PXRD as compared with standard samples.

Example 3

L-Tartrate Salt Form C of 5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (Form C)

Preparation of CP-526,555-18 Form C from Form A or Form B:

L-tartrate salt Form B (~5g) was dissolved in water (10 to 15 ml). Acetonitrile (200 to 300 ml) was added and Form C formed as a white precipitate. The resulting slurry was allowed to stir for 10 minutes and then filtered. The wet cake was then allowed to air dry. Product was determined to be Form C by NIR spectroscopy, DSC and PXRD analysis. This procedure may be run with Form A to yield Form C.

Example 4

L-Tartrate Salt Form A of 5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (Form A)

Preparation of Form A from Form C: L-tartrate salt Form C (~2g) was added to 200 to 300 mL hot ethanol (~75°C) and allowed to stir for 30 minutes. The sample was filtered hot and then dried in a 45°C vacuum oven (house vacuum). The material was determined to be Form A by NIR spectroscopy, DSC, and PXRD analysis.

CLAIMS

1. The tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

2. A compound according to claim 1 which is the L-tartrate salt.

3. A compound according to claim 2 which is anhydrous.

4. A compound according to claim 3 characterized substantially by at least one of the following powder x-ray diffraction pattern peaks expressed in terms of 2θ as measured with copper radiation chosen from: 6.1, 16.8 and 21.9.

5. A compound according to claim 3 characterized substantially by the following principal powder x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ	d-value (Å)
6.1	14.5
12.2	7.2
13.0	6.8
14.7	6.0
16.8	5.3
19.4	4.6
21.9	4.1
24.6	3.6

6. A compound according to claim 5 characterized in that it has a onset of melt of about 223 °C.

7. A compound according to claim 5 characterized substantially by solid state ^{13}C NMR resonance peaks at 178.4, 145.1, and 122.9 ppm.

8. A compound according to claim 5 characterized substantially by solid state ^{13}C NMR resonance peaks at 178.4, 149.3, 147.4, 145.1, and 122.9 ppm.

9. A compound according to claim 3 characterized substantially by at least one powder x-ray diffraction pattern peaks in terms of 2θ measured with copper radiation chosen from: 5.9 and 21.8.

10. A compound according to claim 3 characterized substantially by the principal powder x-ray diffraction pattern peaks in terms of 2θ and d-spacings measured with copper radiation:

Angle 2θ	d-value (Å)
5.9	15.0
12.8	6.9
14.4	6.1
15.3	5.8
16.9	5.2
17.2	5.2
21.8	4.1
23.8	3.7
25.1	3.5

11. A compound according to claim 10 characterized in having an onset of melting of about 215 °C.

12. A compound according to claim 10 characterized substantially by the solid state ^{13}C NMR principal resonance peaks at: 179.2, 178.0, 144.4, 124.8 and 122.5 ppm.

13. A compound according to claim 10 characterized substantially by the solid state ^{13}C NMR principal resonance peaks: 179.2, 178.0, 147.4, 145.2, 144.4, 124.8 and 122.5 ppm.

14. A compound according to claim 10 characterized by the single crystal structure of Figure 8A.

15. A compound according to claim 10 that forms orthorhombic crystals belonging to the P2(1)2(1)2(1) space group.

16. A compound according to claim 2 which is a hydrate.

17. A compound according to claim 16 where the hydrate is a monohydrate.

18. A compound according to claim 16 characterized substantially by at least one of the powder x-ray diffraction pattern peaks in terms of 2θ as measured with copper radiation chosen from: 11.8, 16.5, 23.1 and 26.5.

19. A compound according to claim 16 characterized substantially by the principal powder x-ray diffraction pattern peaks in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
5.9	15.1
11.8	7.5
16.5	5.4
21.2	4.2
23.1	3.8
23.8	3.7
26.5	3.4

20. A compound according to claim 16 characterized by the single crystal structure of Figure 8B.

21. A compound according to claim 16 that forms monoclinic crystals belonging to the P2(1) space group.

22. A compound according to claim 16 characterized in having an onset of solid-solid transition at about 73 °C and an onset of melting transition at about 220 °C.

23. A compound according to claim 16 characterized substantially by solid state ^{13}C NMR principal resonance peaks: 179.0, 176.1, 147.5 and 144.5 ppm.

24. A compound according to claim 16 characterized substantially by solid state ^{13}C NMR principal resonance peaks: 179.0, 176.1, 147.5, 144.5 and 124.6 ppm.

25. A compound according to claim 1 which is the D,L-tartrate salt.

26. A compound according to claim 25 which is anhydrous.

27. A compound according to claim 26 characterized substantially by a powder x-ray diffraction pattern peaks expressed in terms of 2θ as measured with copper radiation at: 6.0.

28. A compound according to claim 26 characterized substantially by the following principal powder x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
6.0	14.6
11.9	7.4
15.0	5.9
17.1	5.2
22.1	4.0
24.5	3.6

29. A compound according to claim 26 characterized in that it has a onset of melt of about 212 °C.

30. A compound according to claim 25 which is a hydrate.

31. A compound according to claim 30 characterized substantially by the powder x-ray diffraction pattern peaks in terms of 2θ as measured with copper radiation at: 6.2 and 25.1.

32. A compound according to claim 30 characterized substantially by the principal powder x-ray diffraction pattern peaks in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
6.2	14.2
12.0	7.4
15.2	5.8
18.1	4.9
24.0	3.7
25.1	3.5

33. A compound according to claim 30 characterized by having an onset of a solid-solid transition at about 131 °C and an onset of melting transition at about 217 °C.

34. A compound according to claim 1 which is the D-tartrate salt.

35. A compound according to claim 34 which is anhydrous.

36. A compound according to claim 34 which is a hydrate.

37. A compound according to claim 1 which is the meso-tartrate salt.

38. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to any of claims 1, 2, 4, 9, 18, 27, 31, 34 or 37.

39. A method of treating inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome,

spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, drug/toxin-induced cognitive impairment (*e.g.*, from alcohol, barbiturates, vitamin deficiencies, recreational drugs, lead, arsenic, mercury), disease-induced cognitive impairment (*e.g.*, arising from Alzheimer's disease (senile dementia), vascular dementia, Parkinson's disease, multiple sclerosis, AIDS, encephalitis, trauma, renal and hepatic encephalopathy, hypothyroidism, Pick's disease, Korsakoff's syndrome and frontal and subcortical dementia), hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (*e.g.*, dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, migraine, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome comprises administering to a subject in need of treatment a therapeutically effective amount of a compound according to any of claims 1, 2, 4, 9, 18, 27, 31, 34 or 37.

40. A method of treatment for nicotine dependency, addiction and withdrawal comprising the administration of a compound according to any of claims 1, 2, 4, 9, 18, 27, 31, 34 or 37 to a subject in need thereof.

41. A process for the preparation of a compound according to claim 4 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with between about 1 and about 2 equivalents of L-tartaric acid; and

(ii) collecting the crystals formed.

42. A process according to claim 41 wherein 1.1 equivalents of L-tartaric acid are employed and the tartaric acid is added to a solution containing the free base.

43. A process according to claim 41 wherein the contacting step is allowed to proceed above 45 °C.

44. A process according to claim 41 wherein the contacting step is allowed to proceed for less than 2 hours.

45. A process according to claim 41 wherein the suitable solvent is selected from the group consisting of an (C_1-C_6)alkyl alcohol, an (C_1-C_6)alkyl ketone, an (C_1-C_6)alkyl ether, acetonitrile and an (C_1-C_6)alkyl ester.

46. A process according to claim 41 wherein the suitable solvent is ethanol or methanol.

47. A process for the preparation of a compound according to claim 9 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with between about 1 and about 2.3 equivalents of L-tartaric acid; and

(ii) collecting the crystals formed.

48. A process according to claim 47 wherein 1.1 equivalents of L-tartaric acid are employed and the free base in solution is added to a solution containing L-tartaric acid.

49. A process according to claim 47 wherein the contact step is allowed to proceed for at least 2 hours.

50. A process according to claim 47 wherein the contact step is allowed to proceed for at least 12 hours.

51. A process according to claim 47 wherein the suitable solvent is selected from the group consisting of an (C_1-C_6)alkyl alcohol, an (C_1-C_6)alkyl ketone, an (C_1-C_6)alkyl ether, acetonitrile and an (C_1-C_6)alkyl ester.

52. A process according to claim 47 wherein the suitable solvent is methanol or ethanol.

53. A process according to claim 47 wherein the suitable solvent is methanol.

54. A process for the preparation of a compound according to claim 18 comprising the steps of

(i) contacting an anhydrous L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene with water; and

(ii) collecting the crystals formed.

55. A process according to claim 54 wherein the contacting of step (i) comprises exposing the anhydrous L-tartrate salt to greater than 70% humidity.

56. A process according to claim 54 wherein the contacting of step (i) comprises slurrying the anhydrous L-tartrate salt with water.

57. A process according to claim 54 wherein step (i) comprises the addition of an organic solvent.

58. A process according to claim 54 wherein step (i) comprises the addition of methanol, ethanol or acetonitrile.

59. A process for the preparation of a compound according to claim 27 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of D,L-tartaric acid; and

(ii) collecting the crystals formed.

60. A process according to claim 59 wherein about 2.2 equivalents of D,L-tartaric acid is employed and the free base in solution is added to a solution containing D,L-tartaric acid.

61. A process according to claim 59 wherein the contact step is allowed to proceed for at least 24 hours.

62. A process according to claim 59 wherein the suitable solvent is anhydrous ethanol.

63. A process for the preparation of a compound according to claim 31 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of D,L-tartaric acid; and

(ii) collecting the crystals formed.

64. A process according to claim 63 wherein about 2.2 equivalents of D,L-tartaric acid is employed and the free base in solution is added to a solution containing D,L-tartaric acid.

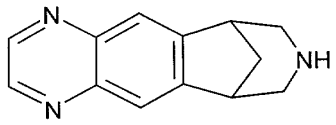
65. A process according to claim 63 wherein the contact step is allowed to proceed for at least 24 hours.

66. A process according to claim 63 wherein the suitable solvent is 20% aqueous ethanol.

ABSTRACT

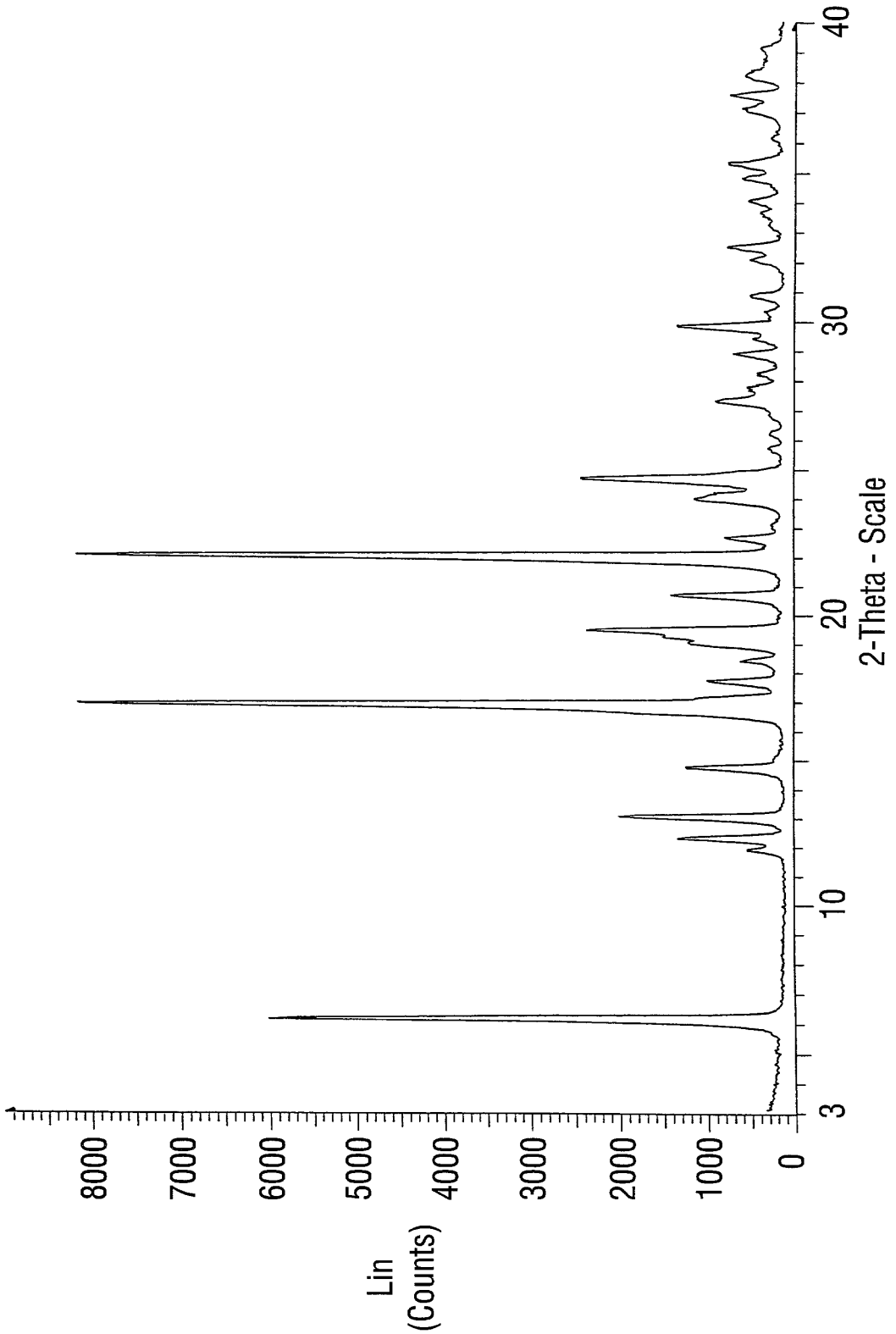
TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

The present invention is directed to the tartrate salts of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene:



and pharmaceutical compositions thereof. The present invention in particular is directed to the L-tartrate salt, and further to the various polymorphs of the L-tartrate salt, including two distinct anhydrous polymorphs (referred to herein as Forms A and B) and a hydrate polymorph (referred to herein as Form C). In addition, the present invention is also directed to the D-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene and the various polymorphs thereof; as well as the D,L-tartrate salt thereof and its polymorphs, and the meso-tartrate salt thereof and its polymorphs.

FIG. 1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2-Theta - Scale

FIG. 2

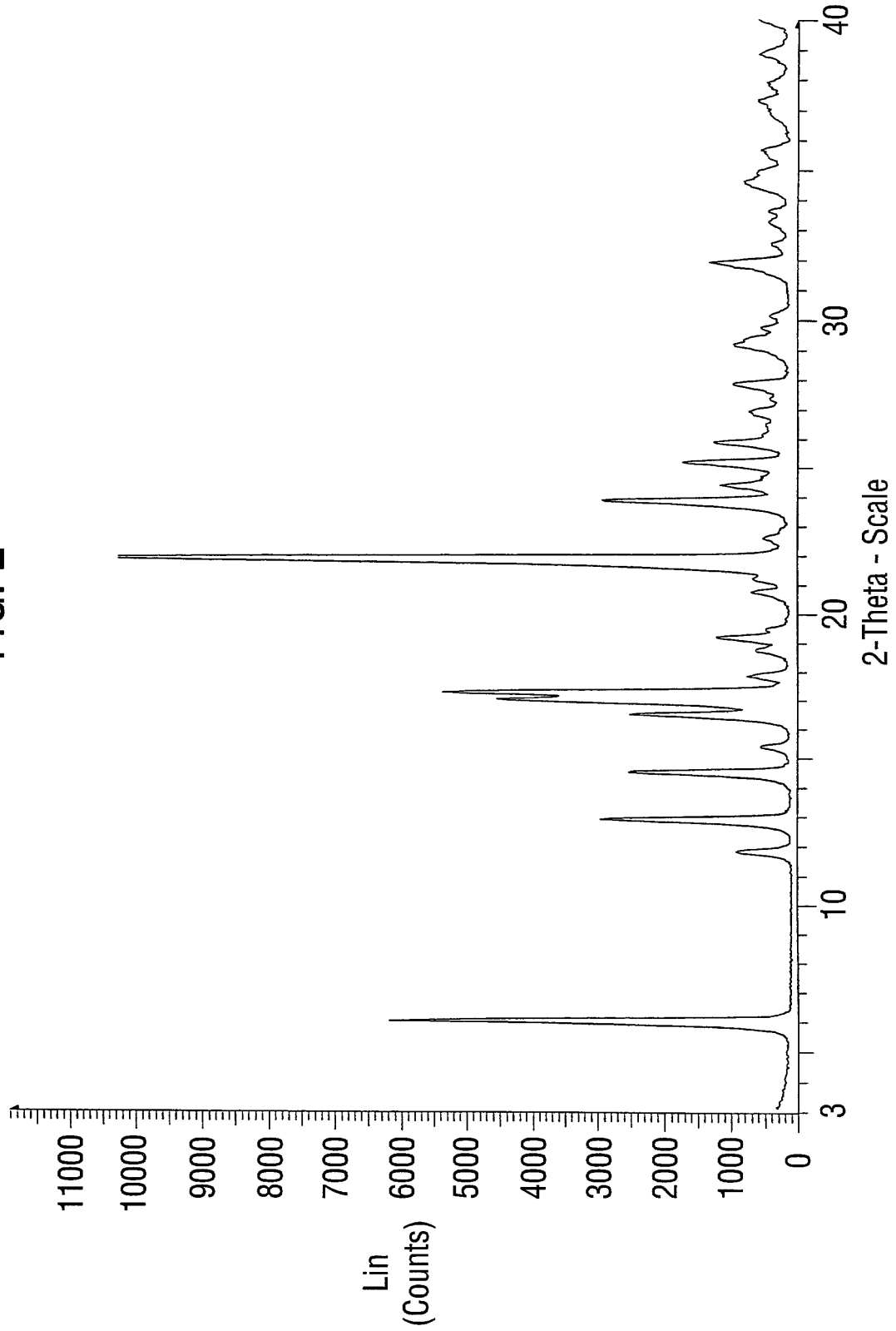
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FIG. 3

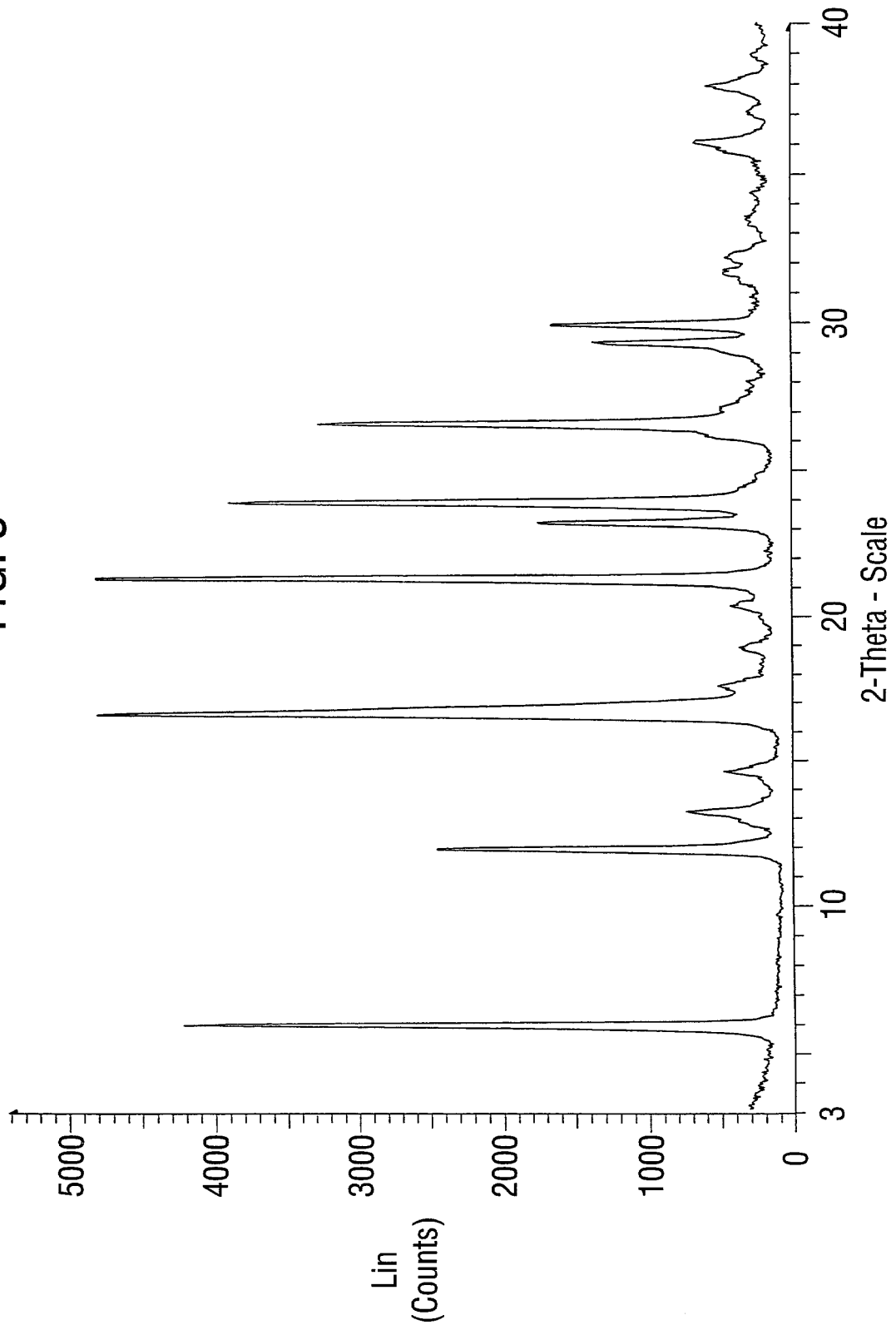
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FIG. 4A

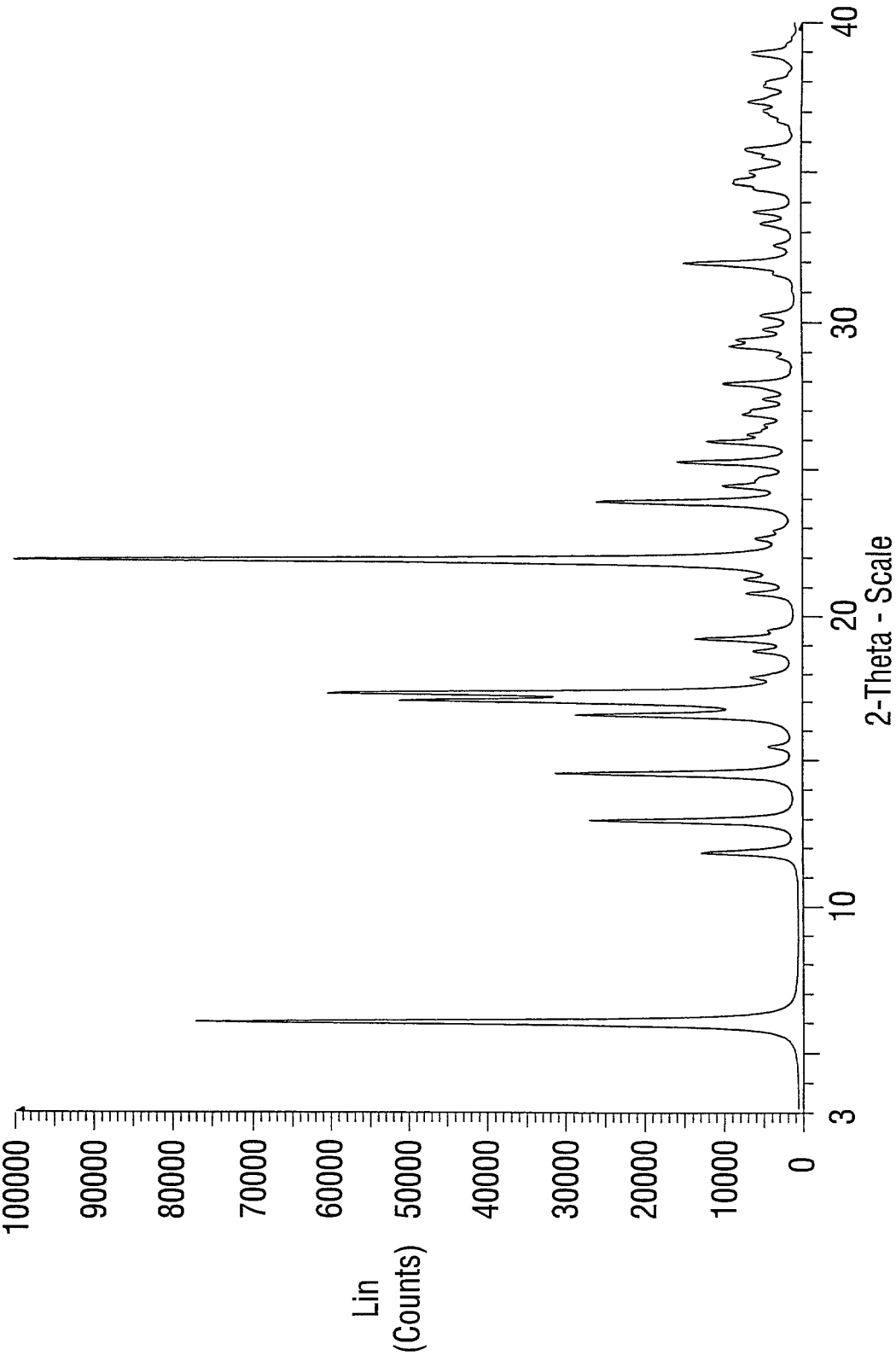
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FIG. 4B

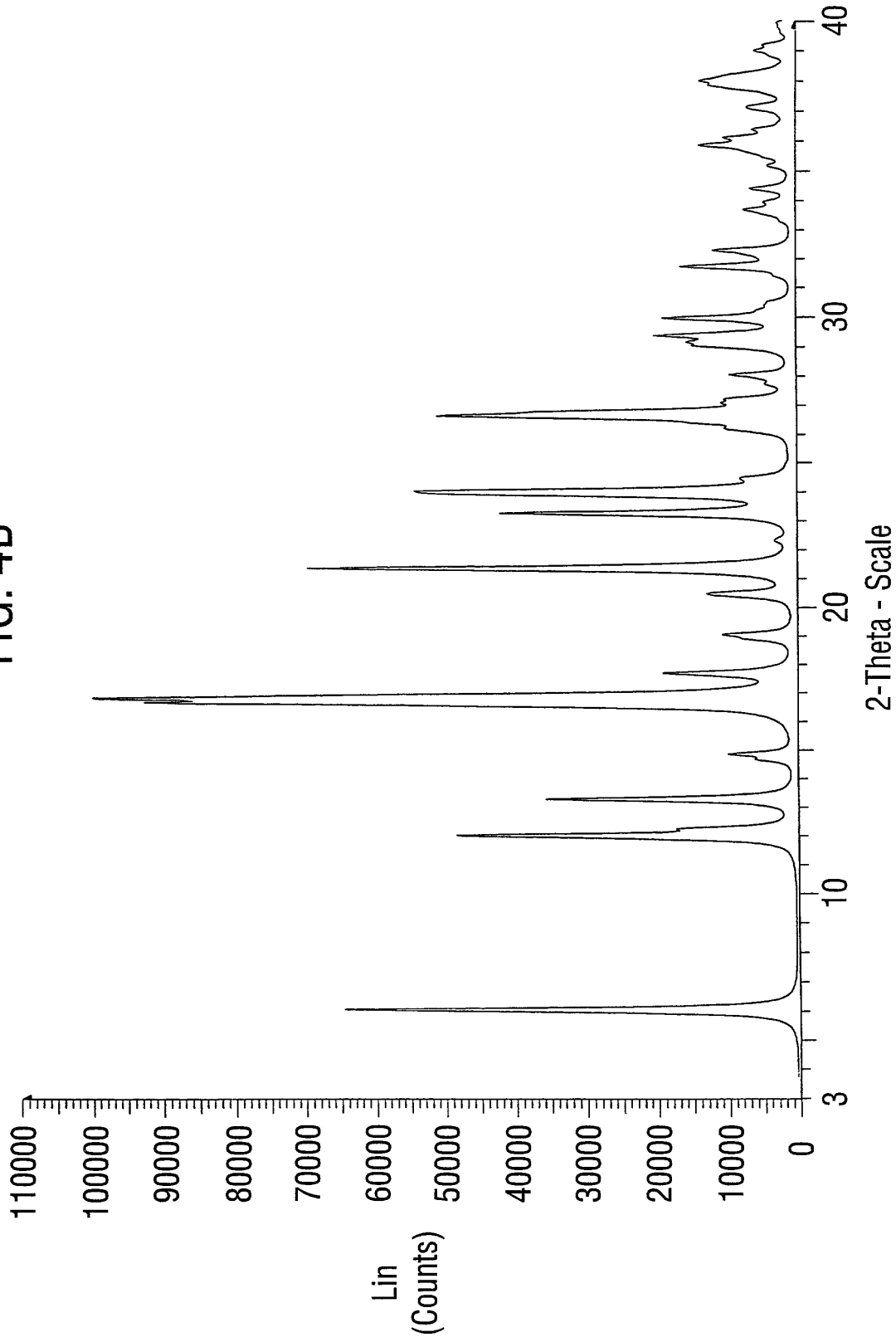


FIG. 5A

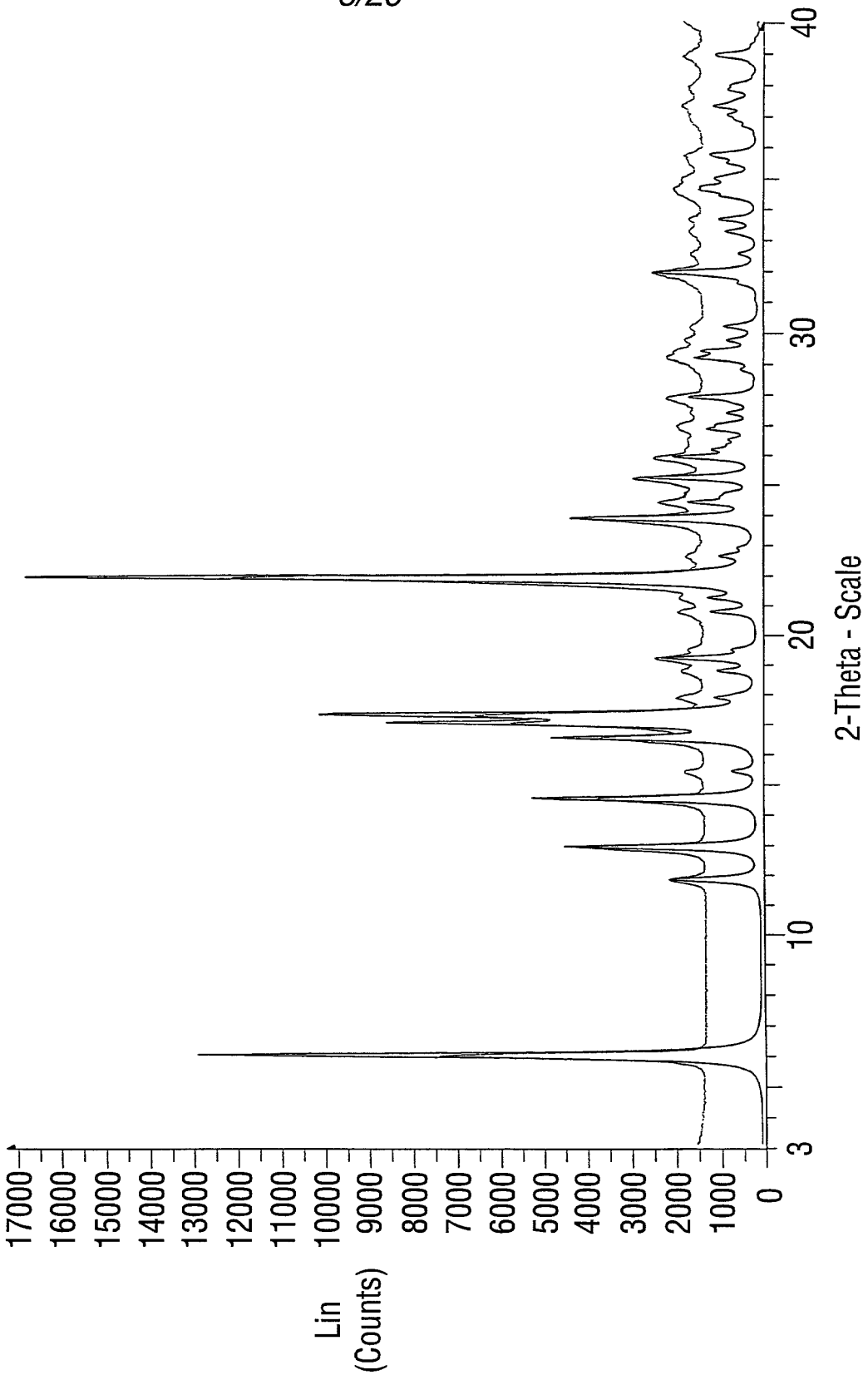
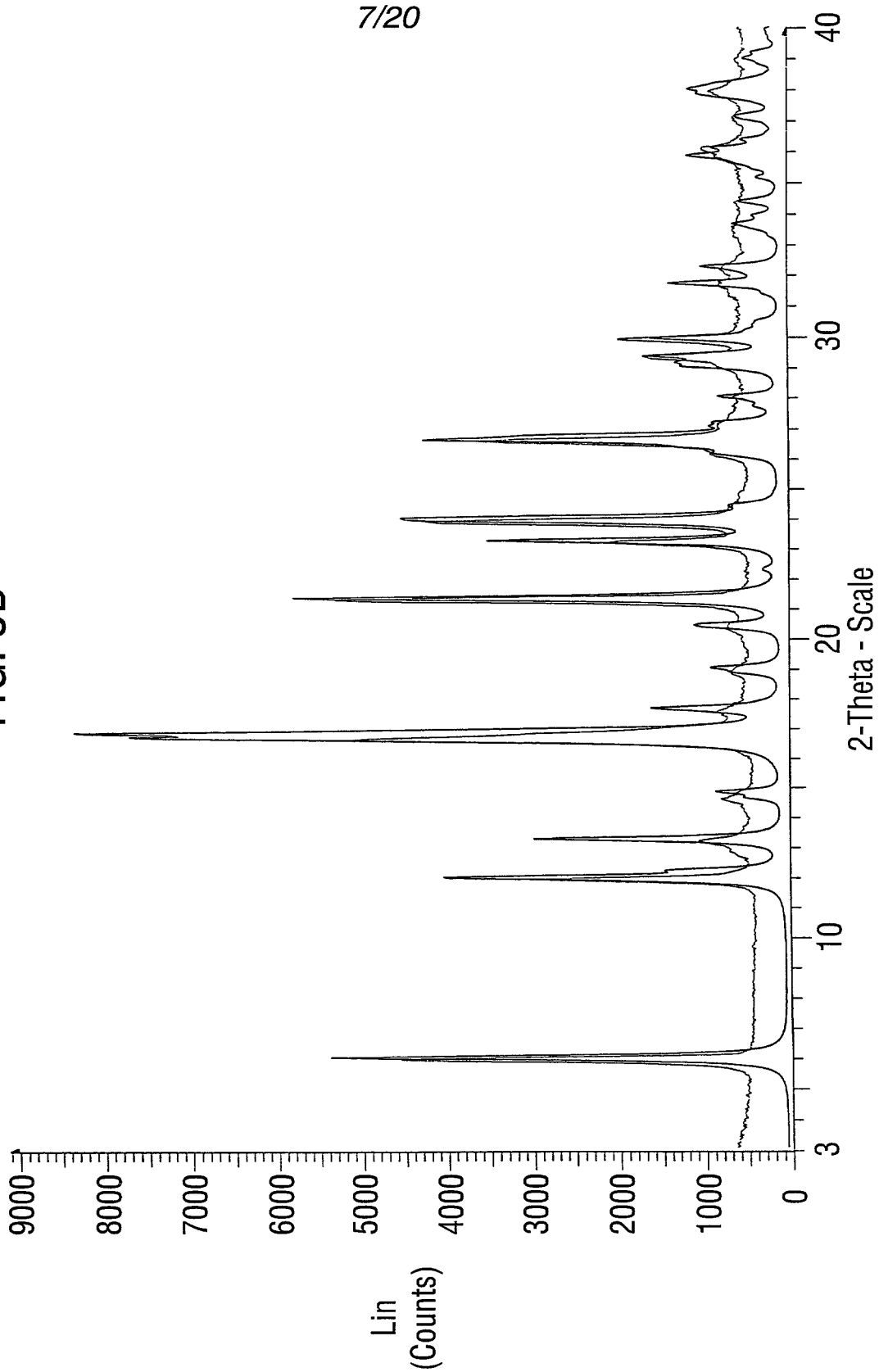


FIG. 5B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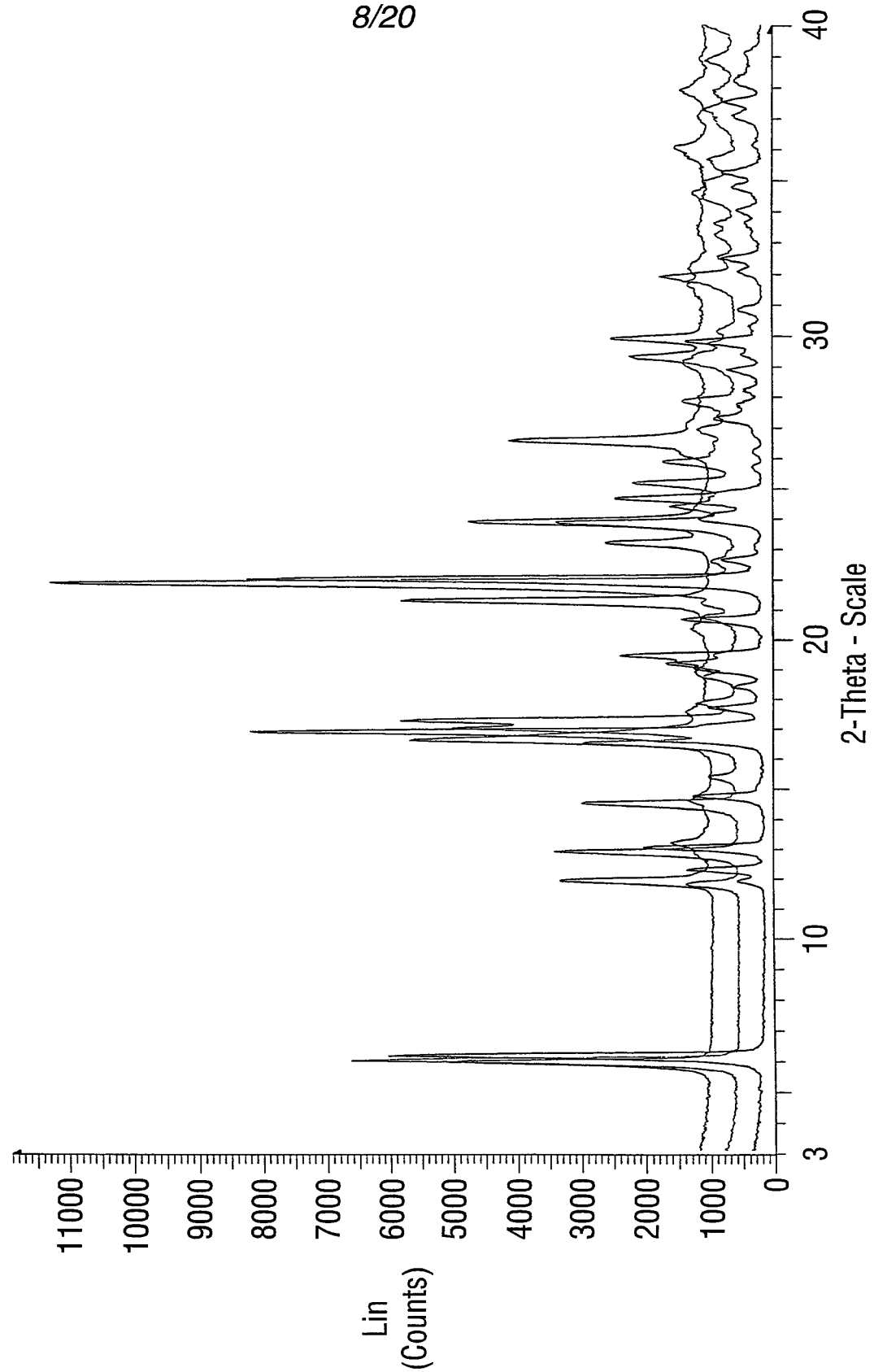
2-Theta - Scale

FIG. 6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10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
3
10
20
30
40
2-Theta - Scale

FIG. 7A

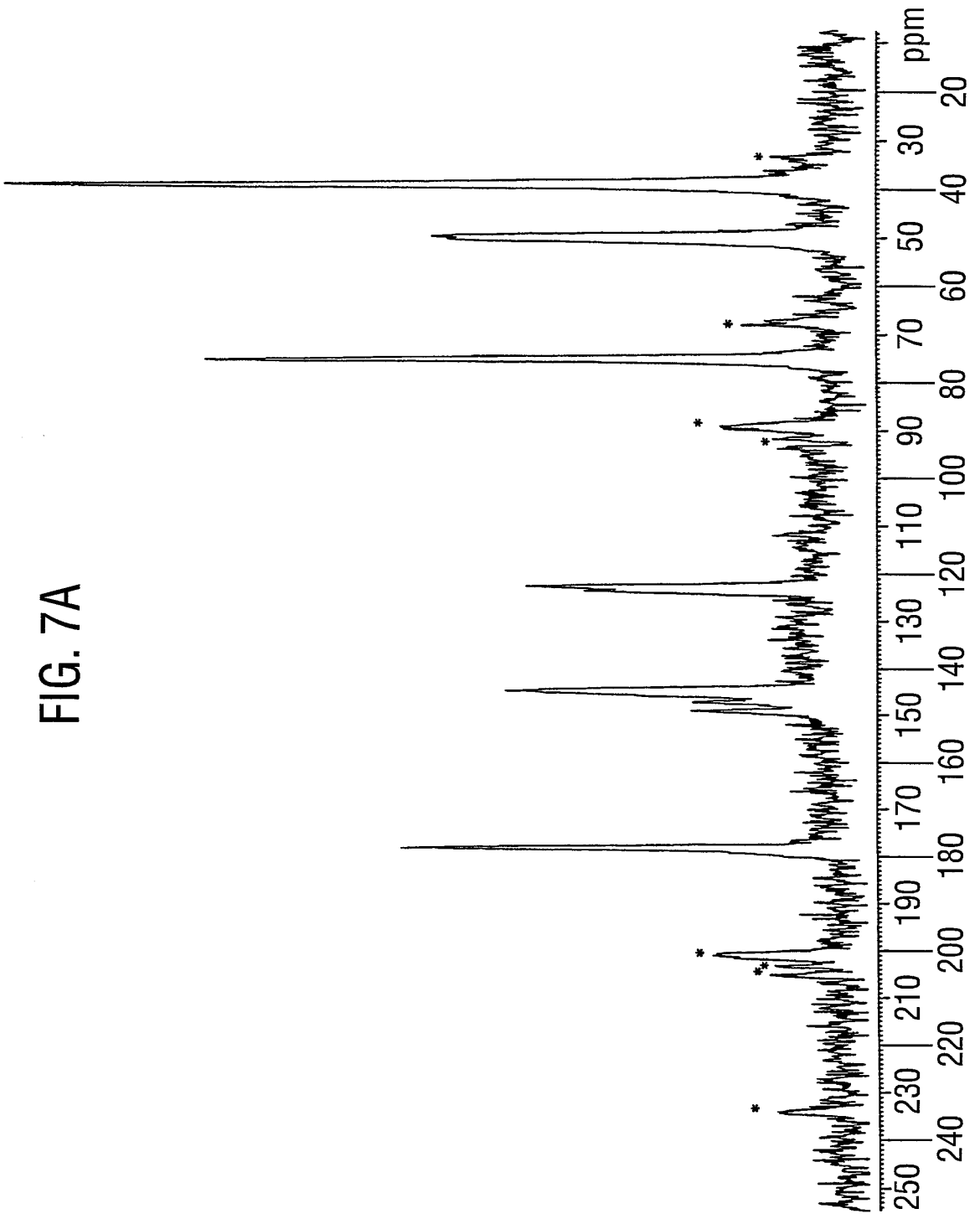


FIG. 7B

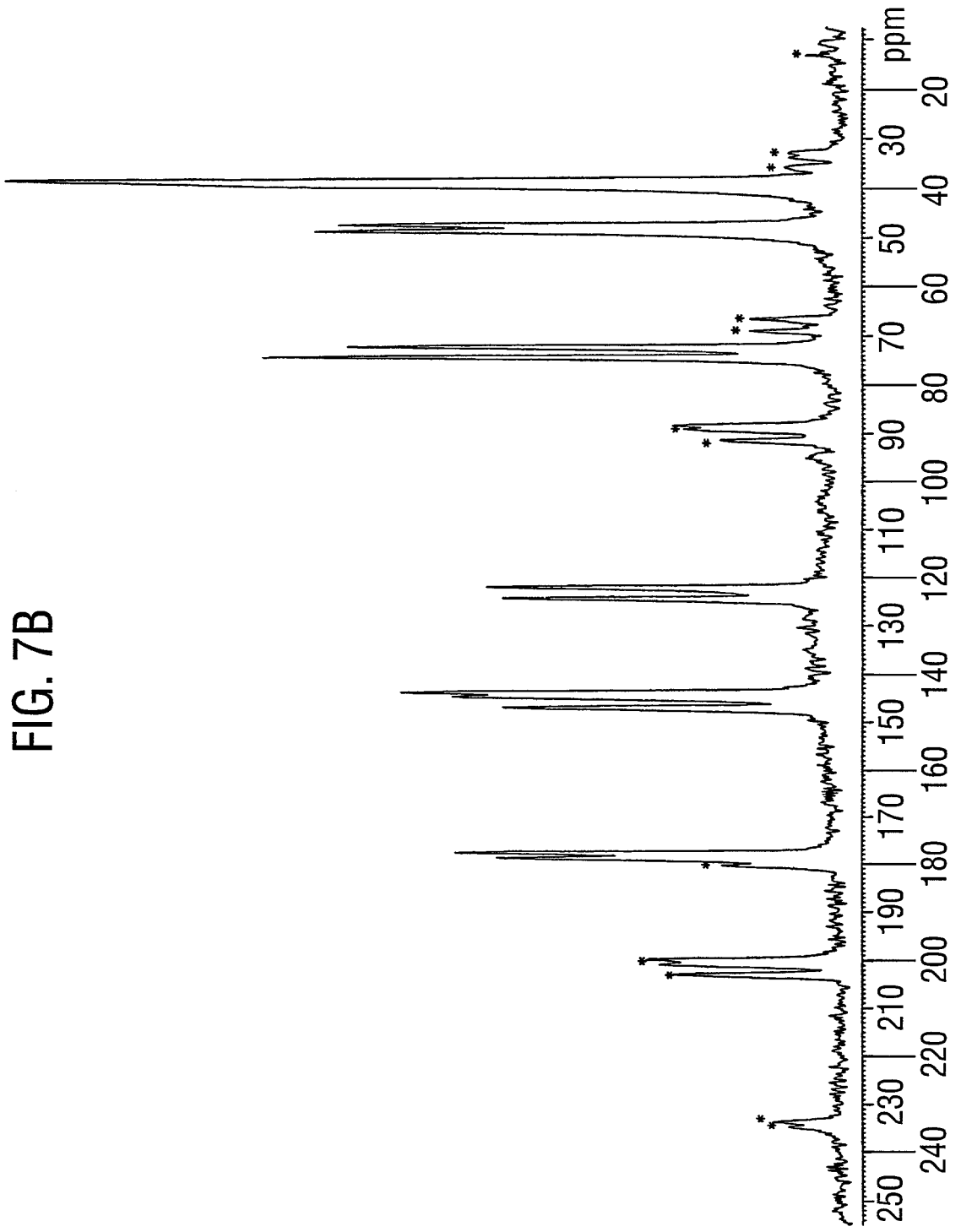


FIG. 7C

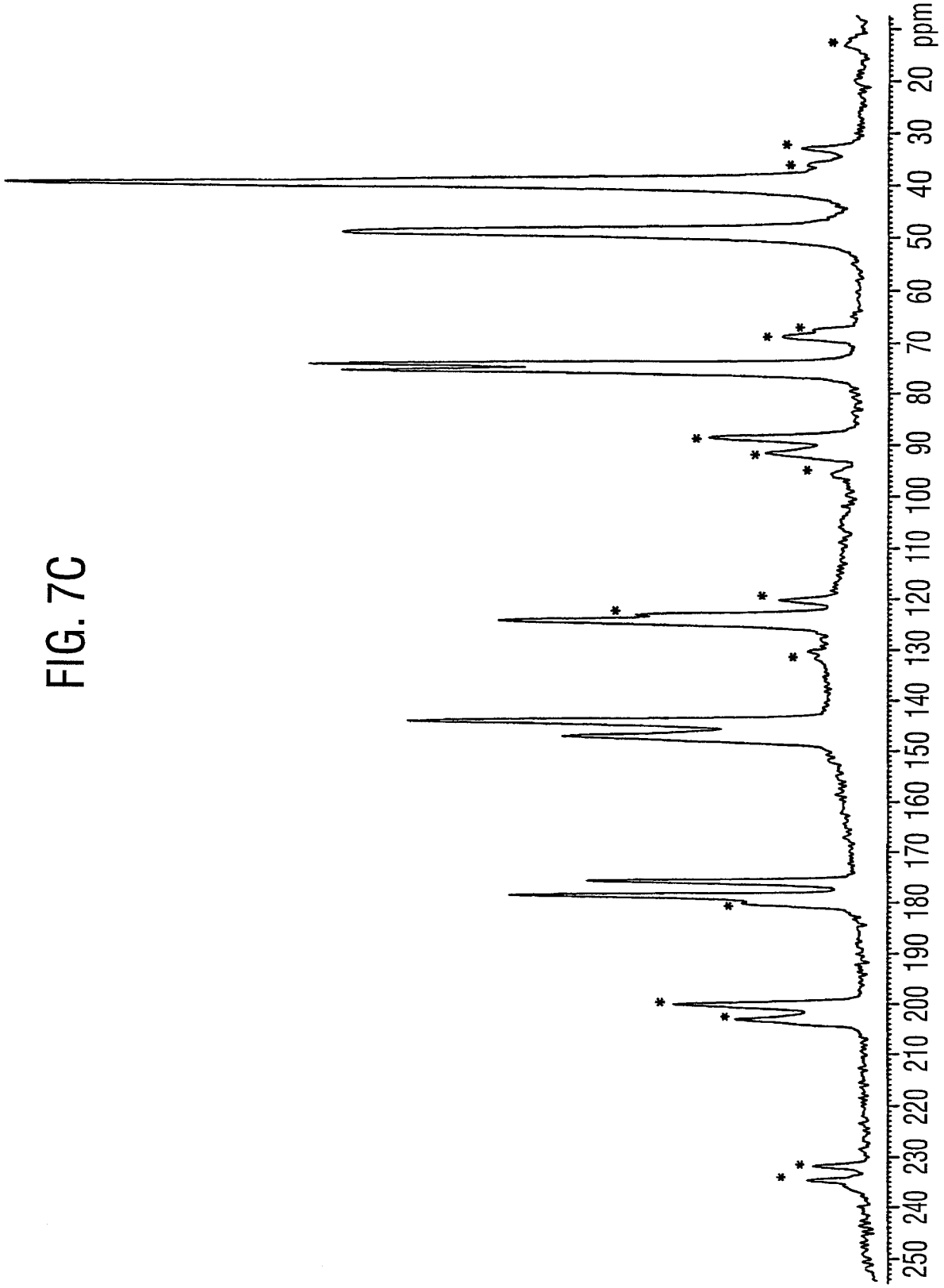
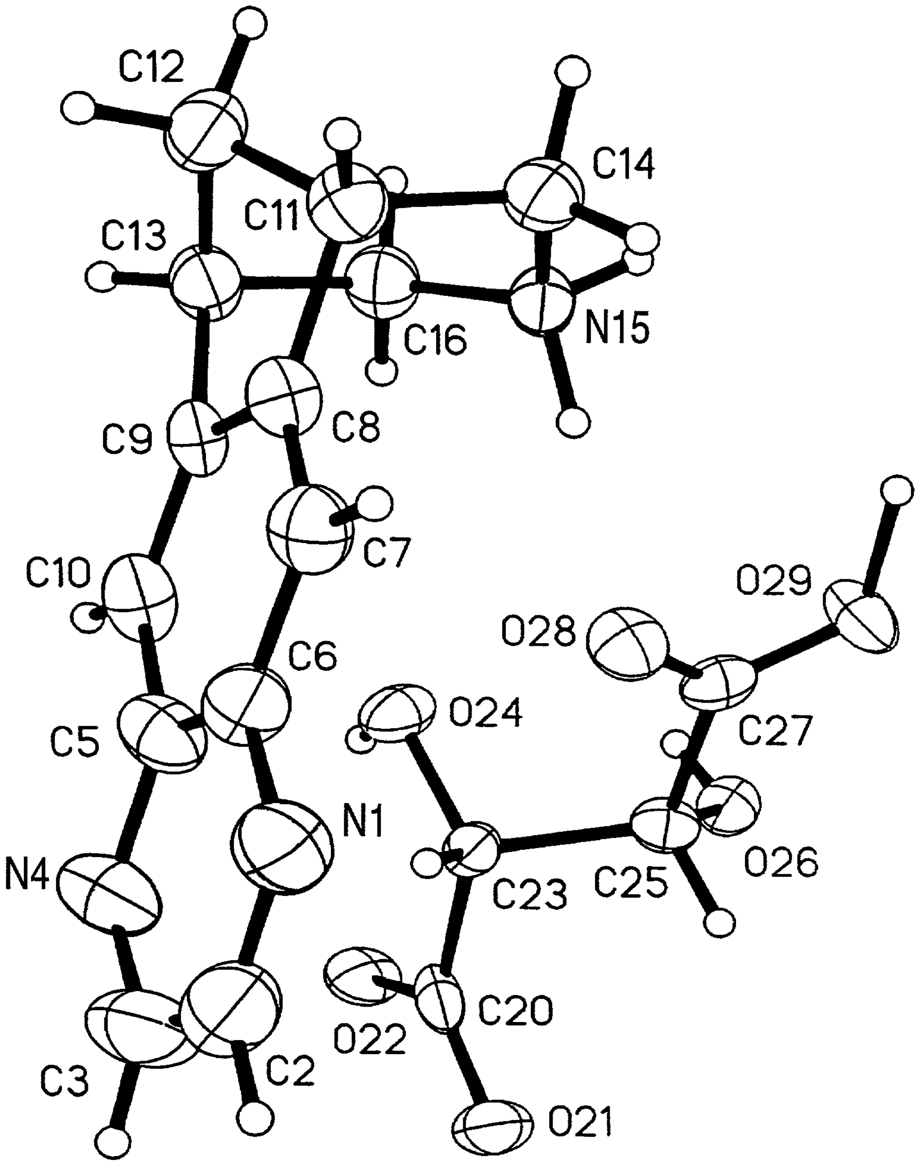


FIG. 8A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C14
C11
C13
C16
N15
C9
C8
C7
C10
O29
O28
C6
O24
C27
C5
N1
N4
O26
C23
C25
C20
O22
C3
C2
O21

FIG. 8B

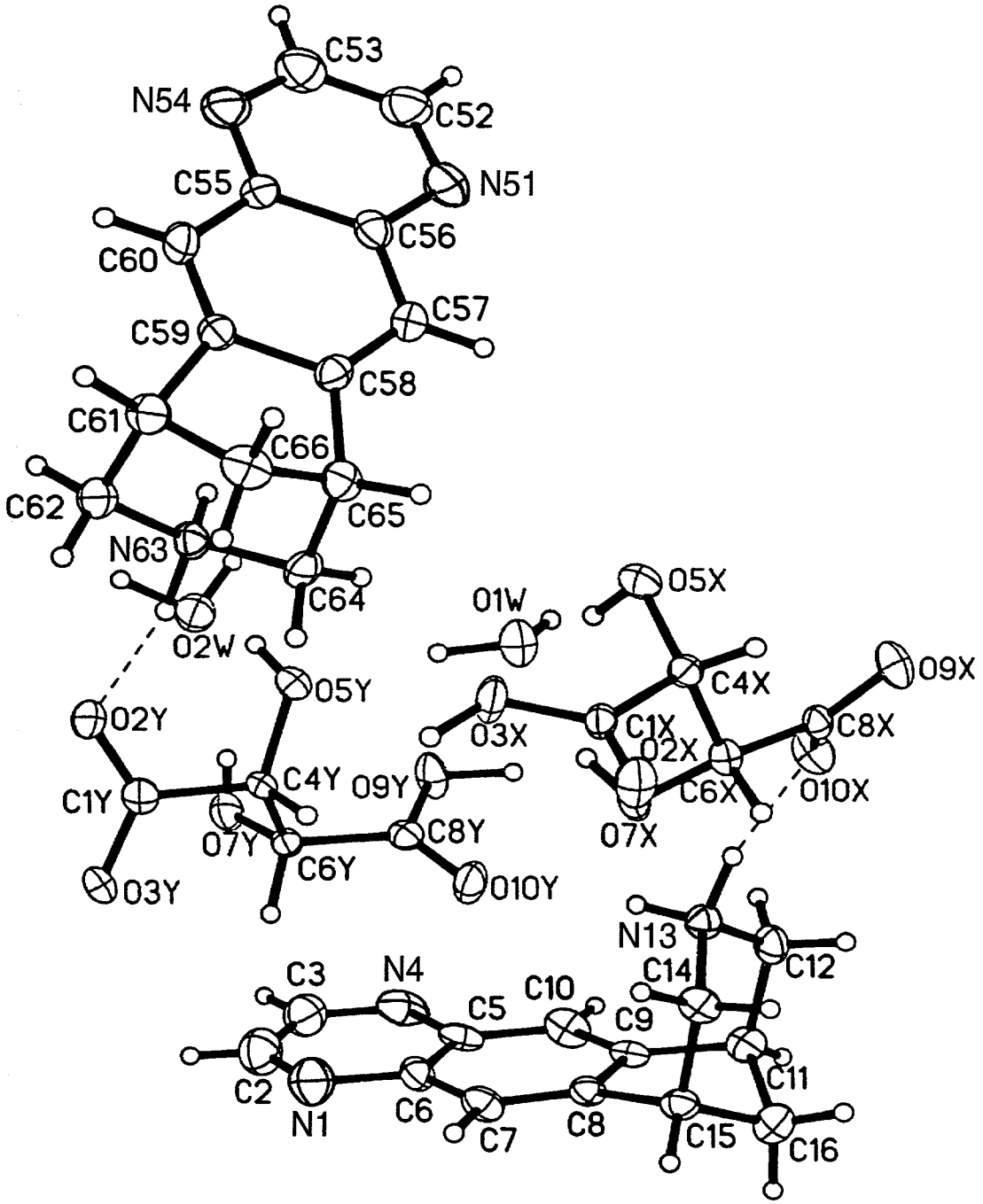


FIG. 9A

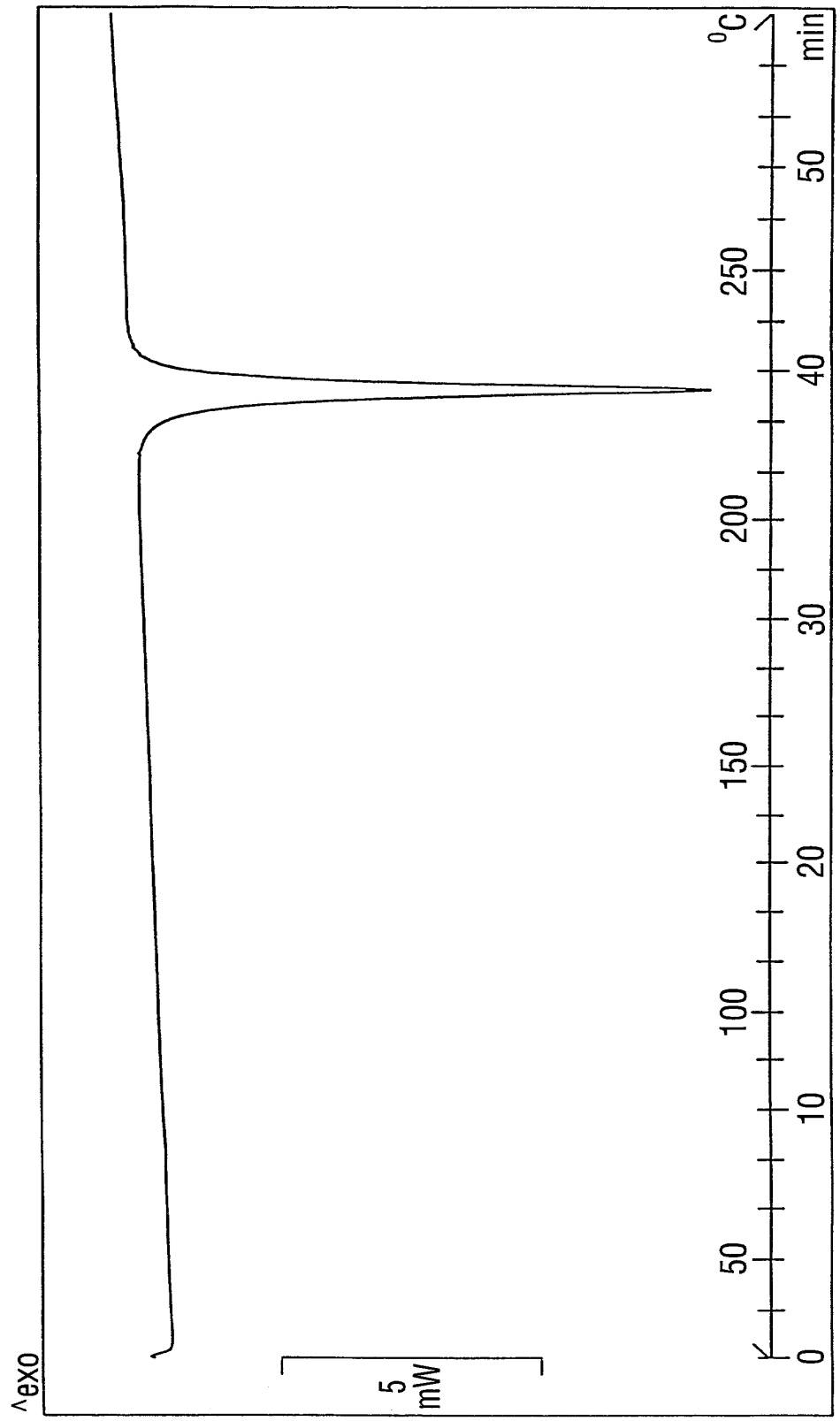


FIG. 9B

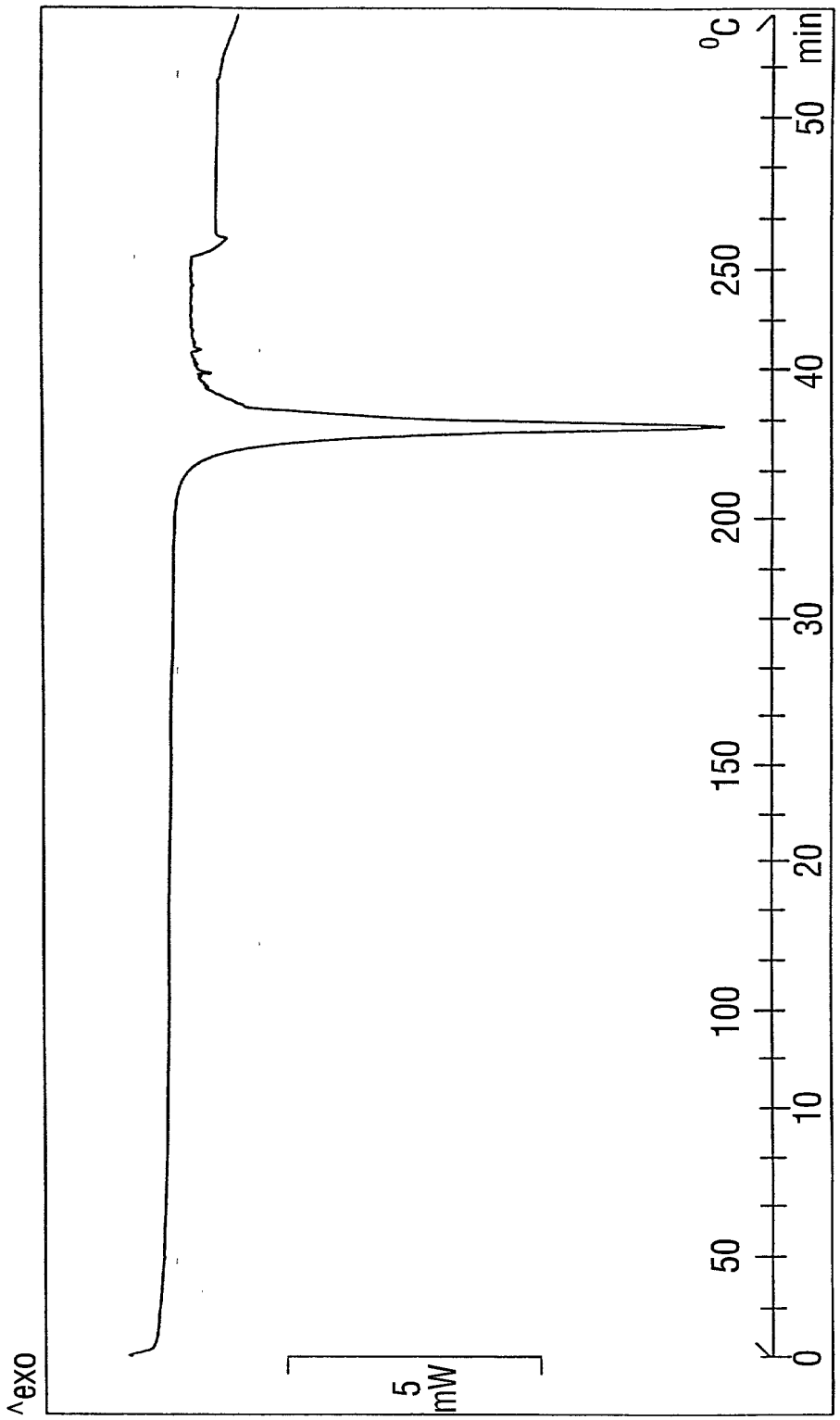


FIG. 9C

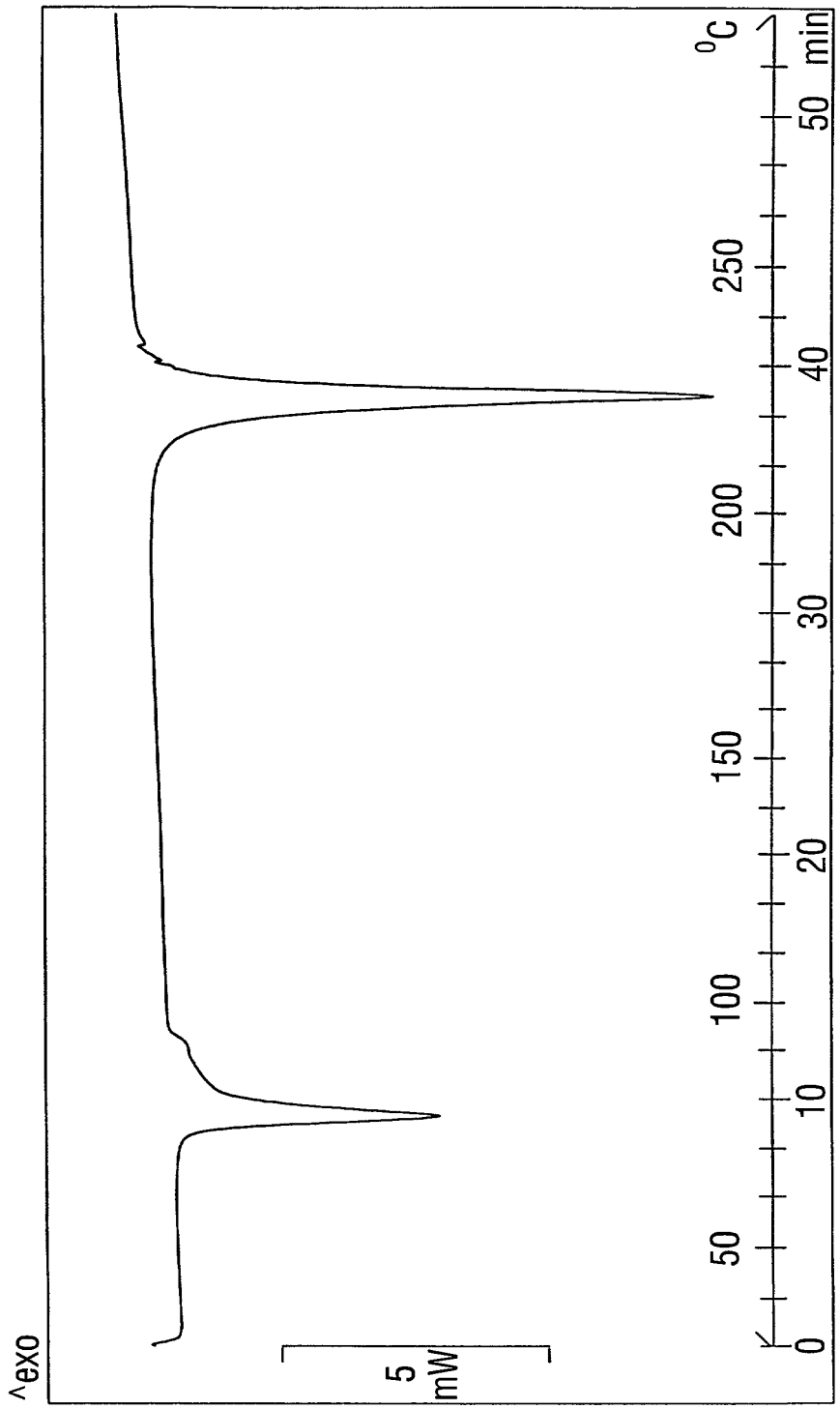


FIG.10A

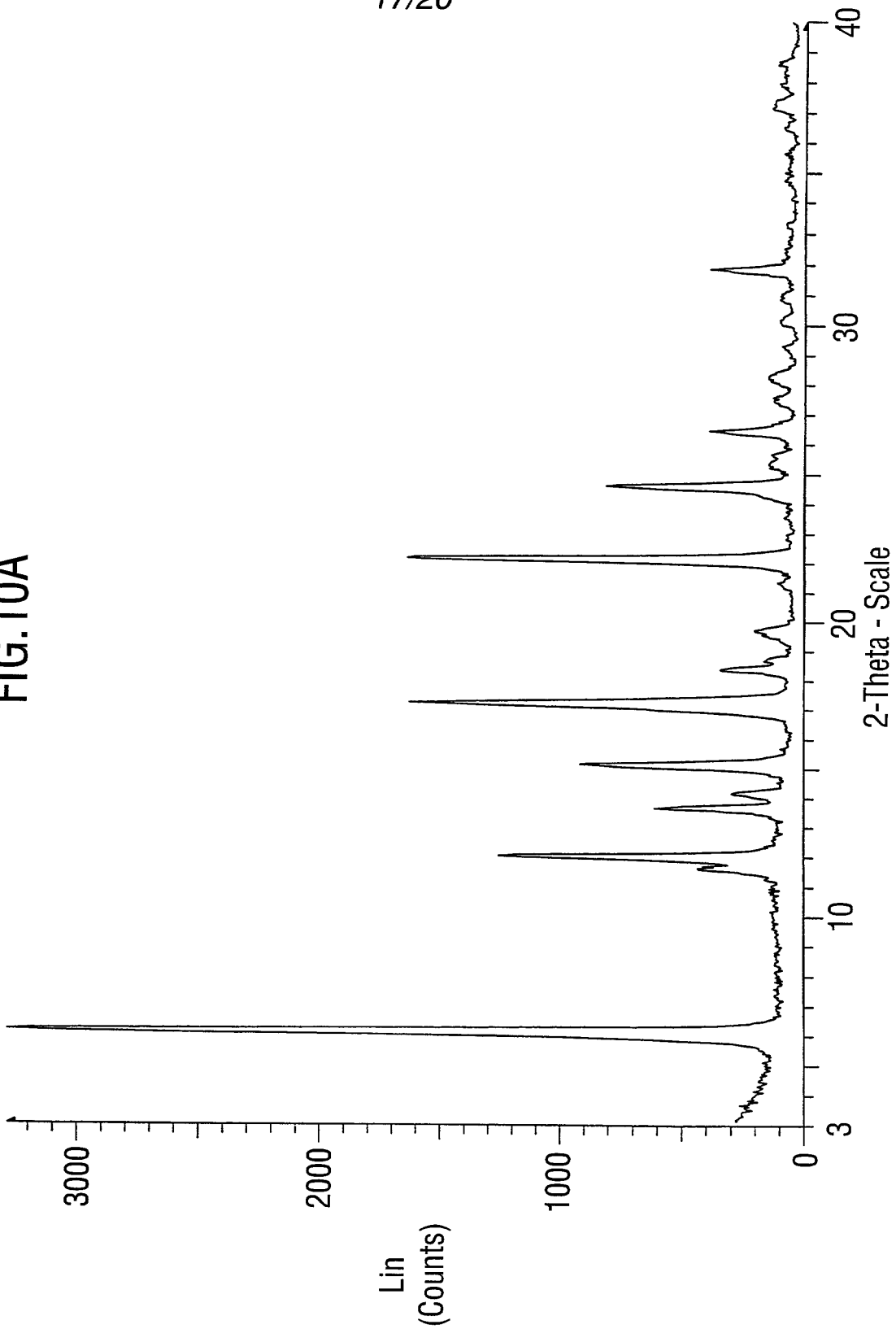


FIG.10B

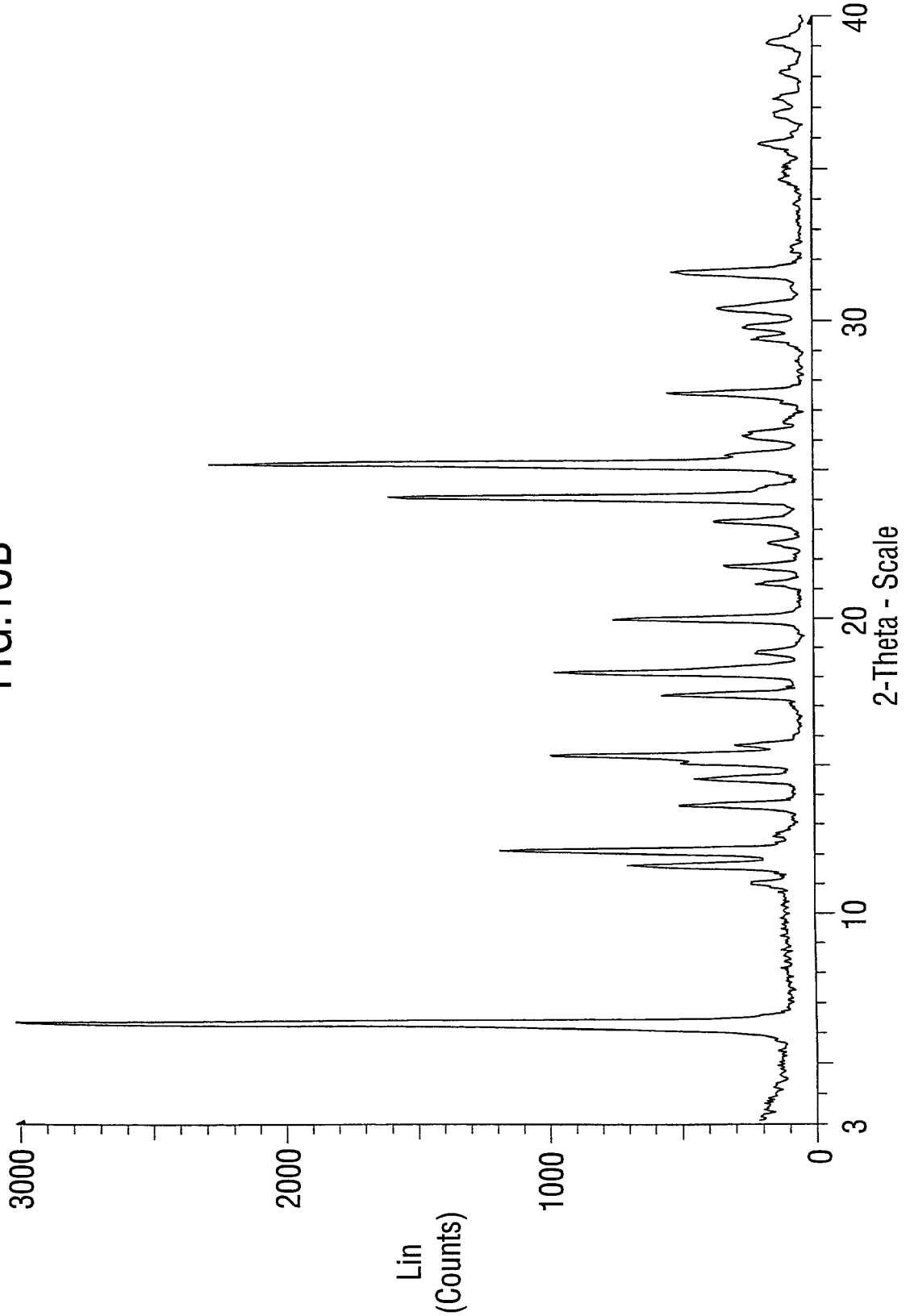


FIG. 11A

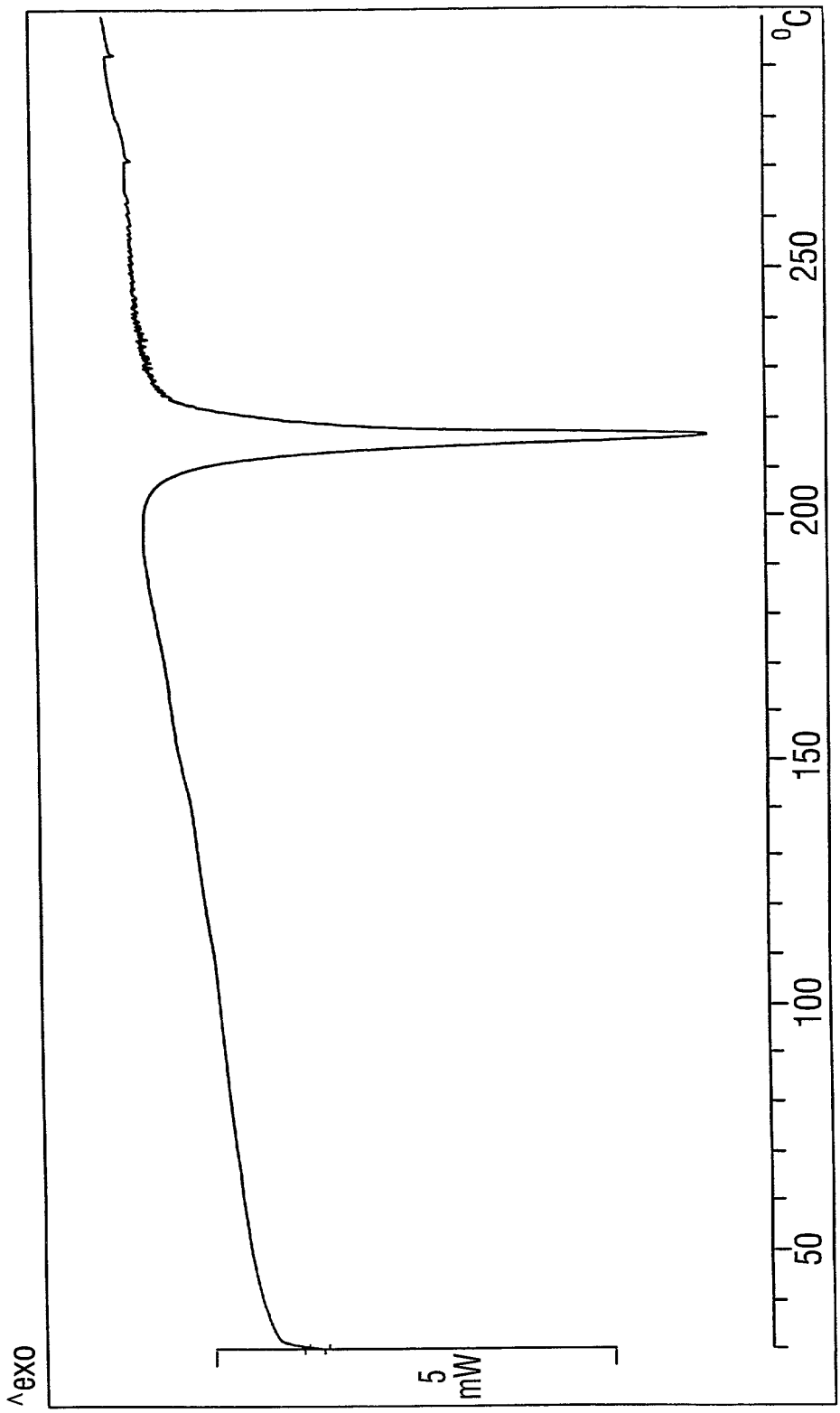
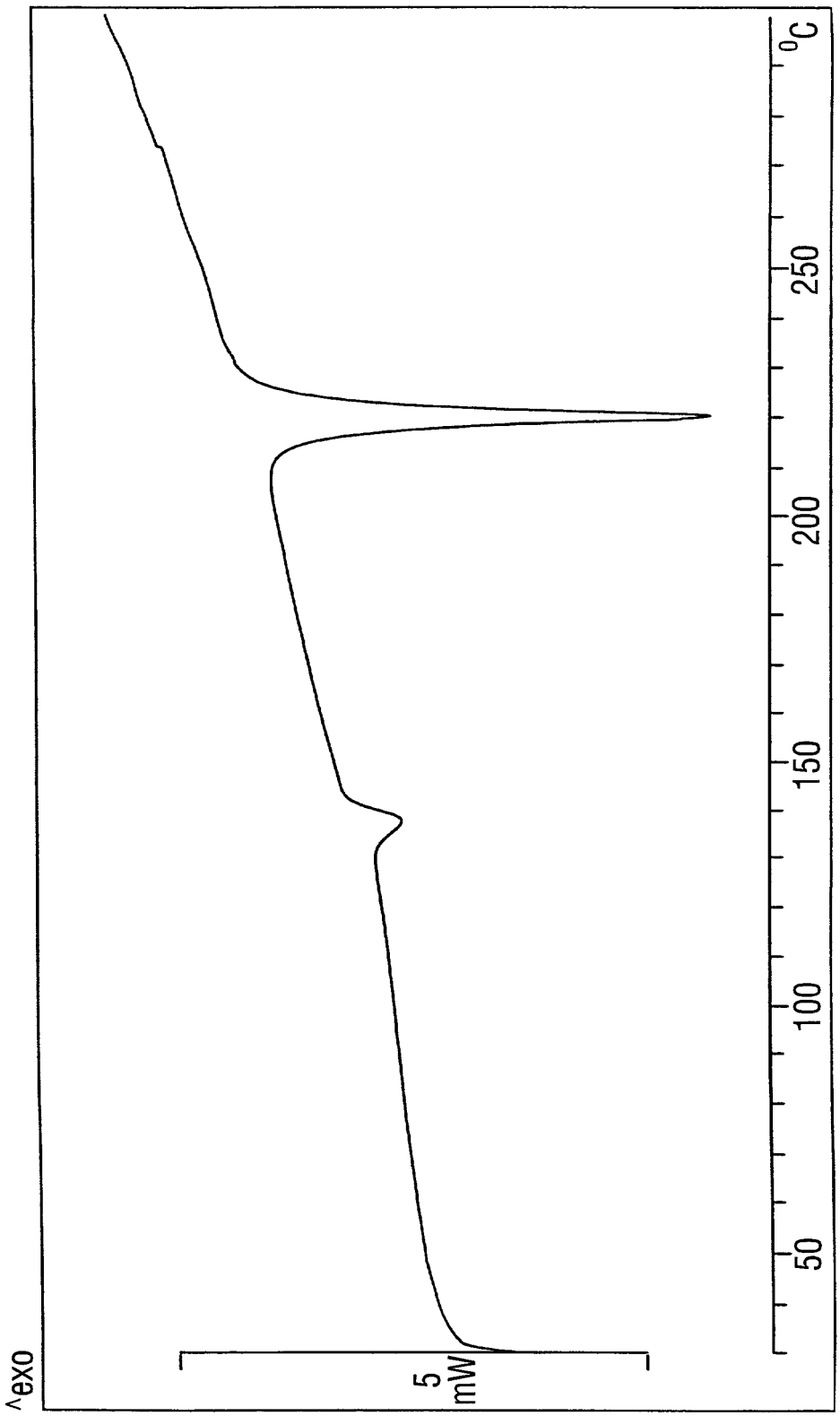


FIG. 11B



JC996 U.S. PTO 10/139730 05/06/02

FC 4913

U.S. UTILITY Patent Application

PATENT NUMBER and ISSUE DATE

APPL NUM	FILING DATE	CLASS	SUBCLASS	GAU	EXAMINER
10139730	05/06/2002	514	249	~~1614~~ 1624	KIFLE

**APPLICANTS: Bogle David; Rose Peter; Williams Glenn;

**CONTINUING DATA VERIFIED:
This appln claims benefit of 60/290,861 05/14/2001

** FOREIGN APPLICATIONS VERIFIED:

PG-PUB	DO NOT PUBLISH ☐	RESCIND ☐	
Foreign priority claimed	☐ yes ☐ no		ATTORNEY DOCKET NO
35 USC 119 conditions met	☐ yes ☐ no		PC11872A
Verified and Acknowledged Examiners's intials			

TITLE : Tartrate salts of 5,8, 14-triazatetracyclo[10.3.1.02,11 04.9]-hexadeca-2(11),3,5,7,9-pentaene and pharmaceutical compositions thereof

U.S.DEPT. OF COMM./PAT.& TM-PTO-436L(Rev. 12-94)

NOTICE OF ALLOWANCE MAILED	Assistant Examiner	CLAIMS ALLOWED	
		Total Claims	Print Claim for O.G.
ISSUE FEE		DRAWING	
Amount Due / Date Paid		Sheets Drwg. / Figs.Drwg. / Print Fig.	
☐ TERMINAL DISCLAIMER	Primary Examiner	Application Examiner	
	PREPARED FOR ISSUE		

WARNING: The information disclosed herein may be restricted. Unauthorized disclosure may be prohibited by the United States Code Title 35, Sections 122, 181 and 368, Possession outside the U.S. Patent & Trademark Office is restricted to authorized employees and contractors only.

FILED WITH: ☐ DISK (CRF) ☐ CD-ROM
(Attached in pocket on right inside flap)

SEARCH

Class	Sub.	Date	Exmr.
540	578	2/3/03	D.K.
514	2/4.03	1	1
	updated	9/19/03	

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.

SEARCH NOTES

(List databases searched. Attach search strategy inside.)

	Date	Exmr.
CAS	1/31/03	D.K.
consulted re 10/139,449		

ISSUE SLIP STAPLE AREA (for additional cross-references)

ISSUING CLASSIFICATION			
ORIGINAL		CROSS REFERENCE(S)	
CLASS	SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)
INTERNATIONAL CLASSIFICATION			
/			
/			
/			
/			
/			^ Continued on Issue Slip Inside File Jacket

INDEX OF CLAIMS

✓ ..... Rejected - (Through numeral) ... Canceled N ..... Non-elected A ..... Appeal
= ..... Allowed + ... Restricted I ..... Interference O ..... Objected

Claim Final	Claim Original	Date	Claim Final	Claim Original	Date	Claim Final	Claim Original	Date
	1			51			101	
	2			52			102	
	3			53			103	
	4			54			104	
	5			55			105	
	6			56			106	
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	46			96			146	
	47			97			147	
	48			98			148	
	49			99			149	
	50			100			150	

If more than 150 claims or 9 actions staple additional sheet here

PTO/SB/05 (2/98)
Approved for use through 09/30/2000. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Please type a plus sign (+) inside this box → +

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37C.F.R. §1.53(b))

Attorney Docket No.	PC11872A
First Named Inventor or Application Identifier	D. Bogle et al.
Title	TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.0^{2,11}.0^{4,9}]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF
Express Mail Label No.	EL 768 265 645 US

APPLICATION ELEMENTS
See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Commissioner for Patents, Box Patent Application, Washington, DC 20231

1. ☒ *Fee Transmittal Form (e.g., *PTO/SB/17*) *(Submit an original, and a duplicate for fee processing)*
2. ☒ Specification [Total Pages 45]
   (preferred arrangement set forth below)
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R&D
   - Reference in Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. ☒ Drawing(s) *(35 U.S.C. 11.3)* [Total sheets 20]
4. ☐ Oath or Declaration [Total pages]
   a. ☐ Newly executed (original or copy)
   b. ☐ Copy from a prior application (37 CFR §1.63(d)) *(for continuation/divisional with Box 17 completed)* ***[Note Box 5 below]***
      i. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§1.63(d)(2) and 1.33(b).
5. ☐ Incorporation By Reference *(useable if Box 4b is checked)* The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. ☐ Microfiche Computer Program *(Appendix)*
7. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. ☐ Computer Readable Copy
   b. ☐ Paper Copy (identical to computer copy)
   c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. ☐ Assignment Papers (cover sheet & document(s))
9. ☐ 37 C.F.R. §3.73(b) Statement ☐ Power of Attorney *(when there is an assignee)*
10. ☐ English Translation Document *(if applicable)*
11. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
12. ☒ Preliminary Amendment
13. ☒ Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
14. ☐ *Small Entity Statement(s) *(PTO/SB/09-12)* ☐ Statement filed in prior application, Status still proper and desired
15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
16. ☒ Other: This application claims the benefit of U.S. Provisional Ser. No. 60/290,861, filed May 14, 2001.

NOTE FOR ITEMS 1 & 14: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

17. If a **CONTINUING APPLICATION,** *check appropriate box, and supply the requisite information below and in a preliminary amendment:*
☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No: /

Prior application information: Examiner _____ *Group/Art Unit:* _____

18. CORRESPONDENCE ADDRESS

☐ *Customer Number or Bar Code Label* *(Insert Customer No. or Attach bar code label here)* or ☒ *Correspondence address below*

Name	Paul H. Ginsburg				
Address	Pfizer Inc				
Address	150 East 42nd Street, Patent Department (150/05/49)				
City	New York	State	New York	Zip Code	10017-5612
Country	United States Of America	Telephone	(212)573-2369	Fax	(212)573-1939

NAME (Print/type)	Roy F. Waldron	*Registration No. (Attorney/Agent)*	42,208
Signature		*Date*	May 6, 2002

UTILITY TRANSMITTAL PTO SB 05, 3/99, (1/1)

EXPRESS MAIL NO. EL 768 265 645 US

PTO/SB/17(2/98)
Approved for use through 09/30/2000.
OMB 0651-0032 Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL

Patent fees are subject to annual revision on October 1. These are the fees effective October 1, 2001.

*Small Entity payments **must** be supported by a small entity statement, otherwise large entity fees must be paid. See Forms PTO/SB/09-12.*

See 37 C.F.R. §§ 1.27 and 1.28.

Total Amount of Payment	($)2448.00

Complete if Known	
Application Number	NOT YET ASSIGNED
Filing Date	CONCURRENTLY HEREWITH
First Named Inventor	D. Bogle et al.
Examiner Name	NOT YET ASSIGNED
Group/Art Unit	NOT YET ASSIGNED
Attorney Docket No.	PC11872A

METHOD OF PAYMENT (check one)

1. ☒ The commissioner is hereby authorized to charge indicated fees and credit any over payments to:

Deposit Account Number: 16-1445

Deposit Account Name: PFIZER INC

☒ Charge Any Additional Fee Required Under 37 C.F.R. §§ 1.16 and 1.17.

☐ Charge the Issue Fee Set in 37 C.F.R. § 1.18 at the Mailing of the Notice of Allowance.

2. ☐ Payment Enclosed:

☐ Check ☐ Money Order ☐ Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	740	201	370	Utility filing fee	740.00
106	330	206	165	Design filing fee	
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	160	214	80	Provisional filing fee	

SUBTOTAL (1) ($)740.00

2. EXTRA CLAIM FEES

			Extra Claims		Fee from below		Fee Paid
Total Claims	90	-20**=	70	X	18	=	1260.00
Independent Claims	5	- 3**=	2	X	84	=	168.00
Multiple Dependent					280.00	=	280.00

** or number previously paid, if greater; For Reissues, see below

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	84	202	42	Independent claims in excess of 3
104	280	204	140	Multiple dependent claim, if not paid
109	84	209	42	**Reissue independent claims over original patent
110	18	210	9	**Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 1708.00

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge – late fee or oath	
127	50	227	25	Surcharge–late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	
117	920	217	460	Extension for reply within third month	
118	1,440	218	720	Extension for reply within fourth month	
128	1,960	228	980	Extension for reply within fifth month	
119	320	219	160	Notice of Appeal	
120	320	220	160	Filing a brief in support of an appeal	
121	280	221	140	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,280	241	640	Petition to revive - unintentional	
142	1,280	242	640	Utility issue fee (or reissue)	
143	460	243	230	Design issue fee	
144	620	244	310	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	180	126	180	Submission of Information Disclosure Statement	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	740	246	370	Filing a submission after final rejection (37 CFR 1.129(a))	
149	740	249	370	For each additional invention to be examined (37 CFR 1.129(b))	
Other Fee (specify)					
Other Fee (specify)					

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($)0.00

SUBMITTED BY				Complete (if Applicable)	
Type or Printed Name	Roy F. Waldron			Reg. Number	42,208
Signature		Date	May 6, 2002	Deposit Account User ID	16-1445/PFIZER INC

EXPRESS MAIL NO. EL 768 265 645 US

FEE TRANSMITTAL PTO SB 17, 3/99

FIG. 1

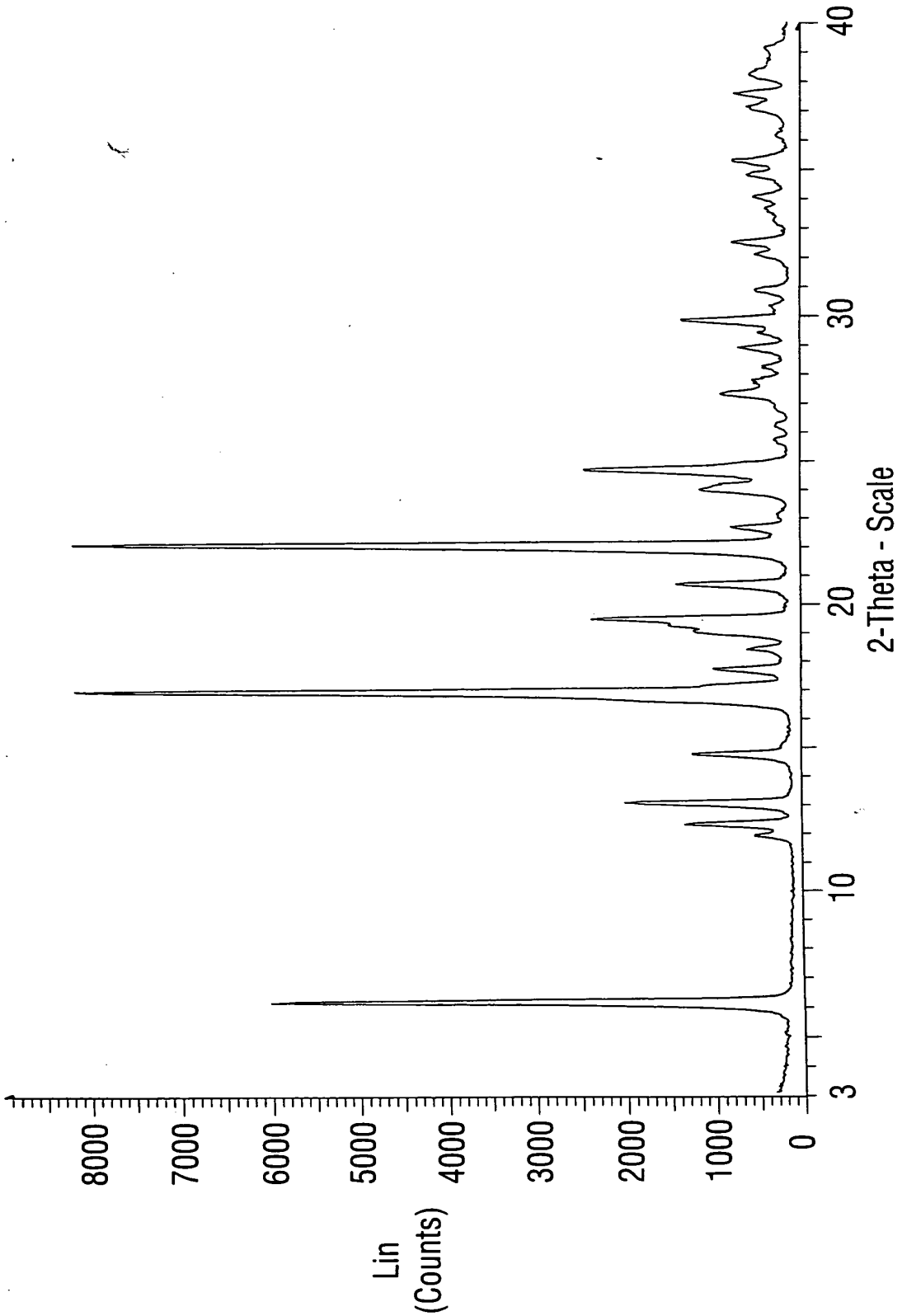


FIG. 2

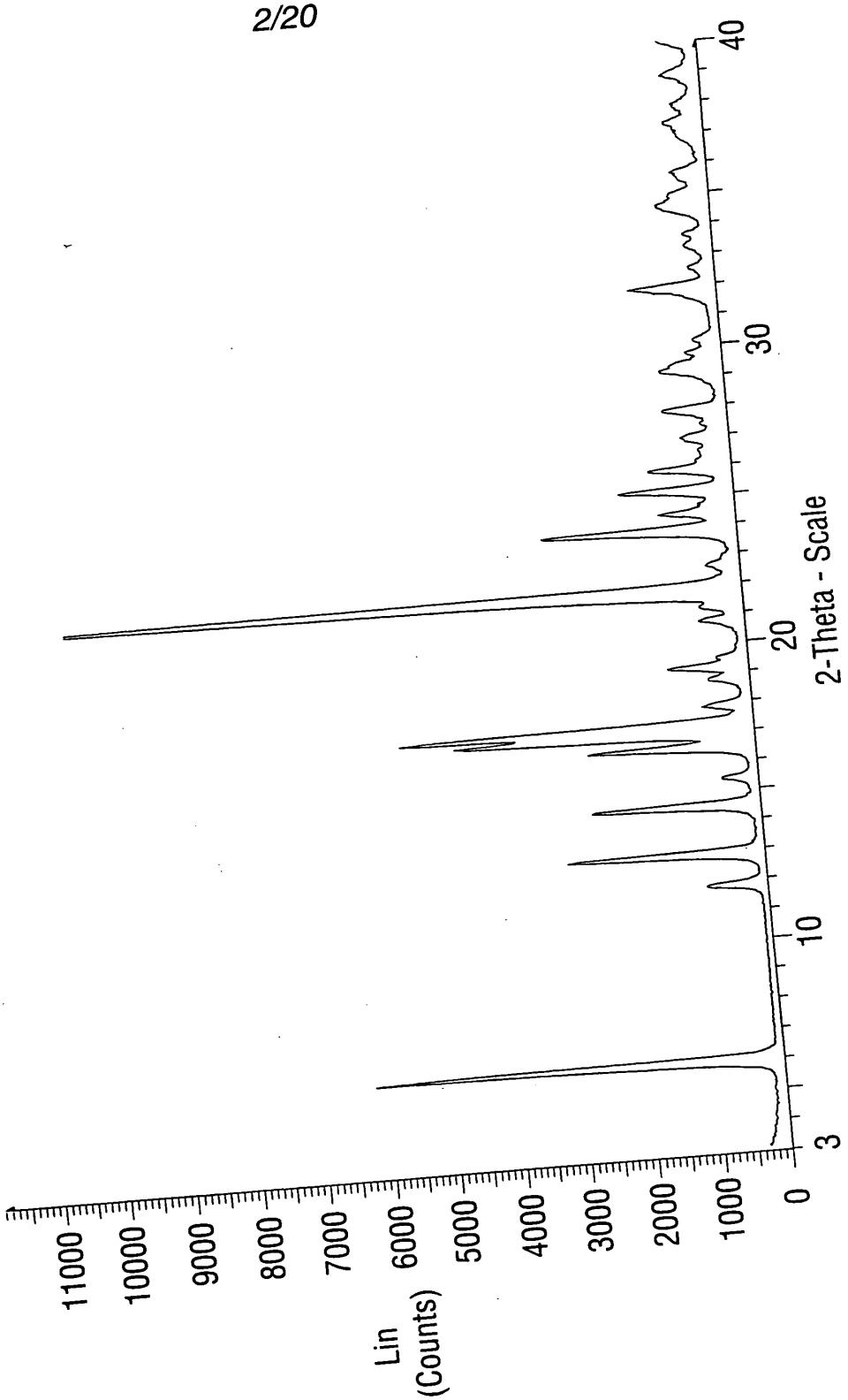


FIG. 3

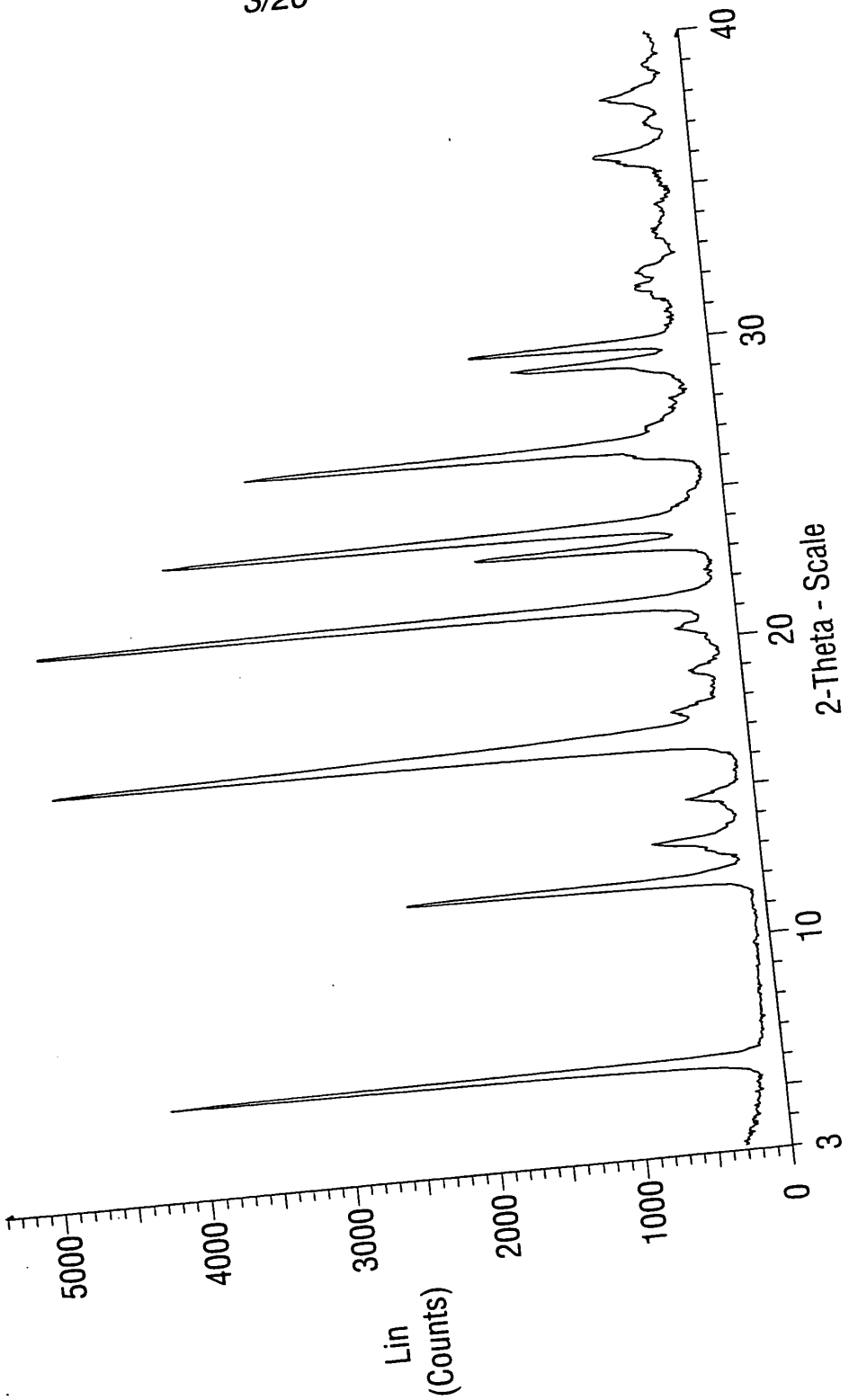


FIG. 4A

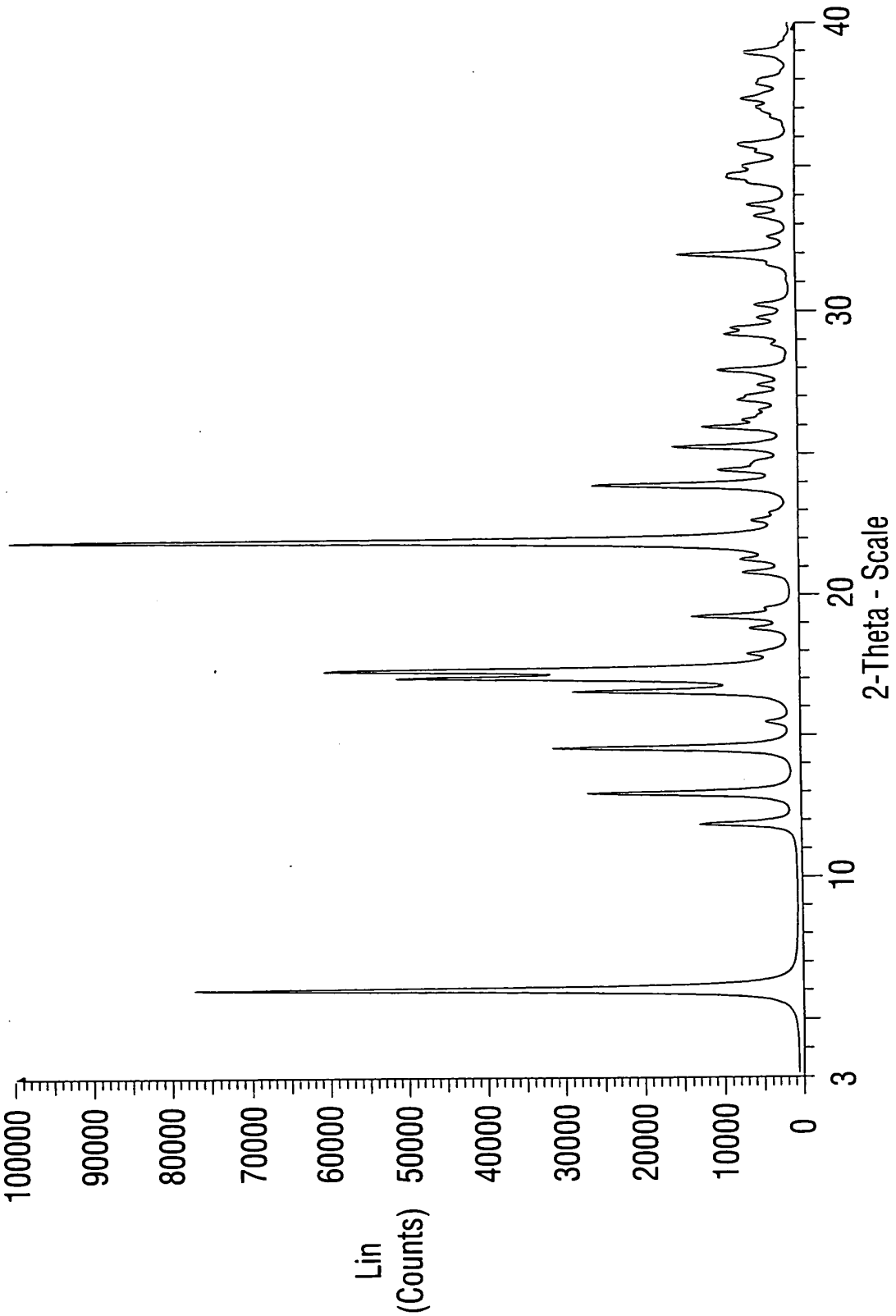


FIG. 4B

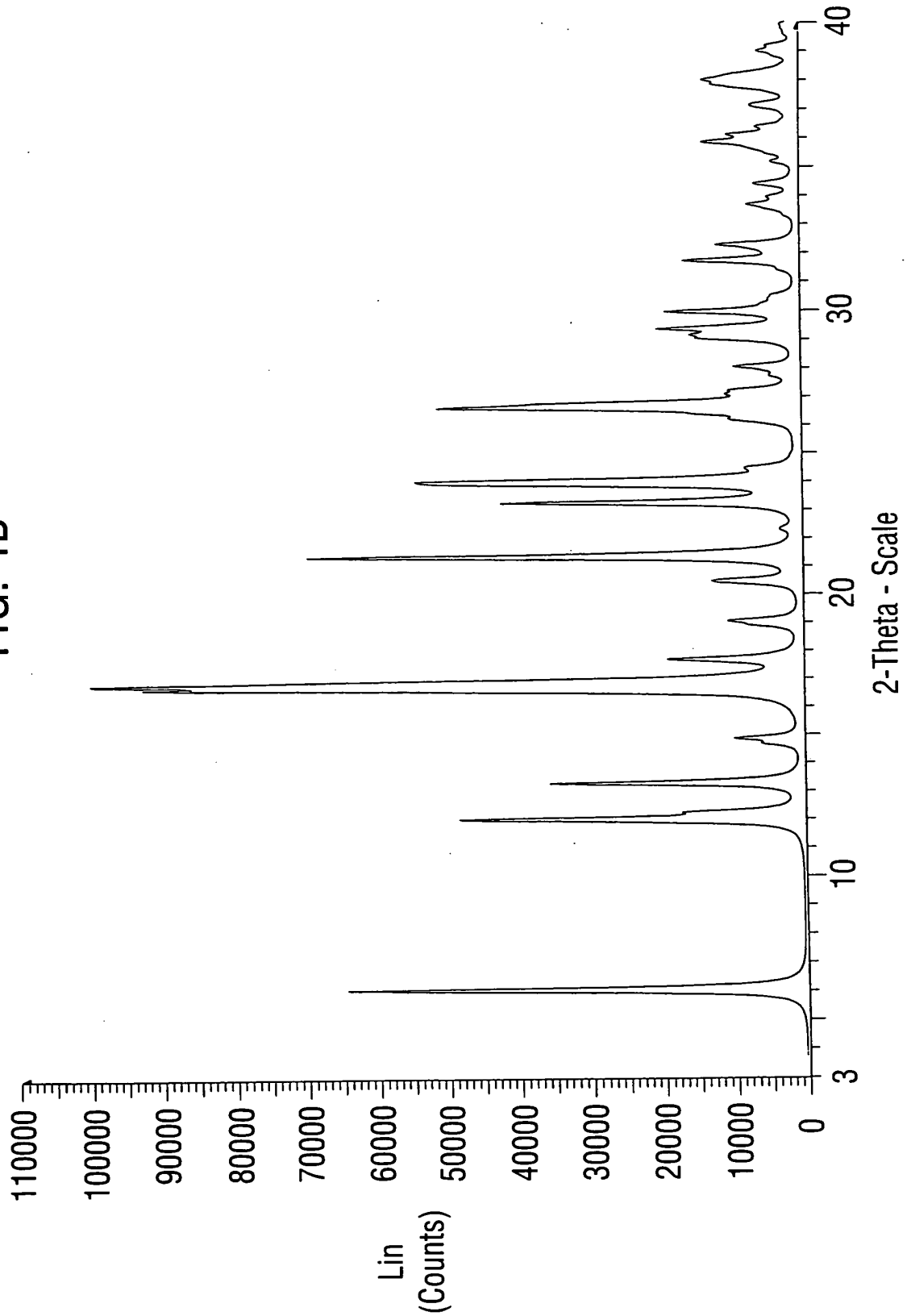


FIG. 5A

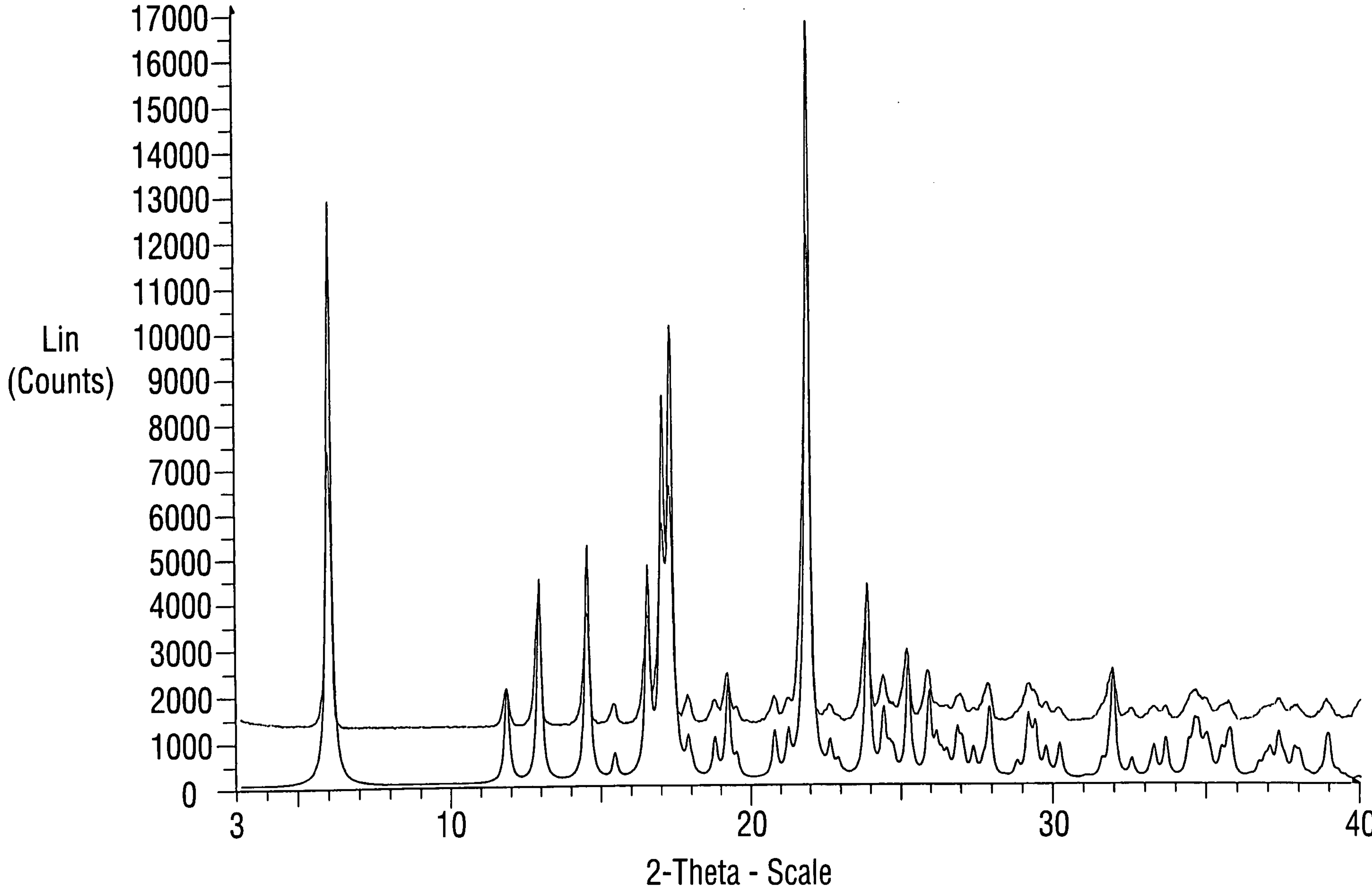


FIG. 5B

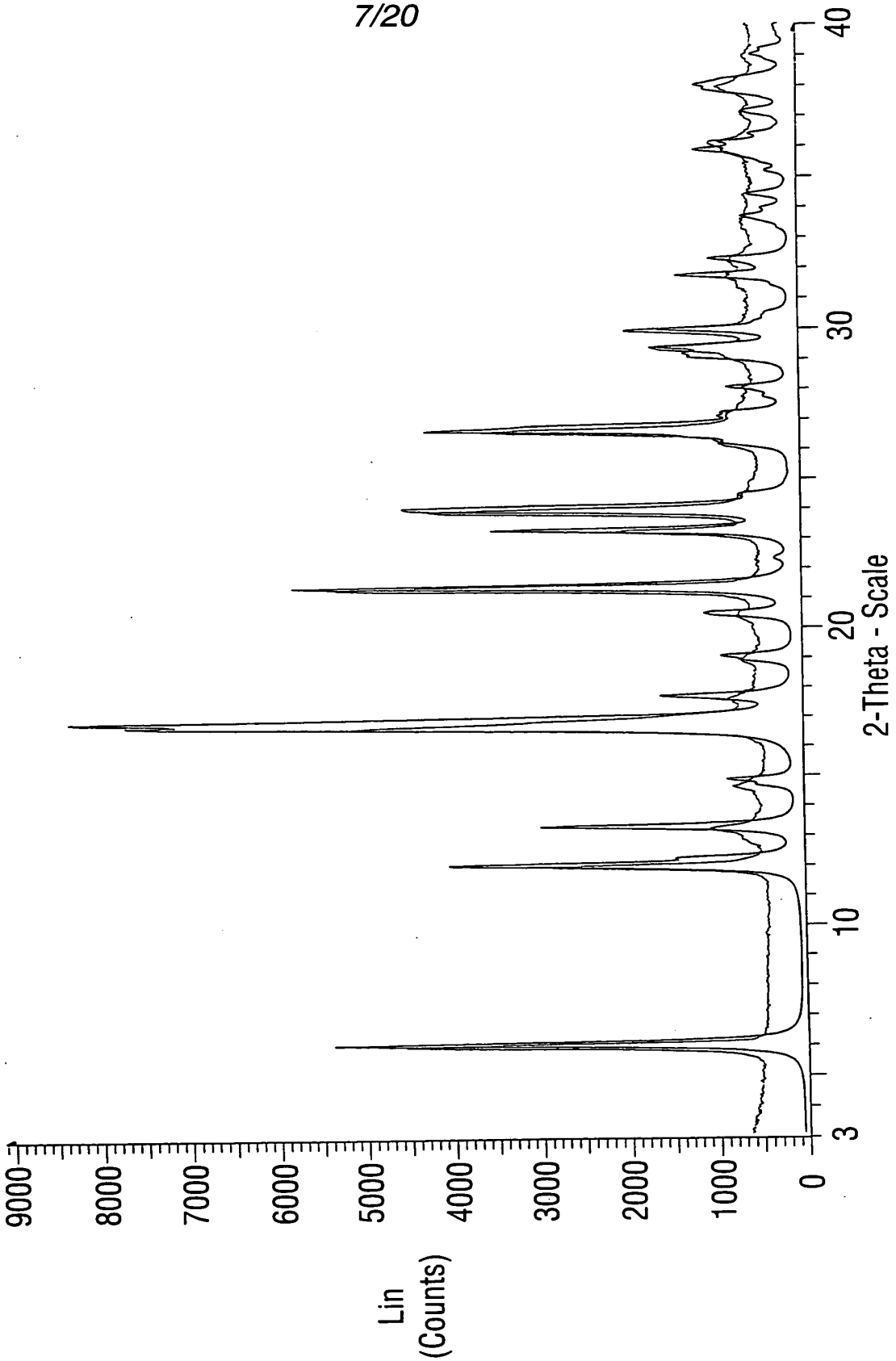
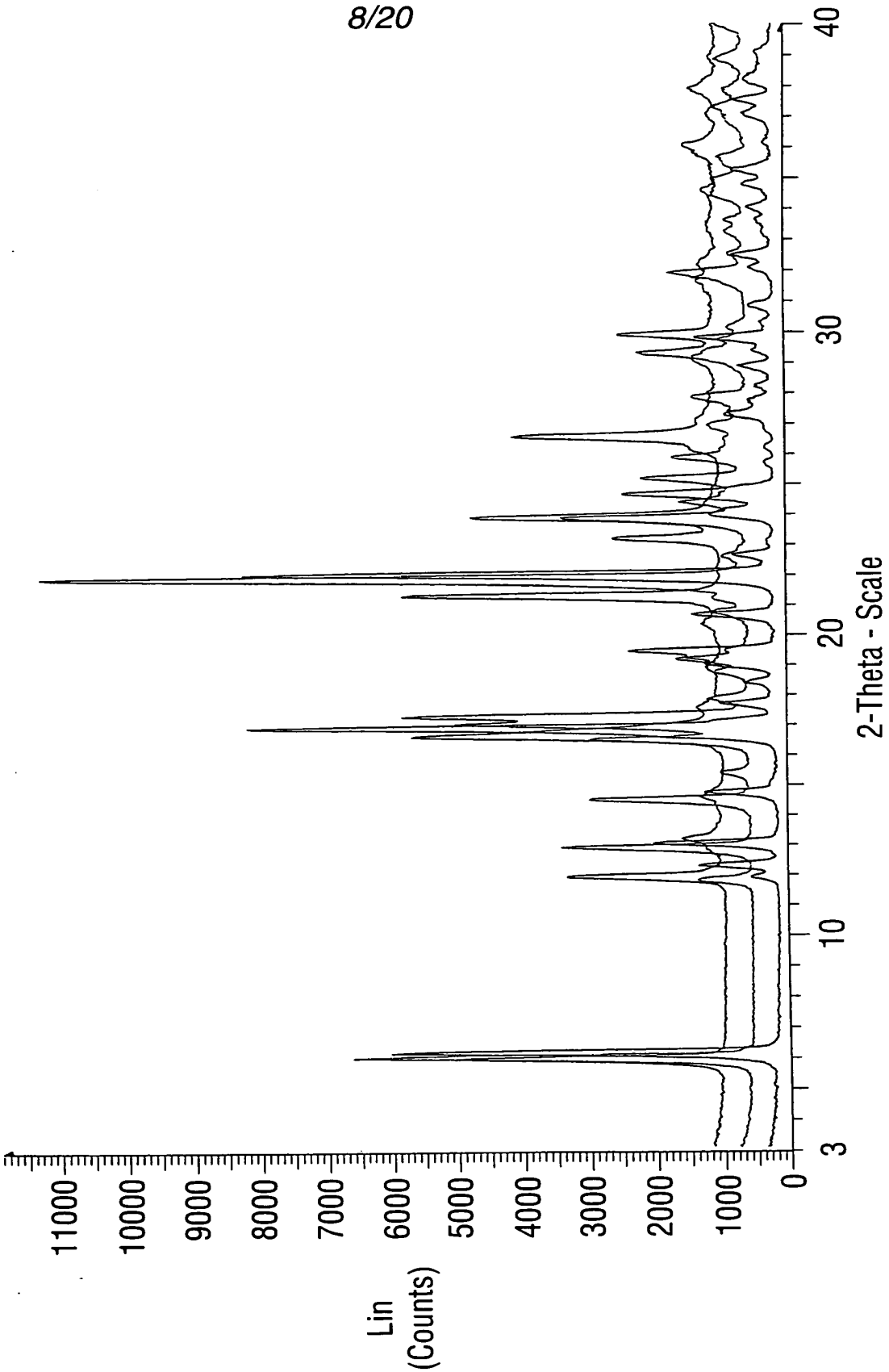


FIG. 6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(Counts)
11000
10000
9000
8000
7000
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4000
3000
2000
1000
0
3
10
20
30
40
2-Theta - Scale

FIG. 7A

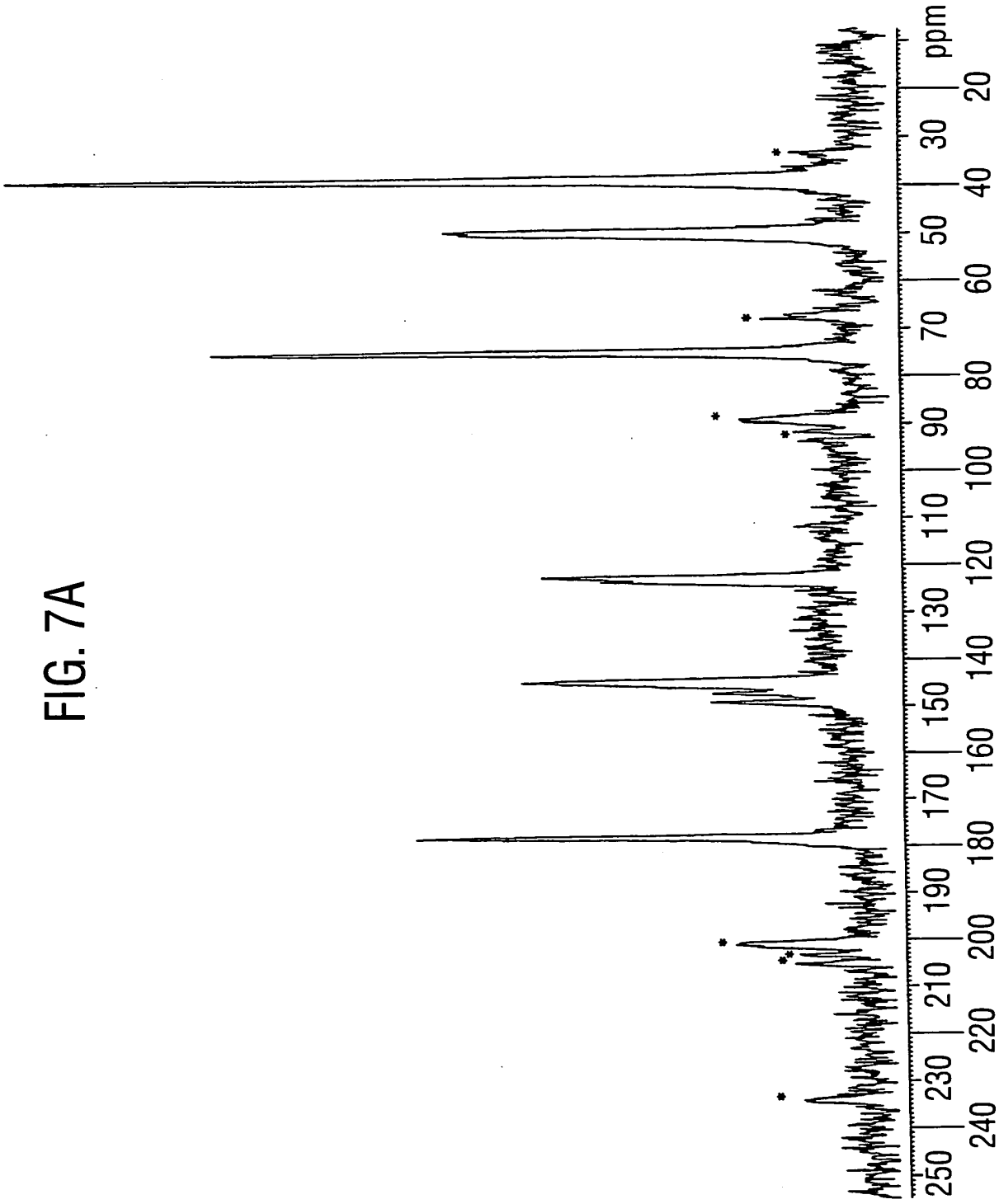


FIG. 7B

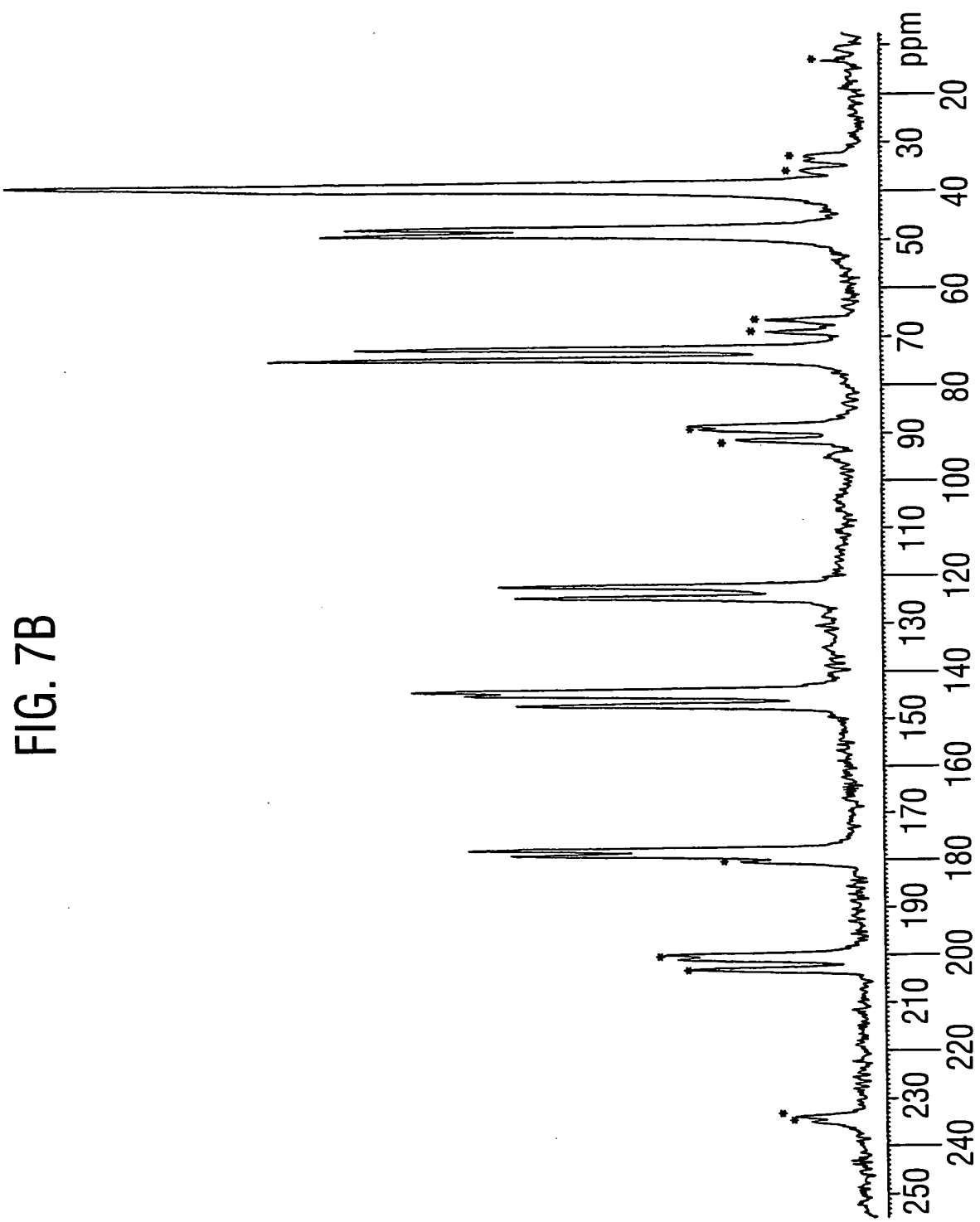


FIG. 7C

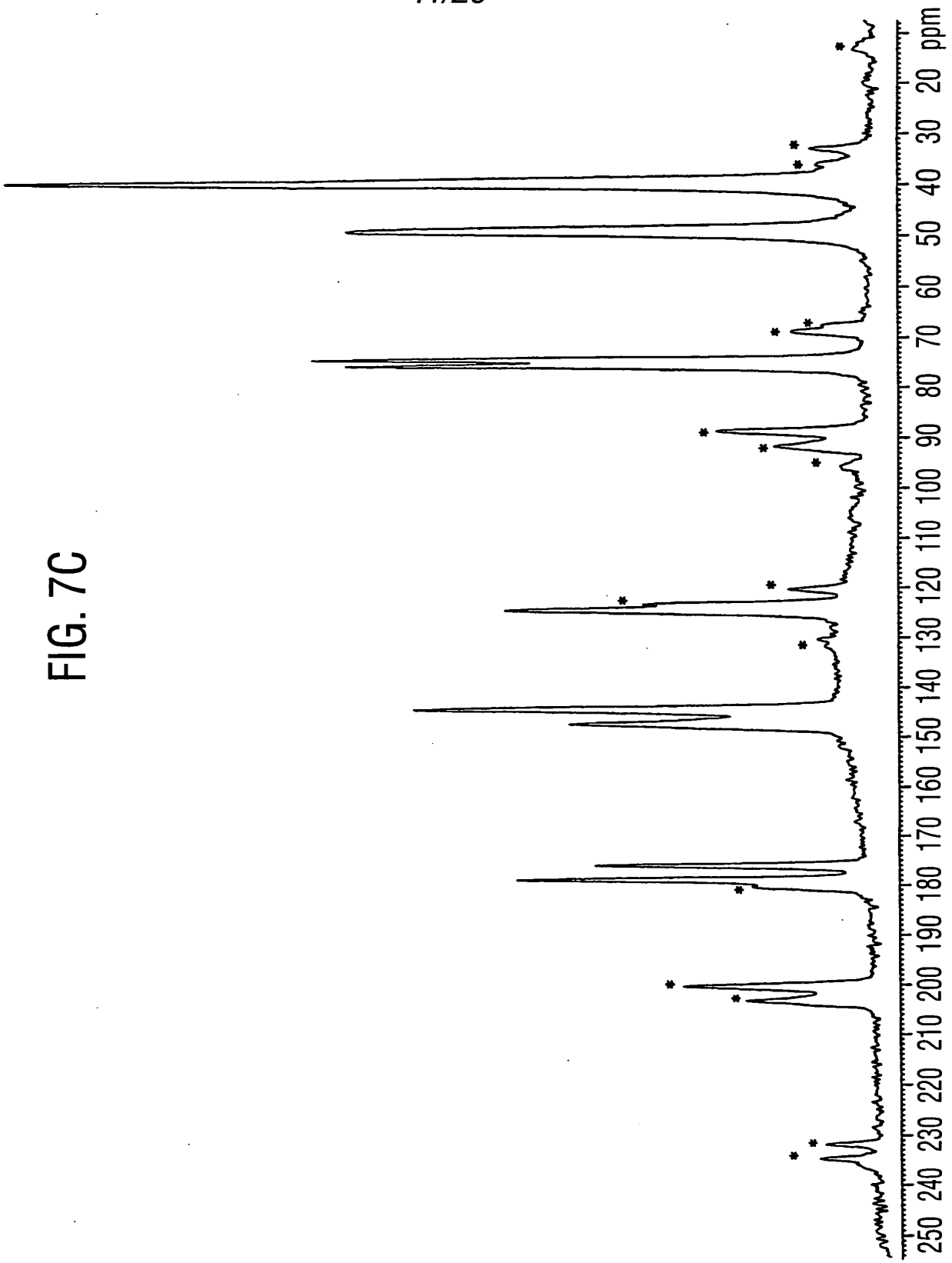


FIG. 8A

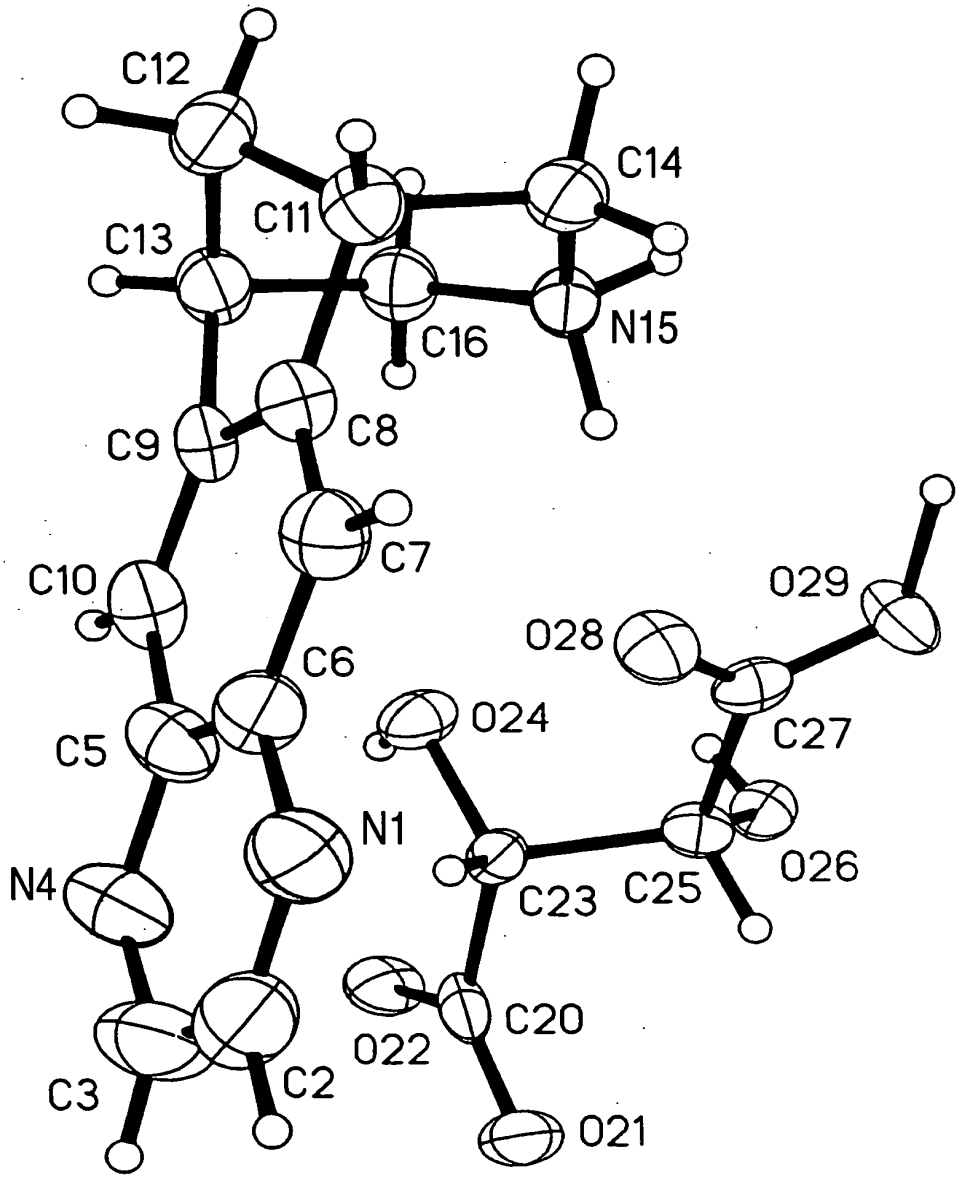


FIG. 8B

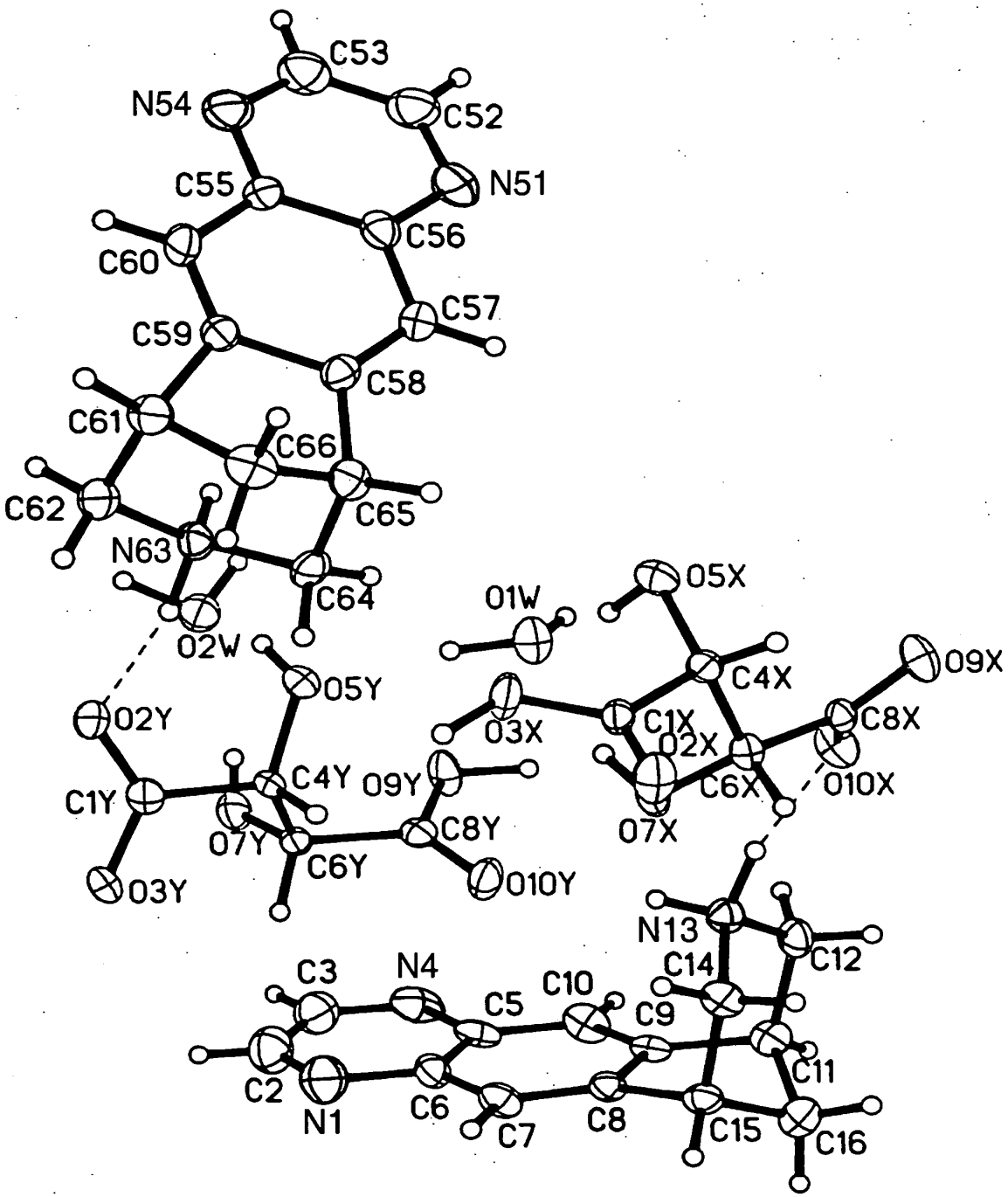


FIG. 9A

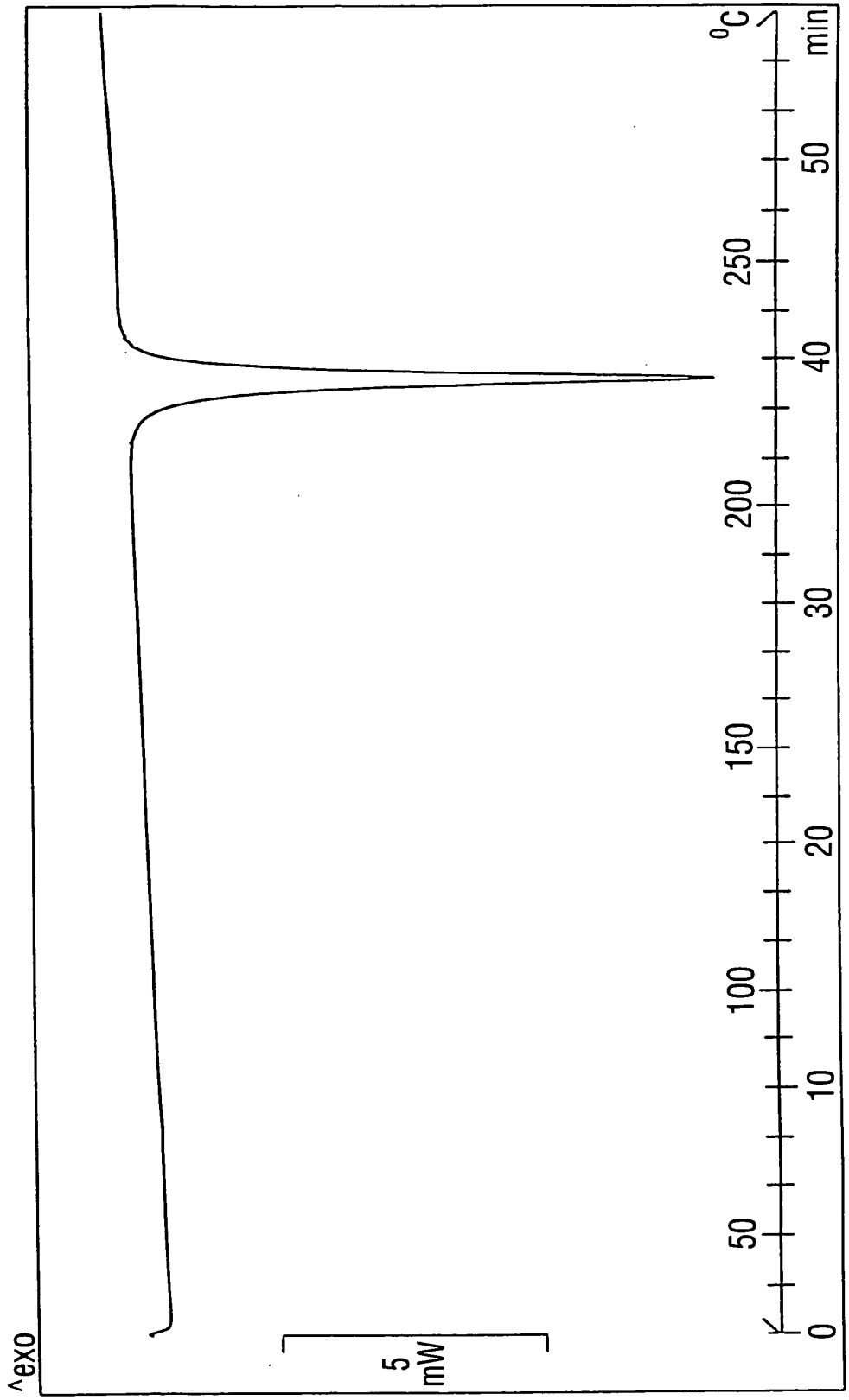


FIG. 9B

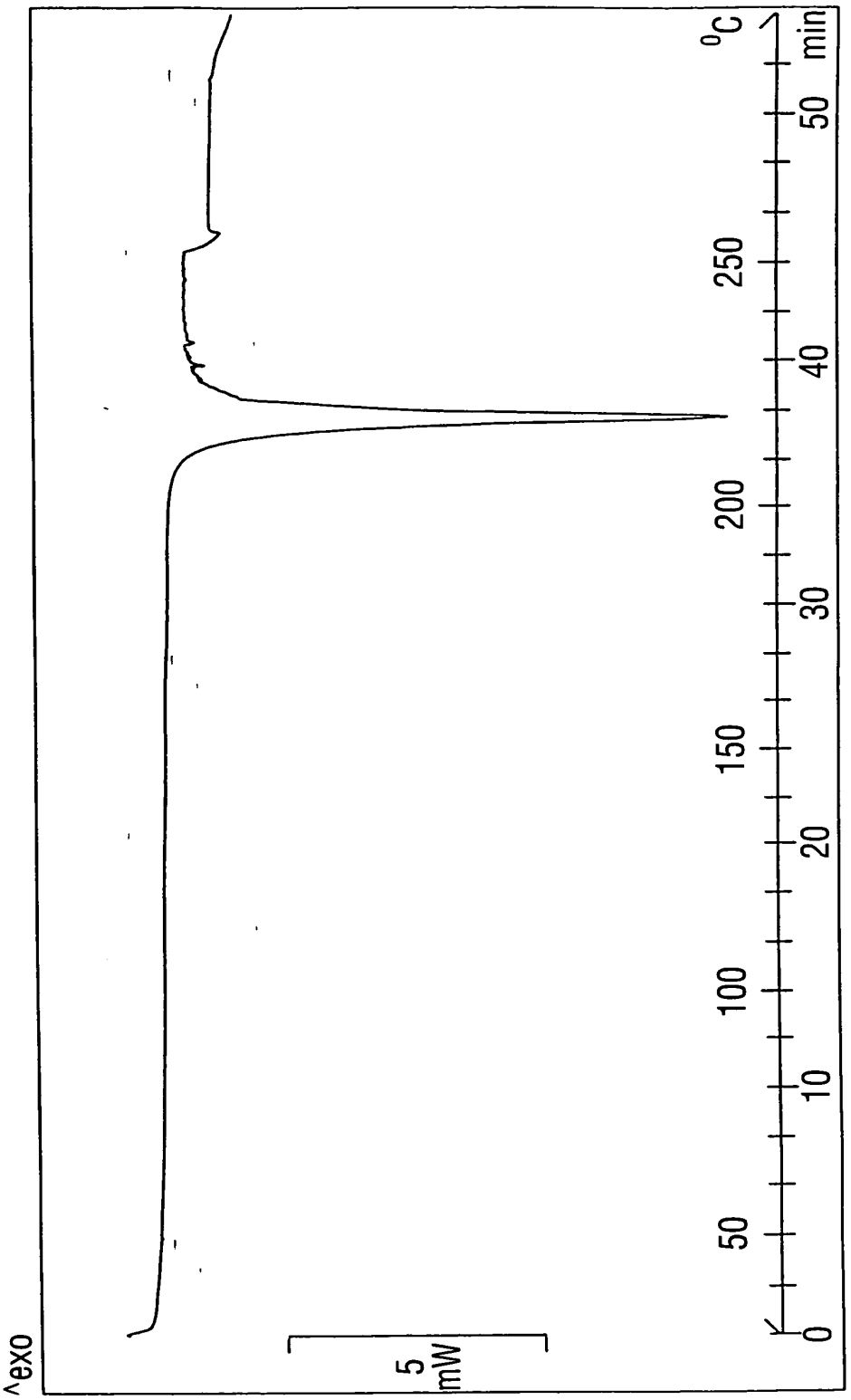


FIG. 9C

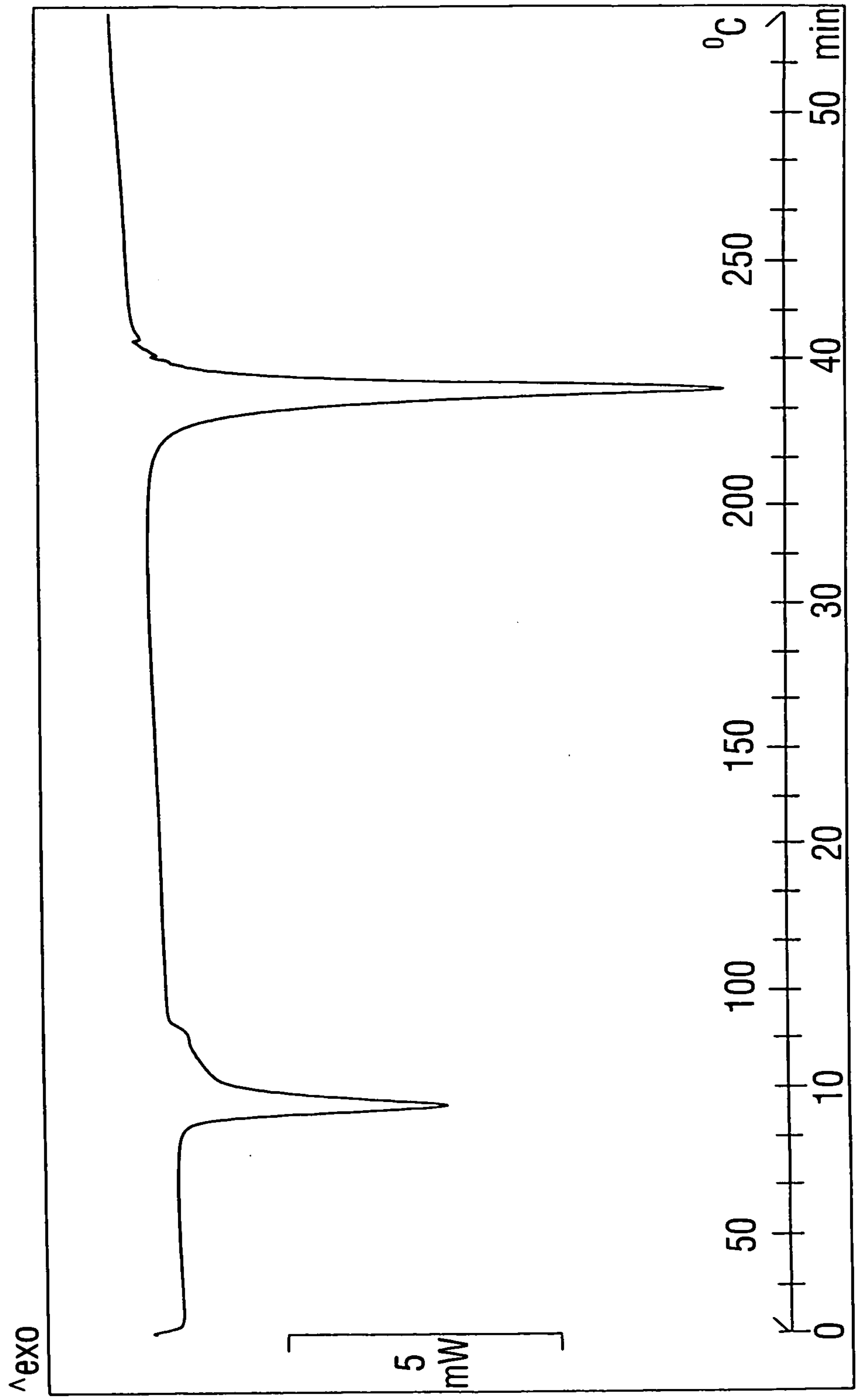


FIG.10A

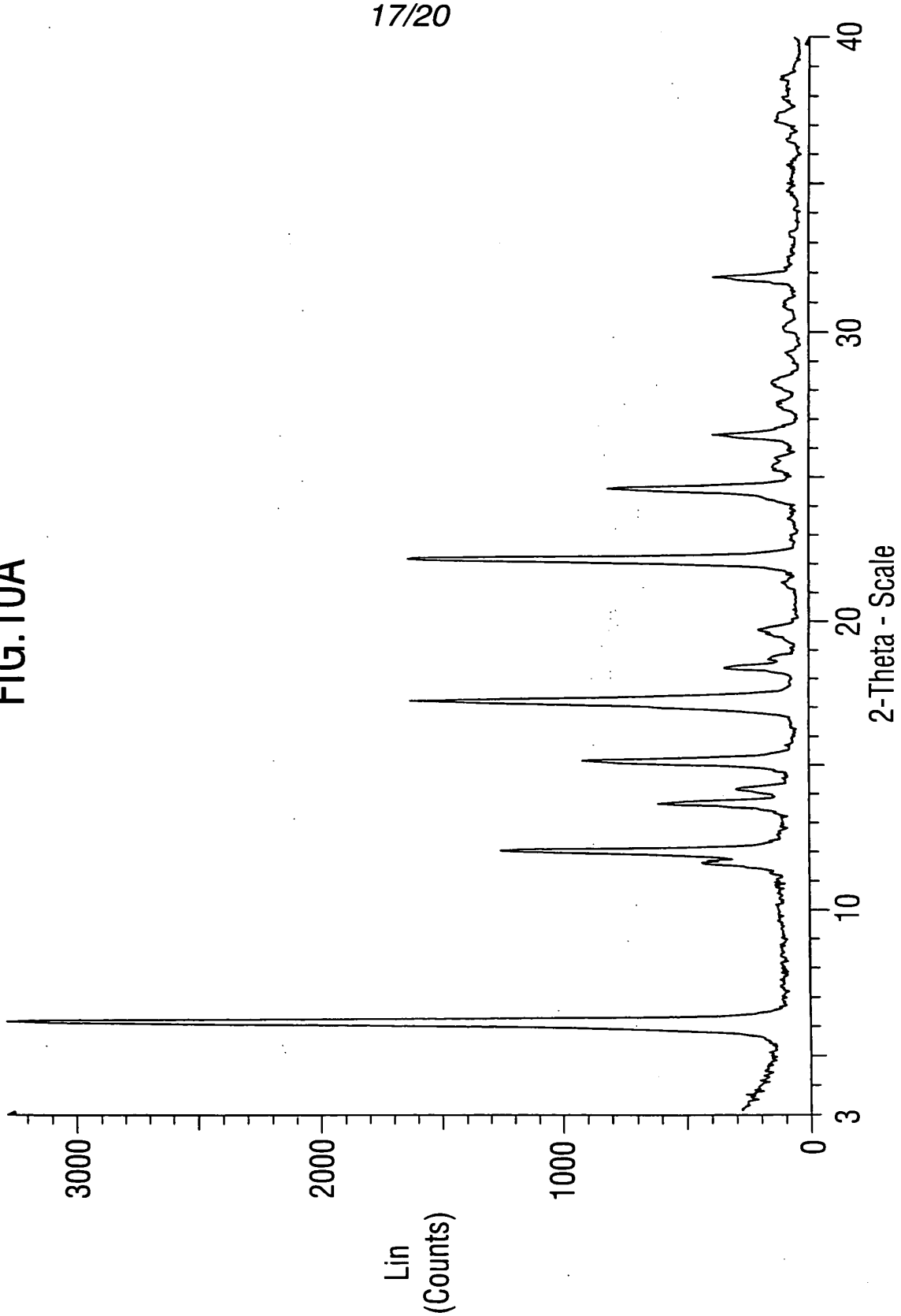


FIG.10B

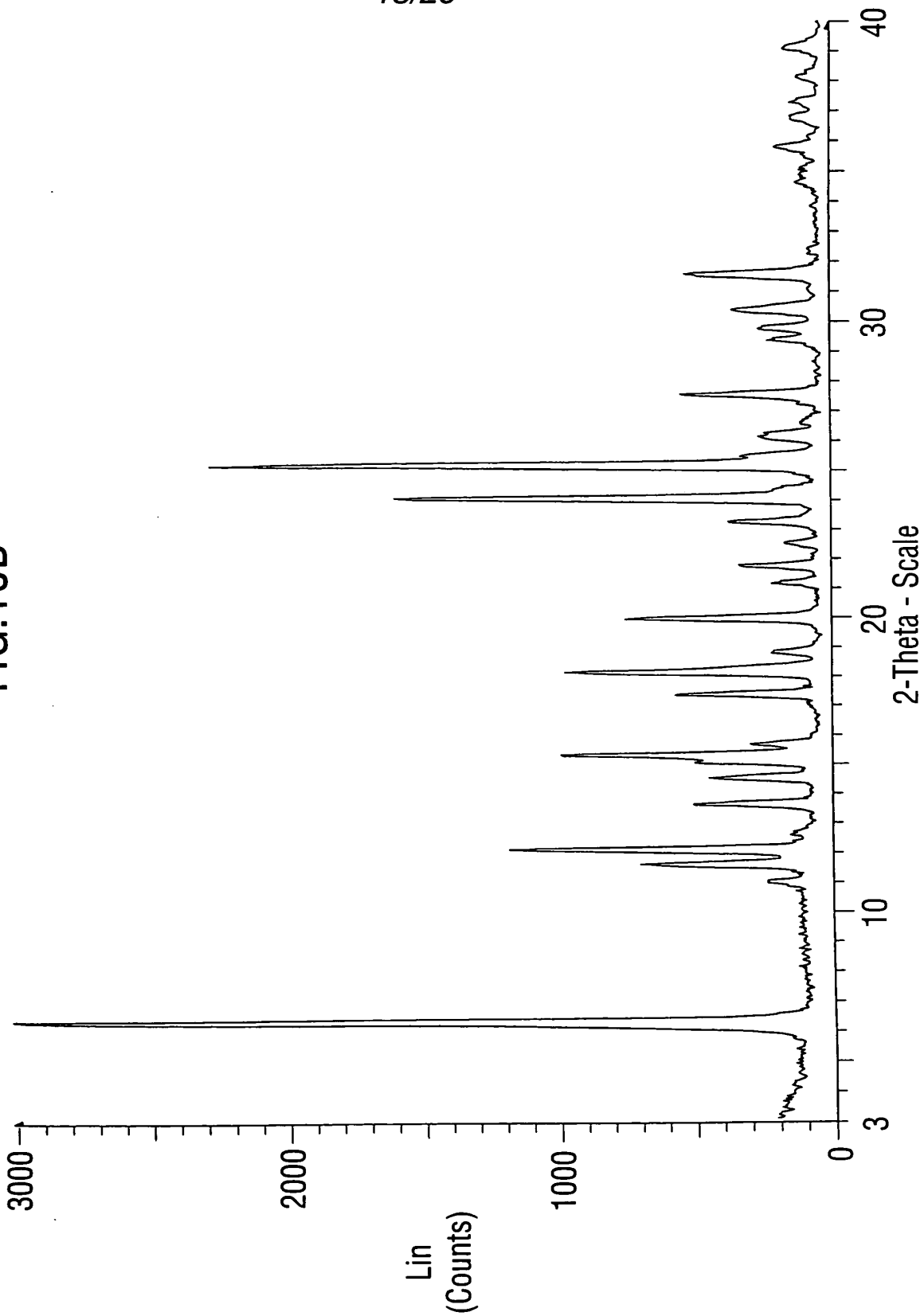


FIG. 11A

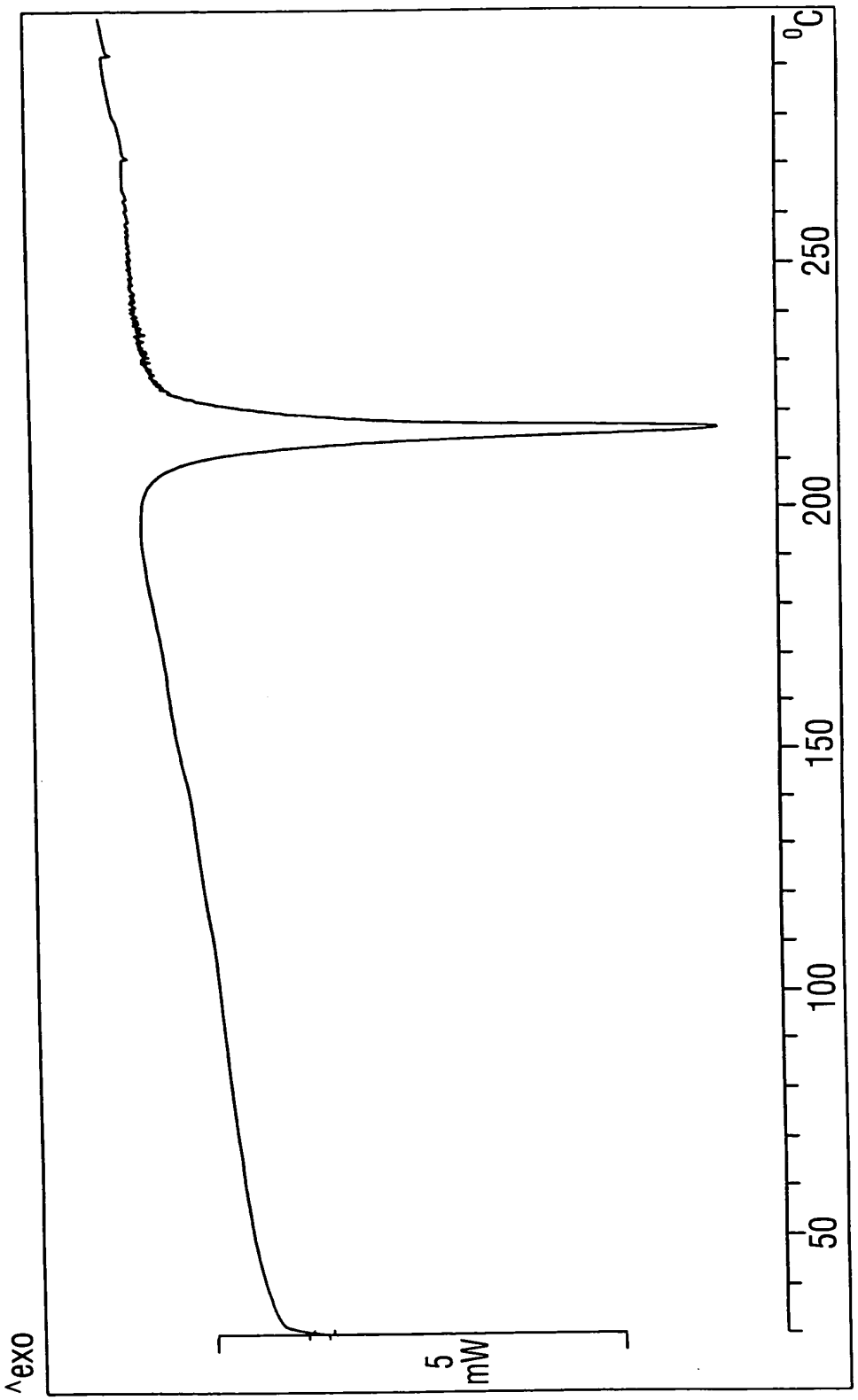
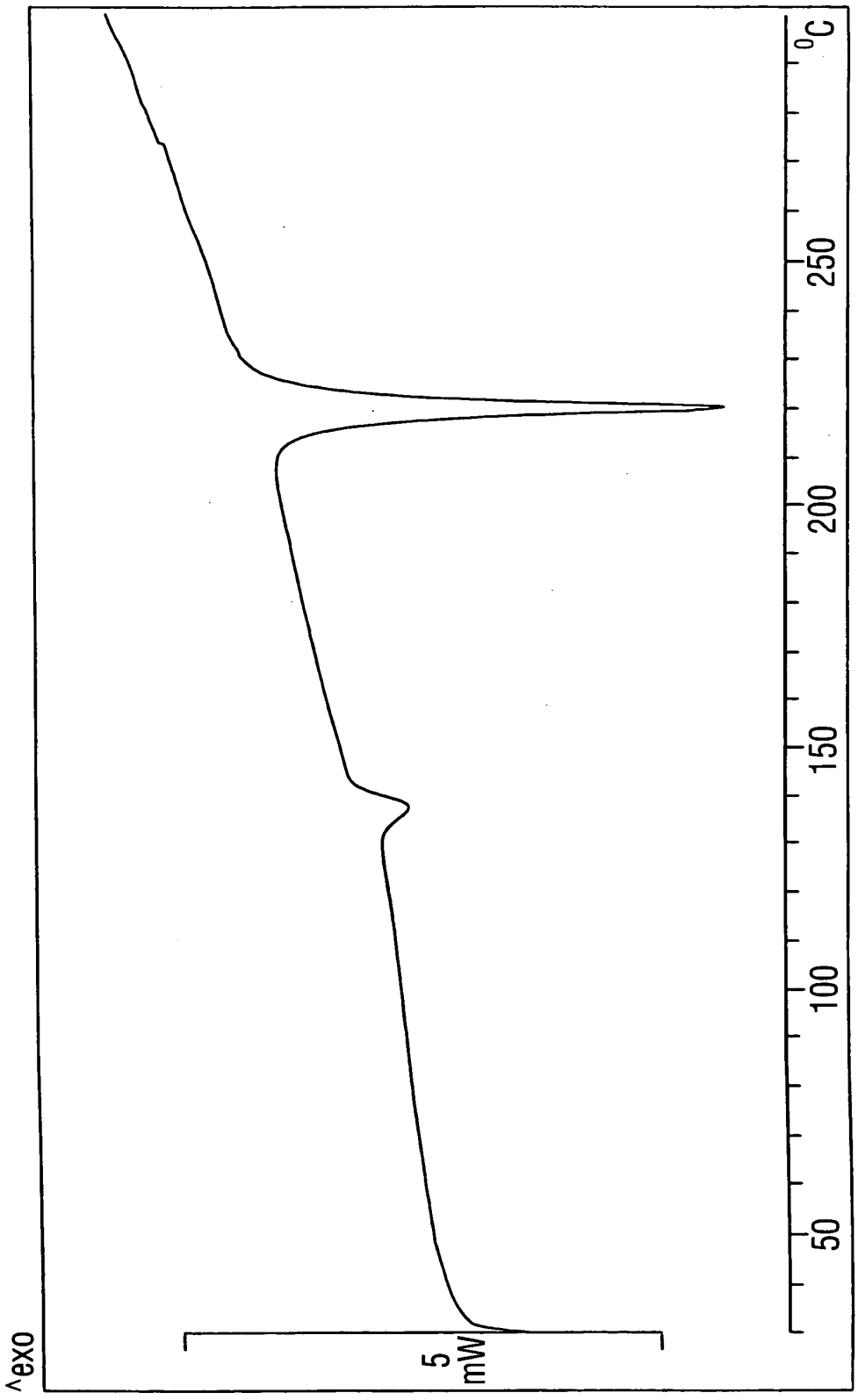


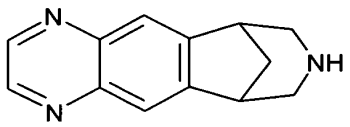
FIG. 11B



TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

INS A1

The present invention is directed to the tartrate salts of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene:



and pharmaceutical compositions thereof. The present invention in particular is directed to the L-tartrate salt, and further to the various polymorphs of the L-tartrate salt, including two distinct anhydrous polymorphs (referred to herein as Forms A and B) and a hydrate polymorph (referred to herein as Form C). In addition, the present invention is also directed to the D-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene and the various polymorphs thereof; as well as the D,L-tartrate salt thereof and its polymorphs, and the meso-tartrate salt thereof and its polymorphs.

The compound, 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, binds to neuronal nicotinic acetylcholine specific receptor sites and is useful in modulating cholinergic function. This compound is useful in the treatment of inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, drug/toxin-induced cognitive impairment (*e.g.*, from alcohol, barbiturates, vitamin deficiencies, recreational drugs, lead, arsenic, mercury), disease-induced cognitive impairment (*e.g.*, arising from Alzheimer's disease (senile dementia), vascular dementia, Parkinson's disease, multiple sclerosis, AIDS, encephalitis, trauma, renal and hepatic encephalopathy, hypothyroidism, Pick's disease, Korsakoff's syndrome and frontal and subcortical dementia), hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (*e.g.*, dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, migraine, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, attention deficit hyperactivity disorder (ADHD), Tourette's Syndrome, particularly, nicotine dependency, addiction and withdrawal; including use in smoking cessation therapy.

The tartrate salts of this invention may also be used in a pharmaceutical composition in combination with an antidepressant such as, for example, a tricyclic antidepressant or a

serotonin reuptake inhibiting antidepressant (SRI), in order to treat both the cognitive decline and depression associated with AD, PD, stroke, Huntington's chorea or traumatic brain injury (TBI); in combination with muscarinic agonists in order to stimulate both central muscarinic and nicotinic receptors for the treatment, for example, of ALS, cognitive dysfunction, age-related cognitive decline, AD, PD, stroke, Huntington's chorea and TBI; in combination with neurotrophic factors such as NGF in order to maximize cholinergic enhancement for the treatment, for example, of ALS, cognitive dysfunction, age-related cognitive decline, AD, PD stroke, Huntington's chorea and TBI; or in combination with agents that slow or arrest AD such as cognition enhancers, amyloid aggregation inhibitors, secretase inhibitors, tau kinase inhibitors, neuronal anti-inflammatory agents and estrogen-like therapy.

Compounds that bind to neuronal nicotinic receptor sites, including 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, and its hydrochloride salt, are referred to in WO 99/35131, published July 15, 1999 (corresponding to U.S Ser. No. 09/402,010, filed September 28, 1999 and 09/514,002, filed February 25, 2000). The foregoing applications, owned in common with the present application and incorporated herein by reference in their entirety, generically recite pharmaceutically acceptable acid addition salts for the compounds referred to therein.

The L-tartrate salt of the present invention exhibits properties, including those of high solid-state stability and compatibility with certain drug product formulation excipients, that render it superior to previously known salts of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene. Further, the D-tartrate and D,L-tartrate salts exhibit properties that also make them appropriate for drug product formulation use.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a powder X-ray diffraction of the anhydrous L-tartrate salt Form A of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta).

Figure 2 is the powder X-ray diffraction of the anhydrous L-tartrate salt Form B of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta).

Figure 3 is the powder X-ray diffraction of the L-tartrate salt hydrate Form C of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta).

Figure 4A is the calculated powder X-ray diffraction pattern of the anhydrous Form B L-tartrate salt of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta). **Figure 4B** is the calculated powder X-ray diffraction pattern of the Form C L-tartrate salt hydrate of 5,8,14-triazatetra-

cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta).

Figure 5A is the calculated powder X-ray diffraction pattern (lower trace) laid over the observed X-ray diffraction pattern (upper trace) for the anhydrous Form B L-tartrate salt of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta). **Figure 5B** is the calculated powder X-ray diffraction pattern (lower trace) laid over the observed X-ray diffraction pattern (upper trace) for the Form C L-tartrate salt hydrate of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta).

Figure 6 is the overlay of the powder X-ray diffraction patterns of the Form A (lower trace), Form B (middle trace) and Form C (upper trace) L-tartrate salts of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta).

Figures 7A, 7B and **7C** are the solid state ^{13}C NMR spectra of the L-tartrate salts of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene Forms A, B and C, respectively, as measured by cross-polarization magic angle spinning (CPMAS) at 295 K on a Bruker 7mm wide-bore magic angle spinning (WB MAS) probe positioned in a Bruker Avance DRX 500 MHz NMR Spectrometer. Peaks marked with asterisks (*) are spinning sidebands which are displaced at multiples of the spinning frequencies along both sides of the real peaks (centerbands).

Figure 8A is the X-ray crystal structure (absolute configuration) for the anhydrous Form B L-tartrate salt of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene. **Figure 8B** is the X-ray crystal structure (absolute configuration) for the Form C L-tartrate salt hydrate of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

Figure 9A, 9B and 9C are the differential scanning calorimetric traces for the L-tartrate salts Forms A, B and C, respectively, of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

Figure 10A and 10B are the powder X-ray diffraction patterns of the D,L-tartrate salt Forms X and Y, respectively, of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta).

Figure 11A and 11B are the differential scanning calorimetric traces for the D,L-tartrate salts Forms X and Y, respectively, of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

SUMMARY OF THE INVENTION

The present invention relates to the tartrate salts of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene. The tartrate salts of the invention include the L-tartrate, D-tartrate, D,L-tartrate and meso-tartrate salts.

In particular, the present invention relates to the L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

In one embodiment of the invention, the L-tartrate of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene is the anhydrous L-tartrate salt, referred to herein as Form A. The L-tartrate Form A is characterized by the principal x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation (within the margins of error indicated):

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
6.1	14.5
12.2	7.2
13.0	6.8
14.7	6.0
16.8	5.3
19.4	4.6
21.9	4.1
24.6	3.6

The L-tartrate crystal Form A is characterized in that it has a onset of melt at about 223 °C as measured by differential scanning calorimetry at a heating rate of 5 degrees per minute. The L-tartrate Form A is also characterized in that when examined by solid state ^{13}C NMR cross-polarization magic angle spinning techniques, it exhibits the following principal resonance peaks (± 0.1ppm) downfield from 100 ppm (adamantane standard 29.5 ppm): 178.4, 149.3, 147.4, 145.1, and 122.9 ppm.

In another embodiment of the invention, the L-tartrate of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene is another anhydrous L-tartrate salt polymorph, referred to herein as Form B. The L-tartrate salt Form B is characterized by the principal x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation (within the margins of error indicated):

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
5.9	15.0
12.8	6.9
14.4	6.1
15.3	5.8
16.9	5.2
17.2	5.2
21.8	4.1
23.8	3.7
25.1	3.5

The L-tartrate salt Form B has a single crystal x-ray structure (absolute configuration) as set forth in Figure 8A. Further, the Form B forms orthorhombic crystals belonging to the P2(1)2(1)2(1) space group. Form B is further characterized in having an onset of melting at about 215 °C as measured by differential scanning calorimetry at a heating rate of 5 degrees per minute. Further, Form B of the invention is also characterized in having an aqueous solubility of about 156 mg/ml and a native pH of about 3.3 in aqueous solution. In addition, Form B has a hygroscopicity of approximately 0.2% at 90% relative humidity.

The L-tartrate Form B is also characterized in that when examined by solid state ^{13}C NMR cross-polarization magic angle spinning techniques, it exhibits the following principal resonance peaks (± 0.1ppm) downfield from 100 ppm (adamantane standard 29.5 ppm): 179.2, 178.0, 147.4, 145.2, 144.4, 124.8 and 122.5 ppm.

In another embodiment of the invention, the L-tartrate of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene is the hydrate L-tartrate salt, referred to herein as Form C. The L-tartrate Form C is characterized by the principal x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation (within the margins of error indicated):

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
5.9	15.1
11.8	7.5
16.5	5.4
21.2	4.2
23.1	3.8
23.8	3.7
26.5	3.4

The hydrate L-tartrate crystal Form C has a single crystal structure as set forth in Figure 8B. Further, the hydrate Form C forms monoclinic crystals belonging to the P2(1) space group. Form C is further characterized in having an onset of a solid-solid transition at

about 72 °C and an onset of melting transition at about 220 °C. Because Form B converts to the hydrate Form C upon contact with 100% relative humidity, Form C has the same aqueous solubility as Form B.

The L-tartrate Form C is also characterized in that when examined by solid state ^{13}C NMR cross-polarization magic angle spinning techniques, it exhibits the following principal resonance peaks (± 0.1ppm) downfield from 100 ppm (adamantane standard 29.5 ppm): 179.0, 176.1, 147.5, 144.5 and 124.6 ppm.

A further embodiment of the invention is directed to the D-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene. In particular, the present invention is directed to the three D-tartrate salt polymorphs (referred to here as Forms A', B' and C') which exhibit the same x-ray diffraction characteristics, hygroscopicity, water content and thermal characteristics as Forms A, B and C of the L-tartrate salt.

In another embodiment, the present invention relates to the D,L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, and in particular, two polymorphs, an anhydrous form (herein referred to as Form X) and a hydrate form (herein referred to as Form Y).

The D,L-tartrate Form X is characterized by the principal x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation (within the margins of error indicated):

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
6.0	14.6
11.9	7.4
15.0	5.9
17.1	5.2
22.1	4.0
24.5	3.6

The D,L-tartrate Form X is further characterized in having an onset of a melting transition at about 212 °C.

The D,L-tartrate Form Y is characterized by the principal x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation (within the margins of error indicated):

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
6.2	14.2
12.0	7.4
15.2	5.8
18.1	4.9
24.0	3.7
25.1	3.5

The D,L-tartrate Form Y is further characterized in having an onset of a solid-solid transition at about 131 °C and an onset of melting transition at about 217 °C.

Another embodiment of the invention relates to a pharmaceutical composition comprising at least one of polymorphic Forms A, B or C, preferably Form B, of the L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene and a pharmaceutically acceptable carrier or excipient, for use in the treatment of inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, drug/toxin-induced cognitive impairment (*e.g.*, from alcohol, barbiturates, vitamin deficiencies, recreational drugs, lead, arsenic, mercury), disease-induced cognitive impairment (*e.g.*, arising from Alzheimer's disease (senile dementia), vascular dementia, Parkinson's disease, multiple sclerosis, AIDS, encephalitis, trauma, renal and hepatic encephalopathy, hypothyroidism, Pick's disease, Korsakoff's syndrome and frontal and subcortical dementia), hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (*e.g.*, dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, migraine, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, attention deficit hyperactivity disorder (ADHD), and Tourette's Syndrome. Another more preferred embodiment of the invention is wherein the pharmaceutical composition is useful in the treatment of nicotine dependency, addiction and withdrawal; most preferably, for use in smoking cessation therapy.

The present invention further relates to pharmaceutical compositions for the uses described in the foregoing paragraph comprising any one of the D-tartrate salt of, the D,L-tartrate salt of, or the meso-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

The present invention further relates to a method of treating inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, drug/toxin-induced cognitive impairment (*e.g.*, from alcohol, barbiturates, vitamin deficiencies, recreational drugs, lead, arsenic, mercury), disease-induced cognitive impairment (*e.g.*, arising from Alzheimer's disease (senile dementia), vascular dementia, Parkinson's disease, multiple sclerosis, AIDS, encephalitis, trauma, renal and hepatic encephalopathy, hypothyroidism, Pick's disease, Korsakoff's syndrome and frontal and subcortical dementia), hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (*e.g.*, dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, migraine, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, attention deficit hyperactivity disorder (ADHD), and Tourette's Syndrome comprises administering to a subject in need of treatment a therapeutically effective amount of any of Forms A, B or C of the L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, preferably Form B. Another more preferred embodiment of the invention relates to a method of treatment for nicotine dependency, addiction and withdrawal, in particular for use in smoking cessation therapy activity, comprising the administration of any of Forms A, B or C of the L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, preferably Form B, to a subject in need thereof.

The present invention further relates to methods of treatment described in the foregoing paragraph comprising the administration of any of the D-tartrate salt, the D,L-tartrate salt or the meso-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene to a subject in need thereof.

The term "treating" as used herein, refers to, and includes, reversing, alleviating, inhibiting the progress of, or preventing a disease, disorder or condition, or one or more symptoms thereof; and the term "treatment" refers to the act of treating, as defined above.

The invention also relates to a process for the preparation of the Form A of L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with between 1 and 2 equivalents of L-tartaric acid; and

(ii) collecting the crystals formed.

A preferred embodiment of this invention relates to the above process wherein 1.1 equivalents of L-tartaric acid is employed and the tartaric acid is added to a solution containing the free base. A preferred mode of practicing this process is wherein the contact step is allowed to proceed for less than 2 hours. A more preferred embodiment of this invention relates to the above process wherein the contact step (*i.e.*, step "(i)" above) is allowed to proceed above 45 °C. Another preferred embodiment of this invention relates to the above process wherein the suitable solvent is selected from the group consisting of a (C_1-C_6)alkyl alcohol, a (C_1-C_6)alkyl ketone or a (C_1-C_6)alkyl ether, acetonitrile and (C_1-C_6)alkyl esters (e.g., ethyl acetate, isopropyl acetate, etc.). More preferably, the suitable solvent is ethanol or methanol.

The invention further relates to a process for the preparation of Form A' of the D-tartrate salt comprising steps (i) and (ii) referred to above for making Form A of the L-tartrate salt, but using D-tartaric acid in step (i) in place of L-tartaric acid.

The invention also relates to a process for the preparation of Form B of L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene comprising the steps of:

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of L-tartaric acid; and

(ii) collecting the crystals formed.

A preferred embodiment of this invention relates to the above process wherein about 1.1 to about 2.2 equivalents, more preferably 1.1 equivalents, of L-tartaric acid is employed and the free base in solution is added to a solution containing L-tartaric acid. A preferred mode of practicing this process is wherein the contact step is allowed to proceed for a minimum of 1 hours; more preferably, for at least 2 hours; most preferably, longer than 12 hours. A preferred embodiment is wherein the suitable solvent is selected from the group consisting of a (C_1-C_6)alkyl alcohol, a (C_1-C_6)alkyl ketone or a (C_1-C_6)alkyl ether, acetonitrile and (C_1-C_6)alkyl esters (e.g., ethyl acetate, isopropyl acetate, etc.). More preferably, the suitable solvent is methanol or ethanol, most preferably methanol.

The invention further relates to a process for the preparation of Form B' of the D-tartrate salt comprising steps (i) and (ii) referred to above for making Form B of the L-tartrate salt, but using D-tartaric acid in step (i) in place of L-tartaric acid.

Another aspect of the present invention relates to a process for the preparation of the Form C of the L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene comprising the steps of:

(i) contacting either of Form A or Form B of the L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene with water; and

(ii) collecting the crystals formed.

A preferred embodiment of this invention relates to the above process wherein the contacting of step (i) comprises slurrying either of Forms A or B with water with subsequent addition of an organic solvent to promote precipitation of the Form C product. A more preferred embodiment of the process is wherein the organic solvent use to promote precipitation is methanol, ethanol or acetonitrile.

The invention further relates to a process for the preparation of Form C' of the D-tartrate salt comprising steps (i) and (ii) referred to above for making Form C of the L-tartrate salt but using Forms A' or B' of the D-tartrate salt in step (i) in place of Forms A or B of the L-tartrate salt.

The present invention further relates to a process for the preparation of Form X of the D,L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene comprising the steps of:

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of D,L-tartaric acid; and

(ii) collecting the crystals formed.

A preferred embodiment of this invention relates to the above process wherein about 2.2 equivalents of D,L-tartaric acid is employed and the free base in solution is added to a solution containing D,L-tartaric acid. A preferred mode of practicing this process involves allowing the contact step to proceed for a minimum of 2 hours; more preferably, for at least 12 hours; and most preferably, at least 24 hours.

Another preferred embodiment of this invention relates to the above process for preparing Form X wherein the suitable solvent is anhydrous or nearly anhydrous and is selected from the group consisting of a (C_1-C_6)alkyl alcohol, a (C_1-C_6)alkyl ketone or a (C_1-C_6)alkyl ether, acetonitrile and (C_1-C_6)alkyl esters (e.g., ethyl acetate, isopropyl acetate, etc.). More preferably, the suitable solvent is ethanol.

The present invention further relates to a process for the preparation of Form Y of the D,L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene comprising the steps of:

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of D,L-tartaric acid; and

(ii) collecting the crystals formed.

A preferred embodiment of this invention relates to the above process wherein about 2.2 equivalents of D,L-tartaric acid is employed and the free base in solution is added to a solution containing D,L-tartaric acid. A preferred mode of practicing this process involves allowing the contact step to proceed for a minimum of 2 hours; more preferably, for at least 12 hours; most preferably, for at least 24 hours.

Another preferred embodiment of this invention relates to the above process for preparing Form Y wherein the suitable solvent is selected from the group consisting of a (C_1-C_6)alkyl alcohol, a (C_1-C_6)alkyl ketone or a (C_1-C_6)alkyl ether, acetonitrile and (C_1-C_6)alkyl esters (e.g., ethyl acetate, isopropyl acetate, etc.) admixed with water. More preferably, the suitable solvent is ethanol admixed with water; most preferably, 20% aqueous ethanol.

DETAILED DESCRIPTION OF THE INVENTION

The compound, 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene is a nicotinic partial agonist for the treatment of a number of CNS diseases, disorders and conditions including, in particular, nicotine dependency, addiction and withdrawal.

Although in general the salts of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene are all crystalline, the majority of such salts are so significantly hygroscopic as to render them poor candidates for pharmaceutical formulation use. The L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene is very slightly hygroscopic, has high aqueous solubility and is high melting. These characteristics, combined with its relative inertness towards common excipients, make it highly suitable for pharmaceutical formulation use. The D-tartrate salt, the D,L-tartrate salt and the meso-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene also exhibit favorable characteristics.

The L-tartrate salt exists as three possible forms: two anhydrous forms and one hydrate form. Of the two anhydrous forms, Form A and Form B, Form A is the kinetic polymorph, which will convert under appropriate conditions to the thermodynamically favored Form B. The hydrate L-tartrate salt Form C is a monohydrate and is relatively stable under ambient conditions. It will maintain its one equivalent of water under vacuum at moderate temperatures for at least a day (*e.g.*, for 24 hours in a 45 °C vacuum oven), but eventually over time (*i.e.*, 48 hours or more) will lose water and convert to the anhydrous Form B. Form B is the most stable of the polymorphs at low humidity. Accordingly, Form B would appear to be the most appropriate and most stable polymorph of the L-tartrate salts of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene for pharmaceutical formulation use.

As noted above, Form A is the anhydrous kinetic polymorph, which converts under appropriate conditions to the thermodynamically-favored Form B. Form A is obtainable from a synthesis involving, e.g., contacting the free base of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene with approximately one equivalent of L-tartaric acid in methanol or ethanol, allowing little or no time for equilibration. Form A is observed as the resulting product initially from the combination of the 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene free base and L-tartaric acid, but Form B begins to form on

continued or prolonged agitation of the reaction mixture. The rate of formation of Form B may be accelerated by using at least a two-fold or more stoichiometric excess of L-tartaric acid (*i.e.*, faster with 2.2 equivalents of L-tartaric acid present than with only 1.1 equivalents) and allowing the reaction to proceed for longer than two hours, preferably for at least a day or more. Conversion to Form B is ordinarily complete after about 5 hours using 2.2 equivalents. In contrast, the conversion may require more than 20 hours using 1.1 equivalents. In any case, conversion to Form B is usually complete under most conditions after 48 hours at 20-25 °C.

The temperature of the L-tartrate salt formation reaction also influences whether Form A or Form B is isolated, since Forms A and B appear to be thermally interconvertable. Running the salt formation reaction above 45 °C give Form A. Conversely, formation of the salt below 45 °C results in the formation of predominantly Form B. Also, stirring Form A in methanol below 40 °C results in the formation of Form B.

Although any number of solvents may be used, including most lower alcohols, Form B is obtained in high yield preferably using methanol, which permits a high filtration rate of the crystalline material and allows the formation of Form B directly. The solubility of both the free base and L-tartaric acid are higher in methanol than in other lower alkyl alcohols.

The rate of formation of Form B may also be accelerated by employing the specific order of addition wherein the 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene free base is added to the solution of L-tartaric acid. To maximize the virtual concentration of L-tartaric acid present in the reaction, the methanolic solution of free base may be added to a solution containing either 1.1 or more equivalents of L-tartaric acid at 20 °C . The desired anhydrous Form B may then be isolated directly and the polymorph conversion completed in less than 2 hours.

One optimized procedure for making the anhydrous Form B comprises charging a speck-free vessel with between 1.1 and 2.2 equivalents of L-tartaric acid and methanol (4 to 50 volumes), and stirring this mixture until dissolved and speck-free filtering the resulting solution into a crystallization vessel. 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene free base (1.0 equivalents) and methanol (4 to 50 volumes) are stirred in a vessel until dissolved at 0 to 50 °C, more preferably at 20 to 25 °C. The resulting solution of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene free base is then added over about a period of time ranging from 1 minute to 2 hours, more preferably over about 30 minutes, to the L-tartaric acid solution. The product was allowed to stir at 0 to 40 °C, more preferably at 20 to 25 °C, for between 1 and 48 hours, more preferably for about 1 hour, and then isolated by filtration. The product is dried generally under vacuum at 20 to 60 °C, more preferably at 35 to 45 °C, to give Form B of the L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

Both anhydrous Forms A and B can be converted to the monohydrate Form C by exposing either to a relative humidity (RH) of 100% or slurrying either of them in water. Form C is most readily obtained from either of Forms A or B by dissolving either in water at 20 to 50 °C followed by addition of an organic solvent in which the salt is not soluble, preferably methanol, ethanol or acetonitrile, and allowing the mixture to stir for between 1 and 30 minutes, preferably about 10 minutes. Upon filtering off the Form C which precipitates out as a white salt, the Form C salt may be air dried.

Noteworthy is that when exposed to conditions of 100% RH, Form B will convert to Form C within 2 days. Conversely, however, Form C readily converts to Form B upon exposure to 0% relative humidity conditions in roughly the same period of time. Hydrate Form C will however more slowly dehydrate upon exposure to conditions of less than 50% RH. Experiments at 23% and 43% RH have verified this phenomena. Nonetheless, both Forms B and C appear to be relatively stable over a several month period at RH greater than 60%, as experiments at 75% and 87% relative humidity have shown.

Further, Form A can be obtained from Form C by dissolving Form C in a hot organic solvent, preferably ethanol, at or near its reflux point, preferably at about 75 °C, and allowing it to stir for from 10 minutes to 3 hours, preferably 30 minutes. Hot filtering the mixture allows the collection of crystals which upon drying in a vacuum oven at 45 °C yields Form A.

The D-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene has three polymorphs (Forms A', B' and C'), which exhibit the same x-ray diffraction characteristics, hygroscopicity, water content and thermal characteristics as the corresponding Forms A, B and C, respectively, of the L-tartrate salt; and are made in an identical manner as the corresponding L-tartrate salt polymorphs, with the exception that D-tartaric acid is employed in those procedures in place of L-tartaric acid.

The preparation of the anhydrous polymorph (Form X) of the D,L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene involves the steps of dissolving 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent, preferably anhydrous ethanol, with about 1 to about 2.3 equivalents of D,L-tartaric acid, preferably 2.2 equivalents, at 20 °C to solvent reflux temperature for at least 2 hours, more preferably for at least 12 hours, most preferably at least 24 hours; collecting the crystals formed, washing the product with solvent and air drying it. The hydrate polymorph (Form Y) of the D,L-tartrate salt may be made in an analogous fashion but with the use of a solvent admixed with water, preferably an ethanol and water mixture, more preferably 20% aqueous ethanol. In addition, the meso-tartrate may be made in an analogous fashion to the D,L-tartrate.

Differential Scanning Calorimetry

The solid state thermal behavior of Forms A, B and C of the L-tartrate salt of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene were investigated by differential scanning calorimetry (DSC). The traces for Forms A, B and C are shown in Figures 9A, 9B and 9C, respectively. The DSC thermograms were obtained on a Mettler Toledo DSC 821^e (STAR^e System). Generally, samples between 1 and 10 mg were prepared in crimped aluminum pans with a small pinhole. The measurements were run at a heating rate of 5 °C per minute in the range of 30 to 300 °C.

As seen in Figure 9A, the L-tartrate salt Form A exhibits an onset of melt transition at 223 °C with a melting peak accompanied by decomposition at 225 °C measured at a rate of 5 °C per minute. As seen in Figure 9B, the L-tartrate salt Form B exhibited an onset of melt transition at 215 °C with a melting peak accompanied by decomposition at 218 °C measured at a rate of 5 °C per minute. As seen in Figure 9C, the L-tartrate salt hydrate Form C exhibits a solid-solid transition onset at 73 °C with a peak at 76 °C. This solid-solid transition is believed to correspond to the loss of water from the crystal lattice. A melt transition onset is also observed at 220 °C, with a peak at 223 °C accompanied by decomposition.

The solid state thermal behavior of Forms X and Y of the D,L-tartrate salt of 5,8,14-triazatetra-cyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene were also investigated by DSC. As seen in Figure 11A, the D,L-tartrate salt Form X (anhydrous) exhibits an onset of melting transition at 212 °C. In Figure 11B, the differential scanning calorimetric trace for the D,L-tartrate salt Form Y indicates an exhibits a solid-solid transition onset at 131 °C with a peak at 137 °C. This solid-solid transition is believed to correspond to or to be associated with the loss of water from the crystal lattice. A melt transition onset for Form Y is also observed at 217 °C and is accompanied by decomposition.

One of skill in the art will however note that in DSC measurements there is a certain degree of variability in actual measured onset and peak temperatures which is dependant on rate of heating, crystal shape and purity, and a number of measurement parameters.

Powder X-ray Diffraction Patterns

The powder x-ray diffraction patterns for both Forms A, B and C of the L-tartrate salt were collected using a Bruker D5000 diffractometer (Bruker AXS, Madison, Wisconsin) equipped with copper radiation (CuK_α), fixed slits (1.0, 1.0, 0.6 mm), and a Kevex solid state detector. Data was collected from 3.0 to 40.0 degrees in two theta (2θ) using a step size of 0.04 degrees and a step time of 1.0 seconds.

The x-ray powder diffraction pattern of the L-tartrate salt Form A was conducted with a copper anode with wavelength 1 at 1.54056 and wavelength 2 at 1.54439 (relative intensity: 0.500). The range for 2θ was between 3.0 to 40.0 degrees with a step size of 0.04 degrees, a step time of 1.00, a smoothing width of 0.300 and a threshold of 1.0.

The diffraction peaks at diffraction angles (2θ) in a measured powder X-ray diffraction analysis for the Form A are shown in Table I. The relative intensities, however, may change depending on the crystal size and morphology. The actual measured powder diffractogram is displayed in Figure 1.

Table I. Powder X-ray Diffraction Pattern for L-Tartrate Form A with Intensities and Peak Locations of Diffraction Lines.

Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)
6.1	14.5	73.3	20.6	4.3	16.8	30.8	2.9	5.6
11.8	7.5	6.1	21.9	4.1	100.0	32.0	2.8	5.8
12.2	7.2	15.8	22.6	3.9	9.1	32.5	2.8	8.9
13.0	6.8	23.9	23.9	3.7	13.4	34.0	2.6	6.0
14.7	6.0	14.6	24.6	3.6	29.2	34.8	2.6	6.9
16.8	5.3	99.5	27.2	3.3	10.5	35.2	2.5	8.8
17.6	5.0	11.7	27.7	3.2	6.1	37.0	2.4	6.9
18.3	4.8	7.0	28.8	3.1	8.0	37.5	2.4	8.6
19.0	4.7	14.4	29.4	3.0	5.3	38.2	2.4	6.5
19.4	4.6	28.4	29.8	3.0	15.9	-	-	-

Table II sets forth the 2θ, d-spacings and relative intensities representative of Form A. The numbers as listed are computer-generated.

Table II. Intensities and Peak Locations Representative of L-Tartrate Form A.

Angle 2θ	d-value (Å)	I (rel.)
6.1	14.5	73.3
12.2	7.2	15.8
13.0	6.8	23.9
14.7	6.0	14.6
16.8	5.3	99.5
19.4	4.6	28.4
21.9	4.1	100.0
24.6	3.6	29.2

The x-ray powder diffraction pattern of the salt Form B was measured with the same equipment and under that same parameters used above for the measurement of Form A. The diffraction peaks at diffraction angles (2θ) in a measured powder X-ray diffraction analysis for the Form B are shown in Table III. Again, the relative intensities, however, may

change depending on the crystal size and morphology. The actual measured powder diffractogram is displayed in Figure 2.

Table III. Powder X-ray Diffraction Pattern for L-Tartrate Form B with Intensities and Peak Locations of Diffraction Lines.

Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)
5.9	15.0	57.0	19.1	4.6	11.1	29.1	3.1	8.6
11.7	7.5	8.2	20.7	4.3	6.3	29.7	3.0	4.9
12.8	6.9	27.2	21.1	4.2	6.0	31.9	2.8	11.9
14.4	6.1	23.2	21.8	4.1	100.0	34.6	2.6	7.2
15.3	5.8	4.9	23.8	3.7	26.9	34.9	2.6	5.5
16.4	5.4	23.0	24.3	3.7	10.5	35.6	2.5	5.0
16.9	5.2	41.8	25.1	3.5	15.8	37.3	2.4	5.4
17.2	5.2	49.3	25.8	3.4	11.4	38.8	2.3	5.4
17.8	5.0	6.8	26.9	3.3	6.6	-	-	-
18.7	4.7	5.6	27.8	3.2	8.7	-	-	-

Table IV sets forth the 2θ, d-spacings, and relative intensities representative of Form B. The numbers as listed are computer-generated.

Table IV. Intensities and Peak Locations Representative of L-Tartrate Form B.

Angle 2θ	d-value (Å)	I (rel.)
5.9	15.0	57.0
12.8	6.9	27.2
14.4	6.1	23.2
15.3	5.8	4.9
16.9	5.2	41.8
17.2	5.2	49.3
21.8	4.1	100.0
23.8	3.7	26.9
25.1	3.5	15.8

The x-ray powder diffraction pattern of the salt Form C was measured with the same equipment and under that same parameters used above for the measurement of Form A. The diffraction peaks at diffraction angles (2θ) in a measured powder X-ray diffraction analysis for the Form C are shown in Table V. Again, the relative intensities, however, may change depending on the crystal size and morphology. The actual measured powder diffractogram is displayed in Figure 3.

Table V. Powder X-ray Diffraction Pattern for L-Tartrate Form C with Intensities and Peak Locations of Diffraction Lines.

Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)
5.9	15.1	85.5	23.8	3.7	78.5	32.1	2.8	8.7
11.8	7.5	49.4	26.1	3.4	11.6	33.5	2.7	5.9
13.1	6.8	14.4	26.5	3.4	65.8	35.8	2.5	10.0
14.5	6.1	9.2	27.0	3.3	9.6	36.0	2.5	13.0
16.5	5.4	97.4	27.9	3.2	5.8	37.0	2.4	5.7
17.5	5.1	10.0	28.9	3.1	9.5	37.9	2.4	11.5
18.8	4.7	7.0	29.3	3.0	27.3	-	-	-
20.3	4.4	8.2	29.9	3.0	33.0	-	-	-
21.2	4.2	100.0	31.3	2.9	6.7	-	-	-
23.1	3.8	35.0	31.6	2.8	9.0	-	-	-

Table VI sets forth the 2θ, d-spacings, and relative intensities representative of Form C. The numbers as listed are computer-generated.

Table VI. Intensities and Peak Locations Representative of L-Tartrate Form C.

Angle 2θ	d-value (Å)	I (rel.)
5.9	15.1	85.5
11.8	7.5	49.4
16.5	5.4	97.4
21.2	4.2	100.0
23.1	3.8	35.0
23.8	3.7	78.5
26.5	3.4	65.8

As shown in Figure 6, the overlay of the observed x-ray powder diffraction patterns for L-tartrate salt Forms A, B and C shows some x-ray powder diffraction peak shifting and that each Form has a distinctive powder pattern fingerprint.

The x-ray powder diffraction pattern of the D,L-tartrate salt Form X (anhydrous) was measured with the same equipment and under that same parameters used above for the measurement of Form A, L-tartrate salt. The diffraction peaks at diffraction angles (2θ) in a measured powder X-ray diffraction analysis for the Form X are shown in Table VII. Again, the relative intensities, however, may change depending on the crystal size and morphology. The actual measured powder diffractogram is displayed in Figure 10A.

Table VII. Powder X-ray Diffraction Pattern for D,L-Tartrate Form X with Intensities and Peak Locations of Diffraction Lines.

Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)
6.0	14.6	100.0	18.3	4.8	10.3	27.5	3.2	3.7
10.9	8.1	3.8	18.7	4.8	4.8	28.2	3.2	4.4
11.5	7.7	13.0	19.6	4.5	6.0	31.8	2.8	11.7
11.9	7.4	38.0	22.1	4.0	49.5	37.2	2.4	4.0
13.6	6.5	18.4	24.5	3.6	24.5	37.3	2.4	3.7
14.1	6.3	8.8	25.3	3.5	4.3			
15.0	5.9	27.6	25.6	3.5	3.9			
17.1	5.2	49.2	26.4	3.4	11.8			

Table VIII sets forth the 2θ, d-spacings, and relative intensities representative of Form X. The numbers as listed are computer-generated.

Table VIII. Intensities and Peak Locations Representative of D,L-Tartrate Form X.

Angle 2θ	d-value (Å)	I (rel.)
6.0	14.6	100.0
11.9	7.4	38.0
15.0	5.9	27.6
17.1	5.2	49.2
22.1	4.0	49.5
24.5	3.6	24.5

The x-ray powder diffraction pattern of the D,L-tartrate salt Form Y (hydrate) was measured with the same equipment and under that same parameters used above for the measurement of Form A, L-tartrate salt. The diffraction peaks at diffraction angles (2θ) in a measured powder X-ray diffraction analysis for the Form Y are shown in Table IX. Again, the relative intensities, however, may change depending on the crystal size and morphology. The actual measured powder diffractogram is displayed in Figure 10B.

Table IX. Powder X-ray Diffraction Pattern for D,L-Tartrate Form Y with Intensities and Peak Locations of Diffraction Lines.

Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)	Angle 2θ	d-value (Å)	I (rel.)
4.1	21.4	5.2	17.3	5.1	18.6	26.1	3.4	8.5
6.2	14.2	100.0	18.1	4.9	32.2	27.5	3.2	17.9
10.9	8.1	7.8	18.7	4.7	7.1	29.3	3.0	7.4
11.5	7.7	23.1	19.9	4.5	24.7	29.7	3.0	8.4
12.0	7.4	39.1	21.1	4.2	7.0	30.3	2.9	11.7
12.5	7.1	4.6	21.7	4.1	11.0	31.5	2.8	17.4
13.5	6.5	16.6	22.5	4.0	5.4	35.8	2.5	6.4
14.4	6.1	14.7	23.2	3.8	12.2	36.7	2.4	4.5
15.0	5.9	16.4	24.0	3.7	52.7	37.3	2.4	4.6
15.2	5.8	32.7	25.1	3.5	75.1	39.1	2.3	5.4
15.6	5.7	9.6	25.5	3.5	10.3			

Table X sets forth the 2θ, d-spacings and relative intensities of Form Y. The numbers as listed are computer-generated.

Table X. Intensities and Peak Locations Representative of D,L-Tartrate Form Y.

Angle 2θ	d-value (Å)	I (rel.)
6.2	14.2	100.0
12.0	7.4	39.1
15.2	5.8	32.7
18.1	4.9	32.2
24.0	3.7	52.7
25.1	3.5	75.1

Single Crystal X-ray Analysis

Single crystals for the L-tartrate salt Forms B and C were obtained and investigated by X-ray diffraction. For each form, a representative crystal was surveyed and a 1Å data set (maximum sin Θ/λ=0.5) was collected on a Siemens R4RA/v diffractometer. Atomic scattering factors were taken from the International Tables for X-Ray Crystallography, Vol. IV, pp. 55, 99 and 149 (Birmingham: Kynoch Press, 1974). Single crystal X-ray data were collected at room temperature. All crystallographic calculations were facilitated by the SHELXTL™ system (SHELXTL™ Reference Manual, Version 5.1, Bruker AXS, Madison, WI 1997). The pertinent crystal data collection and refinement are summarized in Table XI below for Form B and in Table XII below for Form C.

For both Forms, the trial structure was obtained by direct methods and was then refined routinely. A difference map revealed two waters of crystallization – one for each salt molecule. Hydrogen positions were calculated wherever possible. The hydrogens on nitrogen and oxygen were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycles of least squares refinement were all less than 0.1 of the corresponding standard deviations. For Form B, the final R-index was 3.25%. For Form C, the final R-index was 3.47%. A final difference Fourier revealed no missing or misplaced electron density. The refined structure was plotted using the SHELXTL plotting package and is shown in Figure 8A (Form B) and 8B (Form C). The absolute configuration was based on the use of L(+)-tartaric acid.

Table XIII sets forth the atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2 x\ 10^3$) for Form B. Table XIV lists the observed bond lengths [Å] and angles [°] for Form B. In Table XV, the anisotropic displacement parameters ($Å^2 x\ 10^3$) for Form B are set forth to allow calculation of the anisotropic displacement factor exponent which has the form: $-2\pi^2[\ h^2\ a^{*2}U_{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$. Finally, in Table XVI, below, hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for Form B are listed.

Table XVII sets forth the atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2 x\ 10^3$) for Form C. Table XVIII lists the observed bond lengths [Å] and angles [°] for Form C. In Table XIX, the anisotropic displacement parameters ($Å^2 x\ 10^3$) for Form C are set forth to allow calculation of the anisotropic displacement factor exponent which has the form: $-2\pi^2[\ h^2\ a^{*2}U_{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$. Finally, in Table XX, below, hydrogen Coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for Form C are listed.

Table XI. Crystal Structure Data and Measurement Parameters: L-Tartrate Salt Form B

Parameter	L-Tartrate Form B
Empirical formula	$C_{13}H_{14}N_3^+C_4H_5O_6^-$
Formula weight	361.35
Crystal System	Orthorhombic
Space Group	P2(1)2(1)2(1)
Crystal Size, mm^3	0.01 x 0.08 x 0.10
a	7.0753(5) Å
b	7.7846(5) Å
c	29.870(2) Å
α	90°
γ	90°
β	90°
Volume	1645.21(19) $Å^3$
Density calc'd, ρ	1.459 g/cm^3
Z	4
Temperature	298(2) K
Wavelength	1.54178 Å
Absorption coefficient	0.944 mm^{-1}
F(000)	760
Reflections collected	3490
Independent reflections	1318 [R(int) = 0.0542]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1318 / 0 / 251
Goodness-of-fit on F^2	0.856
Final R indices [I>2sigma(I)]	R1 = 0.0325, wR2 = 0.0638
Absolute structure parameter	0.0031(3)
Largest diff. peak and hole	0.115 and -0.150 $e.Å^{-3}$

Table XII. Crystal Structure Data and Measurement Parameters: L-Tartrate Salt Form C

Parameter	L-Tartrate Hydrate Form C
Empirical formula	$C_{13}H_{14}N_3^+C_4H_5O_6^-\cdot H_2O$
Formula weight	379.37
Crystal System	Monoclinic
Space Group	P2(1)
Crystal Size, mm^3	0.04 x 0.38 x 0.30
X-ray Code	F611
a	7.5120Å
b	29.854Å
c	7.671Å
α	90°
γ	90°
β	90.40°
Volume	1720.3$Å^3$
Density calc'd, ρ	1.465g/cm^3
Z	4
Temperature	298(2) K
Wavelength	1.54178 Å
Absorption coefficient	0.974 mm^{-1}
F(000)	800
Reflections collected	1983
Independent reflections	1817 [R(int) = 0.0224]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1817 / 0 / 528
Goodness-of-fit on F^2	1.028
Final R indices [I>2sigma(I)]	R1 = 0.0347, wR2 = 0.0834
Absolute structure parameter	0.0(3)
Largest diff. peak and hole	0.168 and -0.230 e.$Å^{-3}$

Table XIII. Atomic Coordinates ($x10^4$) And Equivalent Isotropic Displacement Parameters ($Å^2x10^3$) For Form B. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
N(1)	8211(8)	10638(7)	12233(1)	61(1)
C(2)	8968(8)	9093(11)	12235(2)	72(2)
C(3)	8093(11)	7629(9)	12047(2)	75(2)
N(4)	6431(8)	7715(6)	11853(1)	64(1)
C(5)	5624(9)	9313(8)	11834(2)	50(1)
C(6)	6502(8)	10752(9)	12025(2)	49(1)
C(7)	5676(8)	12396(7)	11985(1)	48(1)
C(8)	4007(8)	12557(6)	11762(2)	41(1)
C(9)	3107(7)	11097(7)	11572(1)	42(1)
C(10)	3890(8)	9495(7)	11605(1)	49(1)
C(11)	2865(7)	14122(6)	11634(1)	44(1)
C(12)	891(6)	13347(6)	11573(1)	53(1)
C(13)	1397(7)	11686(6)	11315(1)	46(1)
C(14)	3510(6)	14823(6)	11182(1)	43(1)
N(15)	3597(5)	13405(5)	10838(1)	39(1)
C(16)	1962(6)	12183(5)	10838(1)	46(1)
C(20)	7858(9)	6393(6)	10523(1)	37(1)
O(21)	9522(5)	6116(4)	10603(1)	47(1)
O(22)	6680(4)	5324(4)	10349(1)	47(1)
C(23)	7033(6)	8162(5)	10623(1)	32(1)
O(24)	5062(4)	8318(4)	10542(1)	44(1)
C(25)	8063(6)	9486(5)	10339(1)	31(1)
O(26)	7763(4)	9176(4)	9873(1)	35(1)
C(27)	7520(6)	11321(6)	10465(2)	35(1)
O(28)	7065(4)	11655(4)	10852(1)	43(1)
O(29)	7681(4)	12417(4)	10148(1)	47(1)

Table XIV. Bond lengths [Å] and angles [°] for L-Tartrate Form B.

Bond Lengths			
N(1)-C(2)	1.316(6)	C(11)-C(12)	1.532(6)
N(1)-C(6)	1.362(6)	C(12)-C(13)	1.547(6)
C(2)-C(3)	1.413(7)	C(13)-C(16)	1.531(5)
C(3)-N(4)	1.314(7)	C(14)-N(15)	1.510(5)
N(4)-C(5)	1.370(6)	N(15)-C(16)	1.498(5)
C(5)-C(10)	1.411(6)	C(20)-O(21)	1.221(5)
C(5)-C(6)	1.403(7)	C(20)-O(22)	1.288(5)
C(6)-C(7)	1.412(6)	C(20)-C(23)	1.525(6)
C(7)-C(8)	1.361(6)	C(23)-O(24)	1.420(5)
C(8)-C(9)	1.421(6)	C(23)-C(25)	1.521(5)
C(8)-C(11)	1.511(6)	C(25)-O(26)	1.428(5)
C(9)-C(10)	1.368(6)	C(25)-C(27)	1.526(6)
C(9)-C(13)	1.504(6)	C(27)-O(28)	1.227(5)
C(11)-C(14)	1.526(5)	C(27)-O(29)	1.281(5)

Bond Angles			
C(2)-N(1)-C(6)	115.0(5)	C(14)-C(11)-C(12)	107.9(3)
N(1)-C(2)-C(3)	123.9(5)	C(11)-C(12)-C(13)	100.2(3)
N(4)-C(3)-C(2)	121.8(5)	C(9)-C(13)-C(16)	110.0(4)
C(3)-N(4)-C(5)	116.0(5)	C(9)-C(13)-C(12)	100.8(4)
N(4)-C(5)-C(10)	118.3(6)	C(16)-C(13)-C(12)	108.2(4)
N(4)-C(5)-C(6)	121.5(6)	N(15)-C(14)-C(11)	110.6(4)
C(10)-C(5)-C(6)	120.2(6)	C(16)-N(15)-C(14)	115.7(3)
N(1)-C(6)-C(5)	121.8(6)	N(15)-C(16)-C(13)	111.2(3)
N(1)-C(6)-C(7)	117.8(6)	O(21)-C(20)-O(22)	126.1(5)
C(5)-C(6)-C(7)	120.3(5)	O(21)-C(20)-C(23)	119.4(5)
C(8)-C(7)-C(6)	119.0(5)	O(22)-C(20)-C(23)	114.5(5)
C(7)-C(8)-C(9)	120.7(5)	O(24)-C(23)-C(25)	108.5(3)
C(7)-C(8)-C(11)	131.5(5)	O(24)-C(23)-C(20)	114.8(4)
C(9)-C(8)-C(11)	107.7(4)	C(25)-C(23)-C(20)	108.6(3)
C(10)-C(9)-C(8)	121.2(5)	O(26)-C(25)-C(23)	111.0(3)
C(10)-C(9)-C(13)	129.8(5)	O(26)-C(25)-C(27)	111.2(3)
C(8)-C(9)-C(13)	108.7(5)	C(23)-C(25)-C(27)	112.0(4)
C(9)-C(10)-C(5)	118.6(5)	O(28)-C(27)-O(29)	125.4(4)
C(8)-C(11)-C(14)	110.7(4)	O(28)-C(27)-C(25)	119.8(4)
C(8)-C(11)-C(12)	101.6(4)	O(29)-C(27)-C(25)	114.7(4)

Table XV. Anisotropic Displacement Parameters ($Å^2 x\ 10^3$) For Form B. (The Anisotropic displacement factor exponent takes the form: $-2\pi 2[\ h^2\ a^{*2} U_{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$).

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N(1)	63(4)	70(4)	50(3)	12(2)	-2(3)	8(3)
C(2)	54(4)	114(6)	49(4)	20(4)	-3(3)	8(5)
C(3)	79(5)	78(5)	66(4)	14(4)	-6(4)	30(5)
N(4)	78(4)	54(4)	60(3)	8(3)	-9(3)	13(3)
C(5)	65(4)	45(4)	39(3)	5(3)	-3(3)	6(4)
C(6)	41(4)	69(5)	36(3)	8(3)	-9(3)	1(4)
C(7)	51(4)	56(5)	38(3)	3(3)	-2(3)	-5(4)
C(8)	45(4)	41(4)	38(3)	4(3)	1(3)	-3(4)
C(9)	46(4)	40(4)	40(3)	12(3)	9(3)	-4(4)
C(10)	54(4)	52(5)	41(3)	8(3)	-5(3)	-14(4)
C(11)	49(3)	43(3)	38(3)	-1(3)	1(3)	-1(3)
C(12)	45(4)	63(4)	50(3)	6(3)	7(3)	3(3)
C(13)	42(3)	49(3)	48(3)	11(3)	-3(3)	-4(3)
C(14)	43(3)	39(3)	46(3)	-3(3)	2(2)	-1(3)
N(15)	35(3)	41(3)	40(2)	7(2)	3(2)	-2(2)
C(16)	42(3)	51(3)	44(3)	6(3)	-4(3)	-2(3)
C(20)	48(4)	30(4)	33(3)	9(3)	10(3)	-6(4)
O(21)	30(2)	41(2)	68(2)	3(2)	-5(2)	7(2)
O(22)	44(2)	22(2)	73(2)	-5(2)	-2(2)	2(2)
C(23)	26(3)	28(3)	42(3)	0(2)	7(2)	0(3)
O(24)	33(2)	33(2)	68(2)	-10(2)	4(2)	1(2)
C(25)	35(3)	25(3)	32(3)	-7(2)	-1(2)	4(3)
O(26)	35(2)	32(2)	38(2)	-5(1)	3(2)	-1(2)
C(27)	22(3)	40(4)	42(4)	-7(3)	-8(3)	1(3)
O(28)	53(2)	36(2)	41(2)	-7(2)	2(2)	2(2)
O(29)	74(2)	27(2)	41(2)	5(2)	7(2)	4(2)

Table XVI. Hydrogen Coordinates ($x10^4$) And Isotropic Displacement Parameters ($Å^2x10^3$) For Form B.

	x	y	z	U(eq)
H(2A)	10149	8958	12367	80
H(3A)	8710	6576	12062	80
H(7A)	6264	13354	12108	80
H(10A)	3292	8546	11480	80
H(11A)	2887	15004	11868	80
H(12A)	76	14092	11398	80
H(12B)	295	13097	11858	80
H(13A)	372	10840	11321	80
H(14A)	2636	15704	11082	80
H(14B)	4748	15344	11213	80
H(15A)	3600(70)	14000(60)	10578(14)	80
H(15B)	4860(70)	12850(60)	10867(14)	80
H(16A)	2302	11156	10672	80
H(16B)	894	12713	10688	80
H(23A)	7270	8427	10939	80
H(24A)	4680(70)	7400(60)	10401(15)	80
H(25A)	9419	9355	10397	80
H(26A)	6710(70)	9120(70)	9841(17)	80
H(29A)	7180(60)	13930(80)	10298(14)	80

Table XVII. Atomic Coordinates ($x10^4$) And Equivalent Isotropic Displacement Parameters ($Å^2x10^3$) For Form C. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
N(1)	-159(7)	10186(3)	-1642(7)	45(1)
C(2)	-239(10)	10333(3)	-58(10)	52(2)
C(3)	1241(10)	10446(3)	959(9)	50(2)
N(4)	2878(7)	10415(3)	368(6)	42(1)
C(5)	3033(8)	10257(3)	-1310(8)	33(2)
C(6)	1520(7)	10141(3)	-2302(8)	30(2)
C(7)	1723(7)	9967	-4007(7)	32(2)
C(8)	3381(7)	9902(3)	-4622(7)	25(1)
C(9)	4905(7)	10018(3)	-3648(7)	25(1)
C(10)	4759(8)	10194(3)	-2016(8)	36(2)
C(11)	6537(7)	9881(3)	-4655(7)	31(2)
C(12)	7003(7)	9395(3)	-4191(7)	33(2)
N(13)	5380(6)	9102(3)	-4292(6)	27(1)
C(14)	4292(7)	9171(3)	-5922(7)	29(1)
C(15)	4011(7)	9668(3)	-6277(7)	28(1)
C(16)	5826(8)	9887(3)	-6550(8)	41(2)
C(1X)	1541(7)	7444(3)	-5634(8)	23(1)
O(2X)	1182(4)	7444(2)	-7182(5)	36(1)
O(3X)	361(5)	7474(2)	-4418(5)	38(1)
C(4X)	3457(6)	7425(3)	-4997(7)	24(1)
O(5X)	3649(5)	7280(2)	-3247(5)	32(1)
C(6X)	4282(7)	7881(3)	-5336(7)	25(1)
O(7X)	3348(4)	8230(2)	-4482(5)	28(1)
C(8X)	6296(7)	7900(3)	-4948(7)	22(1)
O(9X)	7172(5)	7560(2)	-5428(5)	37(1)
O(10X)	6935(5)	8241(2)	-4266(5)	35(1)
O(1W)	3226(6)	7996(2)	-924(5)	37(1)
N(51)	3493(6)	6295(3)	3311(7)	43(1)
C(52)	3598(9)	6141(3)	4922(9)	47(2)
C(53)	2144(9)	6031(3)	5890(8)	45(2)
N(54)	494(7)	6065(3)	5313(7)	43(1)
C(55)	289(8)	6228(3)	3651(7)	30(1)
C(56)	1799(7)	6340(3)	2642(8)	30(2)
C(57)	1574(8)	6528(2)	950(8)	32(2)
C(58)	-95(8)	6593(3)	320(7)	27(1)
C(59)	-1609(7)	6472(2)	1339(7)	25(1)
C(60)	-1436(7)	6295(3)	2965(9)	35(2)
C(61)	-3249(8)	6621(3)	334(8)	32(2)
C(62)	-3717(7)	7097(3)	850(7)	33(2)
N(63)	-2088(6)	7392(3)	720(6)	26(1)
C(64)	-1014(7)	7329(3)	-916(6)	29(1)
C(65)	-765(7)	6828(3)	-1308(7)	30(1)
C(66)	-2599(8)	6612(3)	-1564(7)	36(2)
C(1Y)	-2999(7)	8598(3)	27(7)	26(1)
O(2Y)	-3633(5)	8257(2)	745(5)	35(1)
O(3Y)	-3884(5)	8934(2)	-462(5)	34(1)
C(4Y)	-986(6)	8611(3)	-356(7)	20(1)
O(5Y)	-53(4)	8261(2)	523(5)	28(1)
C(6Y)	-163(7)	9070(3)	-16(7)	23(1)
O(7Y)	-328(5)	9219(2)	1725(5)	33(1)
C(8Y)	1746(7)	9048(3)	-658(8)	24(1)
O(9Y)	2954(5)	9023(2)	572(5)	36(1)
O(10Y)	2085(5)	9039(2)	-2209(5)	37(1)
O(2W)	54(6)	8500(2)	4066(5)	39(1)

Table XVIII. Bond lengths [Å] and angles [°] for L-Tartrate Form C.

Bond Lengths (Form C)			
N(1)-C(2)	1.294(8)	N(51)-C(52)	1.320(8)
N(1)-C(6)	1.369(7)	N(51)-C(56)	1.375(7)
C(2)-C(3)	1.396(10)	C(52)-C(53)	1.365(9)
C(3)-N(4)	1.316(8)	C(53)-N(54)	1.317(8)
N(4)-C(5)	1.377(8)	N(54)-C(55)	1.373(8)
C(5)-C(6)	1.407(8)	C(55)-C(60)	1.410(8)
C(5)-C(10)	1.421(9)	C(55)-C(56)	1.417(8)
C(6)-C(7)	1.417(8)	C(56)-C(57)	1.424(8)
C(7)-C(8)	1.349(8)	C(57)-C(58)	1.355(8)
C(8)-C(9)	1.407(8)	C(58)-C(59)	1.431(8)
C(8)-C(15)	1.526(8)	C(58)-C(65)	1.514(8)
C(9)-C(10)	1.362(8)	C(59)-C(60)	1.360(8)
C(9)-C(11)	1.511(8)	C(59)-C(61)	1.515(8)
C(11)-C(12)	1.534(8)	C(61)-C(62)	1.518(9)
C(11)-C(16)	1.545(8)	C(61)-C(66)	1.539(8)
C(12)-N(13)	1.501(7)	C(62)-N(63)	1.511(7)
N(13)-C(14)	1.504(6)	N(63)-C(64)	1.508(6)
C(14)-C(15)	1.525(8)	C(64)-C(65)	1.537(8)
C(15)-C(16)	1.528(8)	C(65)-C(66)	1.533(8)
C(1X)-O(2X)	1.216(6)	C(1Y)-O(3Y)	1.259(7)
C(1X)-O(3X)	1.295(6)	C(1Y)-O(2Y)	1.254(7)
C(1X)-C(4X)	1.518(7)	C(1Y)-C(4Y)	1.543(8)
C(4X)-O(5X)	1.417(6)	C(4Y)-O(5Y)	1.424(6)
C(4X)-C(6X)	1.517(8)	C(4Y)-C(6Y)	1.526(8)
C(6X)-O(7X)	1.419(7)	C(6Y)-O(7Y)	1.413(7)
C(6X)-C(8X)	1.541(7)	C(6Y)-C(8Y)	1.521(8)
C(8X)-O(10X)	1.240(7)	C(8Y)-O(10Y)	1.219(6)
C(8X)-O(9X)	1.267(7)	C(8Y)-O(9Y)	1.306(7)
Bond Angles (Form C)			
C(2)-N(1)-C(6)	115.5(6)	C(52)-N(51)-C(56)	115.6(5)
N(1)-C(2)-C(3)	124.4(7)	N(51)-C(52)-C(53)	123.4(6)
N(4)-C(3)-C(2)	122.2(6)	N(54)-C(53)-C(52)	123.6(6)
C(3)-N(4)-C(5)	115.6(5)	C(53)-N(54)-C(55)	116.0(5)
N(4)-C(5)-C(6)	121.1(6)	N(54)-C(55)-C(60)	119.6(5)
N(4)-C(5)-C(10)	119.0(5)	N(54)-C(55)-C(56)	120.4(5)
C(6)-C(5)-C(10)	119.8(6)	C(60)-C(55)-C(56)	120.0(5)
N(1)-C(6)-C(5)	121.3(6)	N(51)-C(56)-C(55)	121.0(6)
N(1)-C(6)-C(7)	118.9(5)	N(51)-C(56)-C(57)	118.8(5)
C(5)-C(6)-C(7)	119.9(5)	C(55)-C(56)-C(57)	120.1(5)
C(8)-C(7)-C(6)	118.8(5)	C(58)-C(57)-C(56)	119.0(5)
C(7)-C(8)-C(9)	121.9(5)	C(57)-C(58)-C(59)	120.4(5)
C(7)-C(8)-C(15)	130.5(5)	C(57)-C(58)-C(65)	131.4(5)
C(9)-C(8)-C(15)	107.4(5)	C(59)-C(58)-C(65)	107.9(5)
C(10)-C(9)-C(8)	120.9(5)	C(60)-C(59)-C(58)	121.9(5)
C(10)-C(9)-C(11)	130.2(5)	C(60)-C(59)-C(61)	130.8(5)
C(8)-C(9)-C(11)	108.7(5)	C(58)-C(59)-C(61)	107.1(5)
C(9)-C(10)-C(5)	118.7(5)	C(59)-C(60)-C(55)	118.7(5)
C(9)-C(11)-C(12)	108.9(5)	C(59)-C(61)-C(62)	109.2(5)
C(9)-C(11)-C(16)	101.6(5)	C(59)-C(61)-C(66)	102.4(5)
C(12)-C(11)-C(16)	107.9(5)	C(62)-C(61)-C(66)	109.8(5)
N(13)-C(12)-C(11)	110.8(5)	N(63)-C(62)-C(61)	109.8(5)
C(14)-N(13)-C(12)	113.6(4)	C(64)-N(63)-C(62)	114.9(4)
Bond Angles (Form C)			

N(13)-C(14)-C(15)	110.8(4)	N(63)-C(64)-C(65)	110.6(4)
C(16)-C(15)-C(14)	108.6(5)	C(58)-C(65)-C(66)	101.8(4)
C(16)-C(15)-C(8)	101.6(4)	C(58)-C(65)-C(64)	109.1(4)
C(14)-C(15)-C(8)	109.8(4)	C(66)-C(65)-C(64)	108.9(5)
C(15)-C(16)-C(11)	99.7(4)	C(65)-C(66)-C(61)	99.3(4)
O(2X)-C(1X)-O(3X)	123.7(5)	O(3Y)-C(1Y)-O(2Y)	125.2(5)
O(2X)-C(1X)-C(4X)	121.2(5)	O(3Y)-C(1Y)-C(4Y)	116.1(5)
O(3X)-C(1X)-C(4X)	115.1(5)	O(2Y)-C(1Y)-C(4Y)	118.7(5)
O(5X)-C(4X)-C(6X)	113.4(4)	O(5Y)-C(4Y)-C(6Y)	112.3(4)
O(5X)-C(4X)-C(1X)	114.0(4)	O(5Y)-C(4Y)-C(1Y)	111.8(4)
C(6X)-C(4X)-C(1X)	107.5(4)	C(6Y)-C(4Y)-C(1Y)	112.7(4)
O(7X)-C(6X)-C(4X)	112.0(4)	O(7Y)-C(6Y)-C(8Y)	114.1(4)
O(7X)-C(6X)-C(8X)	111.8(4)	O(7Y)-C(6Y)-C(4Y)	113.9(4)
C(4X)-C(6X)-C(8X)	113.7(4)	C(8Y)-C(6Y)-C(4Y)	106.7(4)
O(10X)-C(8X)-O(9X)	125.6(5)	O(10Y)-C(8Y)-O(9Y)	123.7(5)
O(10X)-C(8X)-C(6X)	119.3(5)	O(10Y)-C(8Y)-C(6Y)	121.4(5)
O(9X)-C(8X)-C(6X)	115.1(5)	O(9Y)-C(8Y)-C(6Y)	114.9(5)

Table XIX. Anisotropic Displacement Parameters ($Å^2 x\ 10^3$) For Form C. (The Anisotropic displacement factor exponent takes the form: $-2\pi 2[\ h^2\ a^{*2} U_{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$).

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N(1)	42(4)	46(4)	46(4)	-8(3)	4(3)	0(3)
C(2)	53(5)	51(5)	52(5)	-5(4)	9(4)	3(4)
C(3)	63(5)	40(4)	49(4)	-2(4)	19(4)	11(4)
N(4)	59(4)	30(3)	37(3)	-8(3)	-7(3)	11(3)
C(5)	44(4)	19(3)	35(4)	1(3)	-8(3)	9(3)
C(6)	27(3)	25(4)	39(4)	1(3)	3(3)	3(3)
C(7)	30(4)	36(4)	30(4)	-1(3)	-10(3)	4(3)
C(8)	28(4)	27(3)	19(3)	1(2)	-4(3)	3(3)
C(9)	27(3)	20(3)	29(4)	4(3)	-9(3)	0(3)
C(10)	33(4)	32(4)	44(4)	-8(3)	-14(3)	-4(3)
C(11)	30(3)	26(4)	38(4)	0(3)	-1(3)	-6(3)
C(12)	22(3)	44(4)	34(3)	0(3)	0(3)	0(3)
N(13)	27(3)	32(3)	21(3)	1(2)	0(2)	1(2)
C(14)	26(3)	34(4)	27(3)	-4(3)	-11(3)	-1(3)
C(15)	24(3)	29(4)	30(3)	7(3)	-5(3)	-2(3)
C(16)	42(4)	41(4)	39(4)	5(3)	7(3)	-2(3)
C(1X)	23(3)	19(3)	28(4)	-1(3)	8(3)	1(3)
O(2X)	28(2)	56(3)	25(2)	-7(2)	-2(2)	-1(2)
O(3X)	19(2)	69(3)	26(2)	8(2)	5(2)	2(2)
C(4X)	19(3)	30(3)	24(3)	5(3)	-1(2)	1(3)
O(5X)	29(2)	34(2)	33(2)	5(2)	-5(2)	8(2)
C(6X)	20(3)	28(3)	26(3)	-1(3)	2(2)	1(3)
O(7X)	21(2)	25(2)	36(2)	-3(2)	5(2)	4(2)
C(8X)	21(3)	30(4)	16(3)	-2(3)	1(2)	5(3)
O(9X)	19(2)	43(3)	49(3)	-10(2)	-1(2)	4(2)
O(10X)	26(2)	35(3)	45(2)	-10(2)	-7(2)	-1(2)
O(1W)	28(2)	47(3)	35(2)	-9(2)	1(2)	-1(2)
N(51)	29(3)	47(4)	54(4)	7(3)	-3(3)	8(3)
C(52)	44(4)	46(4)	51(5)	11(4)	-9(4)	4(3)
C(53)	50(5)	48(4)	35(4)	2(3)	-4(3)	10(4)
N(54)	53(4)	40(3)	37(3)	4(3)	5(3)	8(3)
C(55)	34(4)	28(3)	27(3)	5(3)	4(3)	3(3)
C(56)	28(4)	25(3)	36(4)	-5(3)	2(3)	2(3)
C(57)	30(4)	34(4)	32(4)	4(3)	7(3)	3(3)
C(58)	32(4)	24(4)	24(3)	-1(3)	5(3)	-1(3)
C(59)	22(3)	21(3)	33(4)	0(3)	1(3)	-2(3)
C(60)	25(3)	32(4)	49(4)	3(3)	10(3)	-3(3)
C(61)	26(3)	30(4)	40(4)	2(3)	-6(3)	-6(3)
C(62)	25(3)	35(4)	38(4)	4(3)	0(3)	-2(3)
N(63)	25(3)	27(3)	27(3)	-2(2)	5(2)	1(2)
C(64)	36(3)	33(4)	18(3)	2(3)	8(3)	1(3)
C(65)	35(3)	33(4)	21(3)	-5(3)	3(3)	6(3)
C(66)	42(4)	32(4)	33(4)	-6(3)	-6(3)	2(3)
C(1Y)	23(3)	38(4)	17(3)	-1(3)	-6(2)	0(3)
O(2Y)	21(2)	42(3)	43(2)	11(2)	5(2)	-2(2)
O(3Y)	19(2)	41(3)	44(3)	11(2)	3(2)	8(2)
C(4Y)	18(3)	22(3)	21(3)	3(2)	-1(2)	4(3)
O(5Y)	21(2)	31(2)	30(2)	3(2)	-2(2)	4(2)
C(6Y)	23(3)	30(3)	17(3)	4(3)	1(2)	7(3)
O(7Y)	32(2)	37(3)	31(3)	-3(2)	6(2)	7(2)
C(8Y)	23(3)	16(3)	33(4)	3(3)	-2(3)	-4(2)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(9Y)	19(2)	61(3)	27(2)	-9(2)	-6(2)	5(2)
O(10Y)	28(2)	57(3)	24(2)	4(2)	6(2)	1(2)
O(2W)	32(2)	50(3)	35(3)	7(2)	-2(2)	3(2)

Table XX. Hydrogen Coordinates ($x10^4$) And Isotropic Displacement Parameters ($Å^2x10^3$) For Form C.

	x	y	z	U(eq)
H(2)	-1359	10366	435	80
H(3)	1066	10546	2094	80
H(7)	732	9899	-4690	80
H(10)	5770	10272	-1377	80
H(11)	7541	10086	-4476	80
H(12A)	7896	9284	-4990	80
H(12B)	7499	9383	-3021	80
H(13X)	5710(100)	8750(30)	-4290(90)	80
H(13Y)	4660(100)	9130(30)	-3380(100)	80
H(14A)	3147	9025	-5797	80
H(14B)	4897	9035	-6903	80
H(15)	3202	9720	-7264	80
H(16A)	5715	10190	-6996	80
H(16B)	6570	9712	-7324	80
H(3XX)	-980(110)	7490(30)	-4900(90)	80
H(4X)	4082	7208	-5730	80
H(5XX)	3350(100)	7550(30)	-2600(100)	80
H(6X)	4144	7936	-6589	80
H(7XX)	3230(100)	8210(30)	-3240(100)	80
H(1WX)	2060(110)	8070(30)	-390(90)	80
H(1WY)	4280(110)	8050(30)	-270(100)	80
H(52)	4720	6106	5423	80
H(53)	2329	5927	7019	80
H(57)	2559	6605	286	80
H(60)	-2435	6220	3610	80
H(61)	-4250	6416	511	80
H(62A)	-4647	7211	87	80
H(62B)	-4158	7101	2035	80
H(63X)	-2480(100)	7730(30)	650(90)	80
H(63Y)	-1300(100)	7360(30)	1730(100)	80
H(64A)	141	7470	-772	80
H(64B)	-1620	7471	-1889	80
H(65)	16	6777	-2307	80
H(66A)	-2509	6308	-2010	80
H(66B)	-3358	6788	-2329	80
H(4Y)	-860	8553	-1607	80
H(5YX)	-140(100)	8240(30)	1670(100)	80
H(6Y)	-797	9286	-757	80
H(7YX)	-100(110)	9020(30)	2280(100)	80
H(9YX)	4230(110)	8990(30)	40(90)	80
H(2WX)	1040(110)	8370(30)	4630(100)	80
H(2WY)	-990(110)	8380(30)	4830(100)	80

The powder X-ray diffraction patterns for Forms B and C were calculated from the respective single crystal data gathered for each L-tartrate salt form via the use of the XFOG and XPOW computer programs provided as part of the SHELXTL™ computer library. The calculated powder pattern for Form B is shown in Figure 4A. The calculated powder pattern for Form C is shown in Figure 4B.

A comparison of the observed Form B powder pattern and the calculated pattern results are displayed in the overlaid powder X-ray diffraction pattern of Figure 5A. The lower pattern trace corresponds to the calculated powder pattern (from single crystal results) and the upper pattern corresponds to a representative experimental powder pattern. The general match between the two patterns indicates the agreement between powder sample and the corresponding single crystal structure.

A comparison of the observed Form C powder pattern and the calculated pattern results are displayed in the overlaid powder X-ray diffraction pattern of Figure 5B. The lower pattern trace corresponds to the calculated powder pattern (from single crystal results) and the upper pattern corresponds to a representative experimental powder pattern. The general match between the two patterns indicates the agreement between powder sample and the corresponding single crystal structure.

Solid State NMR

Forms A, B and C of the L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene were characterized by solid state NMR techniques. Approximately 300 mg of a sample was tightly packed into 7mm ZrO spinner. The ^{13}C spectra were collected using cross-polarization magic angle spinning (CPMAS) at 295 K on Bruker 7mm WB MAS probe positioned into a wide-bore Bruker Avance DRX 500 MHz NMR spectrometer. The samples were spun at 7 kHz. The cross-polarization contact time was set to 1 ms. The total of 512 scans were acquired for most of the samples resulting in approximately 30 minute acquisition times. The spectra were referenced using external sample of adamantane with the most upfield methyl signal set to 29.5 ppm.

The resulting ^{13}C CPMAS spectra of Forms A, B and C are shown in Figures 7A, 7B and 7C, respectively. The samples behaved reasonably well from the point of view of solid state spectra quality. The resolution was good and the sensitivity was acceptable. The spectra features of all the compounds differ substantially from each other suggesting that solid state NMR can easily resolve the minor physical/chemical differences between the samples.

All the peaks marked with asterisks (*) are spinning sidebands in Figure 7A, 7B and 7C. The spinning sidebands are displaced at multiple of the spinning frequencies along both sides of the real peaks (centerbands). The spinning speed was set to 7 kHz which at the 500 MHz magnet translates into 55.7 ppm. The sideband intensities depend on the spinning

speed (the higher the speed the lower the sideband intensity) and on the size of the anisotropic contribution of the chemical shielding for the given carbon. They can be easily distinguished from centerbands by variable spinning speed experiments. Carbonyl and aromatic sites tend to have very intense sidebands due to their large chemical shielding anisotropies. CH and CH_2 type of carbons give origin to relatively small spinning sidebands. Methyl groups (CH_3) usually don't generate any sidebands.

The major resonance peaks (those downfield from 100 ppm; ± 0.1ppm) for the solid state carbon spectrum of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene L-tartrate salt Forms A, B and C are listed in Table XXI.

Table XXI. Major Solid State ^{13}C-NMR Resonance Peaks For 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene L-Tartrate Salt Forms A, B and C (Only Peaks Downfield from 100 ppm Listed) (Adamantane 29.5 ppm Standard).

FORM A ^{13}C (ppm) Solid	FORM B ^{13}C (ppm) Solid	FORM C ^{13}C (ppm) Solid
178.4	179.2	179.0
149.3	178.0	176.1
147.4	147.4	147.5
145.1	145.2	144.5
122.9	144.4	124.6
	124.8	
	122.5	

The L-tartrate, the D-tartrate, the D,L-tartrate and the meso-tartrate salts of the invention (hereafter "the active salts") can be administered via either the oral, transdermal (e.g., through the use of a patch), intranasal, sublingual, rectal, parenteral or topical routes. Transdermal and oral administration are preferred. These salts are, most desirably, administered in dosages ranging from about 0.01 mg up to about 1500 mg per day, preferably from about 0.1 to about 300 mg per day in single or divided doses, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.001 mg to about 10 mg per kg of body weight per day is most desirably employed. Variations may nevertheless occur depending upon the weight and condition of the persons being treated and their individual responses to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval during which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such larger doses are first divided into several small doses for administration throughout the day.

The active salts can be administered alone or in combination with pharmaceutically acceptable carriers or diluents by any of the several routes previously indicated. More

particularly, the active salts can be administered in a wide variety of different dosage forms, *e.g.*, they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, transdermal patches, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents. In addition, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compound is present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc can be used for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar, as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration the active ingredient may be combined with various sweetening or flavoring agents, coloring matter and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

For parenteral administration, a solution of an active salt in either sesame or peanut oil or in aqueous propylene glycol can be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8), if necessary, and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

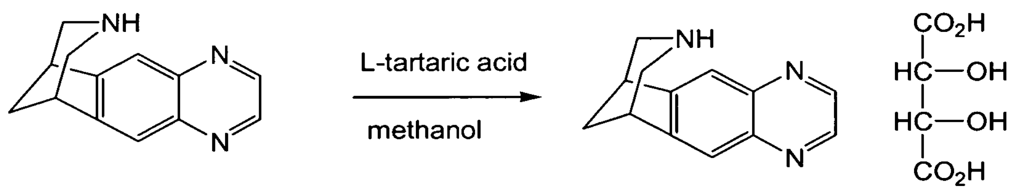
It is also possible to administer the active salts topically and this can be done by way of creams, a patch, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

EXAMPLES

The following examples illustrate the methods and compounds of the present invention. It will be understood, however, that the invention is not limited to the specific Examples.

Example 1

L-Tartrate Salt of 5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (Anhydrous Polymorph, Form B)



CP-526,555
MW 211.27

CP-526,555-18
MW 361.36

A speck-free vessel was charged with L-tartaric acid (780 grams, 1.1 equiv.) and methanol (7.5 L). The contents of the vessel were stirred until solution and speck free filtered into the crystallization vessel. 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene free base (992 grams) and methanol (7.5 L) were dissolved in the vessel; the mixture was maintained at between 20 to 25 °C. The solution of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene free base was added over about 45 minutes to the L-tartaric acid solution through a filter to render the solution speck and fiber free. The product was allowed to stir at 20 to 25 °C overnight and isolated by filtration. The product was dried under vacuum at 35 to 45 °C to give 1618.4 grams (95.4%) of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene L-tartrate salt Form B (MW 361.36). M.p. 210.5 °C; verified as Form B by powder x-ray diffraction.

Example 2

L-Tartrate Salt of 5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (Anhydrous Polymorph, Form A)

A reactor was charged with 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene free base (2 g; 0.0095 mole, 1.0 equiv.) and methanol (60 mL, 30 mL/g). The mixture was stirred at 20 to 25 °C until completely dissolved. A second reactor containing a solution of L-tartaric acid (1.55 g, 0.0103 mole, 1.1 equiv.) dissolved in methanol (60 mL, 30 mL/g) was heated to reflux in methanol (*i.e.*, 60 to 66 °C). The free base solution was added to the L-tartaric acid solution at methanolic reflux temperature over 20 minutes. The resulting slurry was cooled to 20 to 25 °C over a 1 hour period. The reaction mixture was allowed to stir for approximately 2 hours followed by isolation of the product by filtration. The solid product was washed with methanol (10 mL), then dried under vacuum at 30 to 35 °C to

give 3.3 grams (97%) of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene L-tartrate Form A. The identity as Form A was determined by PXRD as compared with standard samples.

Example 3

L-Tartrate Salt Form C of 5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (Form C)

Preparation of CP-526,555-18 Form C from Form A or Form B:

L-tartrate salt Form B (~5g) was dissolved in water (10 to 15 ml). Acetonitrile (200 to 300 ml) was added and Form C formed as a white precipitate. The resulting slurry was allowed to stir for 10 minutes and then filtered. The wet cake was then allowed to air dry. Product was determined to be Form C by NIR spectroscopy, DSC and PXRD analysis. This procedure may be run with Form A to yield Form C.

Example 4

L-Tartrate Salt Form A of 5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene (Form A)

Preparation of Form A from Form C: L-tartrate salt Form C (~2g) was added to 200 to 300 mL hot ethanol (~75°C) and allowed to stir for 30 minutes. The sample was filtered hot and then dried in a 45°C vacuum oven (house vacuum). The material was determined to be Form A by NIR spectroscopy, DSC, and PXRD analysis.

CLAIMS

1. The tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

2. A compound according to claim 1 which is the L-tartrate salt.

3. A compound according to claim 2 which is anhydrous.

4. A compound according to claim 3 characterized substantially by at least one of the following powder x-ray diffraction pattern peaks expressed in terms of 2θ as measured with copper radiation chosen from: 6.1, 16.8 and 21.9.

5. A compound according to claim 3 characterized substantially by the following principal powder x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ	d-value (Å)
6.1	14.5
12.2	7.2
13.0	6.8
14.7	6.0
16.8	5.3
19.4	4.6
21.9	4.1
24.6	3.6

6. A compound according to claim 5 characterized in that it has a onset of melt of about 223 °C.

7. A compound according to claim 5 characterized substantially by solid state ^{13}C NMR resonance peaks at 178.4, 145.1, and 122.9 ppm.

8. A compound according to claim 5 characterized substantially by solid state ^{13}C NMR resonance peaks at 178.4, 149.3, 147.4, 145.1, and 122.9 ppm.

9. A compound according to claim 3 characterized substantially by at least one powder x-ray diffraction pattern peaks in terms of 2θ measured with copper radiation chosen from: 5.9 and 21.8.

10. A compound according to claim 3 characterized substantially by the principal powder x-ray diffraction pattern peaks in terms of 2θ and d-spacings measured with copper radiation:

Angle 2θ	d-value (Å)
5.9	15.0
12.8	6.9
14.4	6.1
15.3	5.8
16.9	5.2
17.2	5.2
21.8	4.1
23.8	3.7
25.1	3.5

11. A compound according to claim 10 characterized in having an onset of melting of about 215 °C.

12. A compound according to claim 10 characterized substantially by the solid state ^{13}C NMR principal resonance peaks at: 179.2, 178.0, 144.4, 124.8 and 122.5 ppm.

13. A compound according to claim 10 characterized substantially by the solid state ^{13}C NMR principal resonance peaks: 179.2, 178.0, 147.4, 145.2, 144.4, 124.8 and 122.5 ppm.

14. A compound according to claim 10 characterized by the single crystal structure of Figure 8A.

15. A compound according to claim 10 that forms orthorhombic crystals belonging to the P2(1)2(1)2(1) space group.

16. A compound according to claim 2 which is a hydrate.

17. A compound according to claim 16 where the hydrate is a monohydrate.

18. A compound according to claim 16 characterized substantially by at least one of the powder x-ray diffraction pattern peaks in terms of 2θ as measured with copper radiation chosen from: 11.8, 16.5, 23.1 and 26.5.

19. A compound according to claim 16 characterized substantially by the principal powder x-ray diffraction pattern peaks in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
5.9	15.1
11.8	7.5
16.5	5.4
21.2	4.2
23.1	3.8
23.8	3.7
26.5	3.4

20. A compound according to claim 16 characterized by the single crystal structure of Figure 8B.

21. A compound according to claim 16 that forms monoclinic crystals belonging to the P2(1) space group.

22. A compound according to claim 16 characterized in having an onset of solid-solid transition at about 73 °C and an onset of melting transition at about 220 °C.

23. A compound according to claim 16 characterized substantially by solid state ^{13}C NMR principal resonance peaks: 179.0, 176.1, 147.5 and 144.5 ppm.

24. A compound according to claim 16 characterized substantially by solid state ^{13}C NMR principal resonance peaks: 179.0, 176.1, 147.5, 144.5 and 124.6 ppm.

25. A compound according to claim 1 which is the D,L-tartrate salt.

26. A compound according to claim 25 which is anhydrous.

27. A compound according to claim 26 characterized substantially by a powder x-ray diffraction pattern peaks expressed in terms of 2θ as measured with copper radiation at: 6.0.

28. A compound according to claim 26 characterized substantially by the following principal powder x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
6.0	14.6
11.9	7.4
15.0	5.9
17.1	5.2
22.1	4.0
24.5	3.6

29. A compound according to claim 26 characterized in that it has a onset of melt of about 212 °C.

30. A compound according to claim 25 which is a hydrate.

31. A compound according to claim 30 characterized substantially by the powder x-ray diffraction pattern peaks in terms of 2θ as measured with copper radiation at: 6.2 and 25.1.

32. A compound according to claim 30 characterized substantially by the principal powder x-ray diffraction pattern peaks in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
6.2	14.2
12.0	7.4
15.2	5.8
18.1	4.9
24.0	3.7
25.1	3.5

33. A compound according to claim 30 characterized by having an onset of a solid-solid transition at about 131 °C and an onset of melting transition at about 217 °C.

34. A compound according to claim 1 which is the D-tartrate salt.

35. A compound according to claim 34 which is anhydrous.

36. A compound according to claim 34 which is a hydrate.

37. A compound according to claim 1 which is the meso-tartrate salt.

38. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to any of claims 1, 2, 4, 9, 18, 27, 31, 34 or 37.

39. A method of treating inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome,

spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, drug/toxin-induced cognitive impairment (*e.g.*, from alcohol, barbiturates, vitamin deficiencies, recreational drugs, lead, arsenic, mercury), disease-induced cognitive impairment (*e.g.*, arising from Alzheimer's disease (senile dementia), vascular dementia, Parkinson's disease, multiple sclerosis, AIDS, encephalitis, trauma, renal and hepatic encephalopathy, hypothyroidism, Pick's disease, Korsakoff's syndrome and frontal and subcortical dementia), hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (*e.g.*, dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, migraine, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome comprises administering to a subject in need of treatment a therapeutically effective amount of a compound according to any of claims 1, 2, 4, 9, 18, 27, 31, 34 or 37.

40. A method of treatment for nicotine dependency, addiction and withdrawal comprising the administration of a compound according to any of claims 1, 2, 4, 9, 18, 27, 31, 34 or 37 to a subject in need thereof.

41. A process for the preparation of a compound according to claim 4 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with between about 1 and about 2 equivalents of L-tartaric acid; and

(ii) collecting the crystals formed.

42. A process according to claim 41 wherein 1.1 equivalents of L-tartaric acid are employed and the tartaric acid is added to a solution containing the free base.

43. A process according to claim 41 wherein the contacting step is allowed to proceed above 45 °C.

44. A process according to claim 41 wherein the contacting step is allowed to proceed for less than 2 hours.

45. A process according to claim 41 wherein the suitable solvent is selected from the group consisting of an (C_1-C_6)alkyl alcohol, an (C_1-C_6)alkyl ketone, an (C_1-C_6)alkyl ether, acetonitrile and an (C_1-C_6)alkyl ester.

46. A process according to claim 41 wherein the suitable solvent is ethanol or methanol.

47. A process for the preparation of a compound according to claim 9 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with between about 1 and about 2.3 equivalents of L-tartaric acid; and

(ii) collecting the crystals formed.

48. A process according to claim 47 wherein 1.1 equivalents of L-tartaric acid are employed and the free base in solution is added to a solution containing L-tartaric acid.

49. A process according to claim 47 wherein the contact step is allowed to proceed for at least 2 hours.

50. A process according to claim 47 wherein the contact step is allowed to proceed for at least 12 hours.

51. A process according to claim 47 wherein the suitable solvent is selected from the group consisting of an (C_1-C_6)alkyl alcohol, an (C_1-C_6)alkyl ketone, an (C_1-C_6)alkyl ether, acetonitrile and an (C_1-C_6)alkyl ester.

52. A process according to claim 47 wherein the suitable solvent is methanol or ethanol.

53. A process according to claim 47 wherein the suitable solvent is methanol.

54. A process for the preparation of a compound according to claim 18 comprising the steps of

(i) contacting an anhydrous L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene with water; and

(ii) collecting the crystals formed.

55. A process according to claim 54 wherein the contacting of step (i) comprises exposing the anhydrous L-tartrate salt to greater than 70% humidity.

56. A process according to claim 54 wherein the contacting of step (i) comprises slurrying the anhydrous L-tartrate salt with water.

57. A process according to claim 54 wherein step (i) comprises the addition of an organic solvent.

58. A process according to claim 54 wherein step (i) comprises the addition of methanol, ethanol or acetonitrile.

59. A process for the preparation of a compound according to claim 27 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of D,L-tartaric acid; and

(ii) collecting the crystals formed.

60. A process according to claim 59 wherein about 2.2 equivalents of D,L-tartaric acid is employed and the free base in solution is added to a solution containing D,L-tartaric acid.

61. A process according to claim 59 wherein the contact step is allowed to proceed for at least 24 hours.

62. A process according to claim 59 wherein the suitable solvent is anhydrous ethanol.

63. A process for the preparation of a compound according to claim 31 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of D,L-tartaric acid; and

(ii) collecting the crystals formed.

64. A process according to claim 63 wherein about 2.2 equivalents of D,L-tartaric acid is employed and the free base in solution is added to a solution containing D,L-tartaric acid.

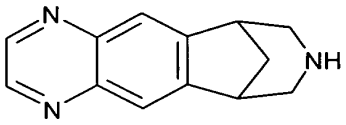
65. A process according to claim 63 wherein the contact step is allowed to proceed for at least 24 hours.

66. A process according to claim 63 wherein the suitable solvent is 20% aqueous ethanol.

ABSTRACT

TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

The present invention is directed to the tartrate salts of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene:



and pharmaceutical compositions thereof. The present invention in particular is directed to the L-tartrate salt, and further to the various polymorphs of the L-tartrate salt, including two distinct anhydrous polymorphs (referred to herein as Forms A and B) and a hydrate polymorph (referred to herein as Form C). In addition, the present invention is also directed to the D-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene and the various polymorphs thereof; as well as the D,L-tartrate salt thereof and its polymorphs, and the meso-tartrate salt thereof and its polymorphs.

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

05/09/2002 GGEBREGI 00000060 161445 10139730

01 FC:101 740.00 CH
02 FC:103 1260.00 CH
03 FC:104 280.00 CH

PTO-1556
(5/87)

*U.S. Government Printing Office: 2001 — 481-697/59173

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number: PC11872A

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	66	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	90 minus 20=	* 70
INDEPENDENT CLAIMS	1 minus 3 =	* 0
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	370.00	OR	BASIC FEE	740.00
X$ 9=		OR	X$18=	1260
X42=		OR	X84=	
+140=		OR	+280=	280
TOTAL		OR	TOTAL	

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
***If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

CLAIMS ONLY

SERIAL NO. 10/135730 | FILING DATE 05-06-02

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
.	IND.	DEP.	IND.	DEP.	IND.	DEP.
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TOTAL IND.						
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TOTAL CLAIMS						

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100						
TOTAL IND.	1					
TOTAL DEP.	89					
TOTAL CLAIMS	90					

* MAY BE USED FOR ADDITIONAL CLAIMS OR ADMENDMENTS

FORM PTO-2022 (1-96)

U.S.DEPARTMENT OF COMMERCE
Patent and Trademark Office

*U.S. Government Printing Office: 1998 - 433-214/70303

Patent Application
Attorney Docket No. PC11872A

"EXPRESS MAIL" LABEL NO. EL 768 265 645 US, Date of Deposit: May 6, 2002. I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to: Commissioner for Patents, Box Patent Application, Washington, D.C. 20231.

#8A
PS

By _____
(Signature of person mailing)
ROY F. WALDRON
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: D. Bogle et al. :

Examiner: Not Yet Assigned

SER. NO.: Not Yet Assigned :

Group Art Unit: Not Assigned

FILING DATE: Concurrently Herewith :

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF :

Commissioner for Patents
Box Patent Application
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

Prior to examination on the merits and calculation of filing fees, please enter the following amendments to the abstract, specification and claims. Marked up versions of the amendments to the abstract, specification and claims are found in the Appendix attached hereto.

IN THE SPECIFICATION

at page 1, line 3, insert the following new paragraph:

A1

This application claims the benefit of U.S. Provisional Application Ser. No. 60/290,861, filed May 14, 2001.

REMARKS

Applicants have inserted a statement on page 1 of the application to indicate the priority required by 37 C.F.R. § 1.78. This amendment adds no new matter to the application.

Applicants believe the set of pending claims are condition for allowance and request the issuance of a Notice of Allowance.

EXPRESS MAIL CERTIFICATION

"Express Mail" Label No. EL 768 265 645 US, Date of Deposit: May 6, 2002. I hereby certify that the accompanying Specification: 37 pages; Claims: 7 pages; Abstract 1 page; Drawings: 20 pages; Utility Patent Application Transmittal; Fee Transmittal (2 copies) and Preliminary Amendment; is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to: Commissioner for Patents, Box Patent Application, Washington, D.C. 20031.

By _____
(Signature of person transmitting and mailing)
ROY F. WALDRON
(Typed or printed name of person)

If a telephone interview would assist the furtherance of the prosecution of this application, the Examiner is invited to contact the undersigned.

Respectfully submitted,

Date: 5/6/2002

Roy F. Waldron
Registration No. 42,208
Attorney for Applicant(s)

Pfizer, Inc
Patent Department
150 East 42nd Street (150/05/49)
New York, NY 10017
(212) 733-5086

APPENDIX TO PRELIMINARY AMENDMENT

MARKED-UP VERSIONS OF AMENDED SPECIFICATION AND CLAIMS

IN THE SPECIFICATION

at page 1, line 7, insert the following new paragraph:

This application claims the benefit of U.S. Provisional Application Ser. No. 60/290,861, filed May 14, 2001.

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/139,730	05/06/2002	D. Bogle	~~11872A

CONFIRMATION NO. 5317

Paul H. Ginsburg
Pfizer Inc
Patent Department (150/05/49)
150 East 42nd Street
New York, NY 10017-5612

FORMALITIES LETTER

OC000000008259029

Date Mailed: 06/10/2002

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(l) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.

Items Required To Avoid Processing Delays:

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$130** for a Large Entity

- **$130** Late oath or declaration Surcharge.

A copy of this notice MUST be returned with the reply.

Haimanot Tegbaru

Customer Service Center
Initial Patent Examination Division (703) 308-1202
PART 3 - OFFICE COPY

Patent Application
Attorney Docket No.PC11872A

I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231 on this 6th day of September, 2002.

By _____
(Signature of person mailing)
A. David Joran
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: D. Bogle, et al.

APPLICATION NO.: 10/139,730 : Examiner:

FILING DATE: May 6, 2002 : Group Art Unit: 1614

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATERACYCLO[10.3.1.02,11 04.9]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Commissioner for Patents
Washington, D.C. 20231

Sir:

INFORMATION DISCLOSURE STATEMENT
PURSUANT TO 37 C.F.R. § 1.97 ET SEQ.

Applicant(s) herein make(s) available to the U.S. Patent and Trademark Office a copy of PTO-FB-A820 which lists the references cited by the applicant(s), copies of which are enclosed.

The Examiner is requested to consider carefully the complete text of these references in connection with the examination of the above-identified application in accord with 37 C.F.R. § 1.104(a). It is believed the Examiner will concur with applicant's belief that the subject matter presently claimed is neither anticipated nor rendered obvious by the foregoing references.

It is requested that the references listed on the attached form PTO-FB-A820 be included in the "References Cited" portion of any patent issuing from this application (M.P.E.P. § 1302.12).

Please charge all appropriate fees to cover this submission to Pfizer Deposit Account No. 16-1445.

A prompt and favorable response is earnestly solicited.

Respectfully submitted,

Date: September 6, 2002

A. David Joran
Attorney for Applicant(s)
Reg. No. 37,858

Pfizer Inc
Patent Department, 5th Floor
150 East 42nd Street
New York, NY 10017-5755
(212)733 -3381

#4

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
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WASHINGTON, D.C. 20231
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APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/139,730	05/06/2002	D. Bogle	PC11872A

CONFIRMATION NO. 5317

Paul H. Ginsburg
Pfizer Inc
Patent Department (150/05/49)
150 East 42nd Street
New York, NY 10017-5612

FORMALITIES LETTER

OC000000008259029

Date Mailed: 06/10/2002

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

10/17/2002 MDAMTE1 00000081 161445 10139730
01 FC:1051 130.00 CH

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(l) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.

Items Required To Avoid Processing Delays:

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$130** for a Large Entity

- **$130** Late oath or declaration Surcharge.

A copy of this notice MUST be returned with the reply.

Haimanot Tegbaru

Customer Service Center
Initial Patent Examination Division (703) 308-1202
PART 2 - COPY TO BE RETURNED WITH RESPONSE

Patent Application
Attorney Docket No. PC11872A

I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents Washington, D.C. 20231 on this 9th day of October.

By _____
(Signature of person mailing)
A. David Joran
(Typed or printed name of person)

OIPE
OCT 15 2002
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle, et al.

APPLICATION SERIAL NO.: 10/139,730 : Examiner:

FILING DATE: May 6, 2002 : Group Art Unit: 1614

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRA-CYCLO[10.3.1.02,11.04,9]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Commissioner for Patents
Washington, D.C. 20231

Sir:

FILING OF MISSING PARTS OF APPLICATION
PURSUANT TO NOTICE ON FORM PTO-1533

Enclosed herewith is a Declaration and Power of Attorney for the above-identified application which is due October 10, 2002.

The Commissioner hereby authorized to charge the appropriate fee, estimated to be $ 130 ; and any additional fees required under 37 C.F.R. §§ 1.16 and 1.17, or to credit any overpayment to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

A copy of the Notice to File Missing Parts is also enclosed.

Respectfully submitted,

Date: October 9, 2002

A. David Joran, Ph.D.
Attorney for Applicant(s)
Reg. No. 37,858

Pfizer, Inc
Patent Department, 5th Floor
150 East 42nd Street
New York, NY 10017-5755
(212) 733-3381

[redacted] PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

#4

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE RECD	ATTY DOCKET NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
10/139,730	[redacted]2002	1614	2280	[redacted]	20	66	1

CONFIRMATION NO. 5317

Paul H. Ginsburg
Pfizer Inc
Patent Department (150/05/49)
150 East 42nd Street
New York, NY 10017-5612

FILING RECEIPT

[redacted]

OC000000008259028

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ORIGINALLY FILED

Date Mailed: 06/10/2002

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections, facsimile number 703-746-9195. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

D. Bogle, ~~Residence Not Provided;~~ Jewett City, CT; P. R. Rose, Ledyard, CT; G. R. Williams, East Aurora, NY

Domestic Priority data as claimed by applicant

THIS APPLN CLAIMS BENEFIT OF 60/290,861 05/14/2001

Foreign Applications

If Required, Foreign Filing License Granted 06/10/2002

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No

Title

Tartrate salts of 5,8,14-triazateracyclo[10.3.1.02,11 04,9]-hexadeca-2(11),3,5,7,9-pentaene and pharmaceutical compositions thereof

Preliminary Class

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#4

PTO/SB/17(2/98)
Approved for use through 09/30/2000.
OMB 0651-0032 Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

OIPE JC97 PATENT & TRADEMARK OFFICE

FEE TRANSMITTAL

OCT 15 2002

Patent fees are subject to annual revision on October 1. These are the fees effective October 1, 2001

Small Entity payments must be supported by a small entity statement, otherwise large entity fees must be paid. See Forms PTO/SB/09-12.

See 37 C.F.R. §§ 1.27 and 1.28.

Total Amount of Payment ($) 530.00

Complete If Known	
Application Number	10/139,730
Filing Date	May 6, 2002
First Named Inventor	David E. Bogle
Examiner Name	
Group/Art Unit	1614
Attorney Docket No.	PC11872A

METHOD OF PAYMENT (check one)

1. ☒ The commissioner is hereby authorized to charge indicated fees and credit any over payments to:

Deposit Account Number: 16-1445

Deposit Account Name: Pfizer Inc.

☒ Charge Any Additional Fee Required Under 37 C.F.R. §§ 1.16 and 1.17.

☐ Charge the Issue Fee Set in 37 C.F.R. § 1.18 at the Mailing of the Notice of Allowance.

2. ☐ Payment Enclosed:

☐ Check ☐ Money Order ☐ Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	740	201	370	Utility filing fee	
106	330	206	165	Design filing fee	
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	160	214	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES

			Extra Claims		Fee from below		Fee Paid
Total Claims		-20**=		X		=	
Independent Claims		- 3**=		X		=	
Multiple Dependent						=	

** *or number previously paid, if greater; For Reissues, see below*

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	84	202	42	Independent claims in excess of 3
104	280	204	140	Multiple dependent claim, if not paid
109	84	209	42	**Reissue independent claims over original patent
110	18	210	9	**Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge – late fee or oath	130
127	50	227	25	Surcharge–late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	400
117	920	217	460	Extension for reply within third month	
118	1,440	218	720	Extension for reply within fourth month	
128	1,960	228	980	Extension for reply within fifth month	
119	320	219	160	Notice of Appeal	
120	320	220	160	Filing a brief in support of an appeal	
121	280	221	140	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,280	241	640	Petition to revive - unintentional	
142	1,280	242	640	Utility issue fee (or reissue)	
143	460	243	230	Design issue fee	
144	620	244	310	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	180	126	180	Submission of Information Disclosure Statement	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	740	246	370	Filing a submission after final rejection (37 CFR 1.129(a))	
149	740	249	370	For each additional invention to be examined (37 CFR 1.129(b))	
Other Fee (specify)					
Other Fee (specify)					

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 530.00

SUBMITTED BY				Complete (if Applicable)	
Type or Printed Name	A. David Joran			Reg. Number	37,858
Signature		Date	October 9, 2002	Deposit Account User ID	16-1445

PTO/SB/01A (10-00)
Approved for use through 10/31/2002. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

As the below named inventor(s), I/we declare that:

This declaration is directed to: COPY OF PAPERS ORIGINALLY FILED

☐ The attached application, or

☒ Application No. 10/139,730, filed on May 6, 2002

☒ as amended on May 6, 2002 if applicable);

I/we believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought;

I/ we have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

I/we acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in 37 CFR 1.56, including material information which became available between the filing date of the prior application and the National or PCT International filing date of the continuation-in-part application, if applicable; and

All statements made herein of my/own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

Full Name of Inventor(s)

Inventor 1	David E. Bogle		
Signature	David E Bogle David E Bogle	Citizen of	US
Inventor 2	Peter R. Rose		
Signature		Citizen of	US
Inventor 3	Glenn R. Williams		
Signature		Citizen of	US

☐ Additional inventors are being named on

Burden Hour Statement: This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is used by the public to file (and the PTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This form is estimated to take 1 minute to complete. This time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

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All statements made herein of my/own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

Full Name of Inventor(s)

Inventor 1	David E. Bogle	
Signature		Citizen of US
Inventor 2	Peter R. Rose	
Signature		Citizen of US
Inventor 3	Glenn R. Williams	
Signature		Citizen of US

☐ Additional inventors are being named on

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OCT 15 2002

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Full Name of Inventor(s)

Inventor 1	David E. Bogle	
Signature		Citizen of US
Inventor 2	Peter R. Rose	
Signature		Citizen of US
Inventor 3	Glenn R. Williams	
Signature		Citizen of US

☐ Additional inventors are being named on

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PTO/SB/81(02-01)
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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Please type a plus sign (+) inside this box →

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POWER OF ATTORNEY OR AUTHORIZATION OF AGENT

Application Number	10/139,730
Filing Date	May 6, 2002
First Named Inventor	David E. Bogle
Title	TARTRATE SALTS OF 5,8, 14-TRIAZATERACYCLO[10.3.1.02,11.04,9]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF
Group Art Unit	1614
Examiner Name	Not Yet Assigned
Attorney Docket Number	PC11872A

I hereby appoint:

☒ Practitioners at Customer Number 23913 →

OR

☐ Practitioners named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Please change the correspondence address for the above-identified application to:

☐ The above-mentioned Customer Number.

OR

☐ Practitioners at Customer Number →

OR

☐ Firm or Individual Name					
Address					
Address					
City		State		Zip	
Country					
Telephone		Fax			

I am the:

☒ Applicant/Inventor.

☐ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

SIGNATURE of Applicant or Assignee of Record

Name	Peter R. Rose
Signature	
Date	8/14/02

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of forms are submitted.

Burden Hour Statement: This form is estimated to take 3 minutes to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC

#6

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POWER OF ATTORNEY OR AUTHORIZATION OF AGENT

Application Number	10/139,730
Filing Date	May 6, 2002
First Named Inventor	David E. Bogle
Title	TARTRATE SALTS OF 5,8, 14-TRIAZATERACYCLO[10.3.1.02,11.04,9]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF
Group Art Unit	1614
Examiner Name	Not Yet Assigned
Attorney Docket Number	PC11872A

I hereby appoint:

☒ Practitioners at Customer Number 23913 →

OR

☐ Practitioners named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Please change the correspondence address for the above-identified application to:

☐ The above-mentioned Customer Number.

OR

☐ Practitioners at Customer Number →

OR

☐ Firm or Individual Name					
Address					
Address					
City		State		Zip	
Country					
Telephone		Fax			

I am the:

☒ Applicant/Inventor.

☐ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

SIGNATURE of Applicant or Assignee of Record

Name	Glenn R. Williams
Signature	Glenn R Williams
Date	09/28/02

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of forms are submitted.

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PTO/SB/81(02-01)
Approved for use through 10/31/2002. OMB 0651-0035
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Please type a plus sign (+) inside this box → +

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OCT 15 2002
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POWER OF ATTORNEY OR AUTHORIZATION OF AGENT

Application Number	10/139,730
Filing Date	May 6, 2002
First Named Inventor	David E. Bogle
Title	TARTRATE SALTS OF 5,8, 14-TRIAZATERACYCLO[10.3.1.02,11.04,9]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF
Group Art Unit	1614
Examiner Name	Not Yet Assigned
Attorney Docket Number	PC11872A

I hereby appoint:

☒ Practitioners at Customer Number 23913 →

OR

☐ Practitioners named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

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☐ The above-mentioned Customer Number.

OR

☐ Practitioners at Customer Number →

OR

☐ Firm or Individual Name					
Address					
Address					
City		State		Zip	
Country					
Telephone		Fax			

I am the:

☒ Applicant/Inventor.

☐ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

SIGNATURE of Applicant or Assignee of Record

Name	David E. Bogle
Signature	David E. Bogle
Date	5-12-02

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of forms are submitted.

Burden Hour Statement: This form is estimated to take 3 minutes to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC

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#7

Application Data Sheet

Application Information

PC11872A::

Application Type::	Regular
Subject Matter::	Utility
Title::	TARTRATE SALTS OF 5,8, 14-TRIAZATERACYCLO [10.3.1.02,11 04.9]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF
Attorney Docket Number::	**PC11872A**

Inventor Information

Inventor Authority Type::	INVENTOR
Primary Citizenship Country::	US
Given Name::	David E.
Family Name::	Bogle
City of Residence::	Jewett City
State or Prov of Residence::	CT
Country of Residence::	US
Street::	10 Beaulieu Avenue
City::	Jewett City
State or Province::	CT
Postal or Zip Code::	06351

Inventor Authority Type::	INVENTOR
Primary Citizenship Country::	US
Given Name::	Peter R.
Family Name::	Rose
City of Residence::	Ledyard
State or Prov of Residence::	CT
Country of Residence::	US
Street::	34 Silas Deane Road
City::	Ledyard
State or Province::	CT
Postal or Zip Code::	06355

Inventor Authority Type::	INVENTOR
Primary Citizenship Country::	US

Given Name::	Glenn R.
Family Name::	Williams
City of Residence::	East Aurora
State or Prov of Residence::	NY
Country of Residence::	US
Street::	903 Mill Road
City::	East Aurora
State or Province::	NY
Postal or Zip Code::	14052

Correspondence Information

Correspondence Customer Number::	23913

Representative Information

Representative Customer Number::	23913

Assignee Information

Assignee Name::	Pfizer Inc.

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This application	Non Prov of Prov	60/290,861	05/14/01

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Patent Application
Attorney Docket No. PC11872A

I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to Commissioner of Patents Washington, D.C. 20231 on this 9th day of October, 2002.

By _____
(Signature of person mailing)
A. David Joran
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle, et al.

APPLICATION NO.: 10/139,730 : Examiner:

FILING DATE: May 6, 2002 : Group Art Unit: 1614

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRA-CYCLO[10.3.1.02,11.04,9]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Commissioner for Patents
Washington, D.C. 20231

Sir:

PETITION FOR EXTENSION OF TIME PURSUANT TO 37 C.F.R. §1.136(a)

Pursuant to the provisions of 37 C.F.R. §1.136(a), it is requested that the term for response to the Examiner's Action in this application, mailed on June 10, 2002, and having an original period for response of two months, which expired on August 10, 2002, be extended by 2 month(s), such that it expires on October 10, 2002.

Authorization is hereby provided to charge the amount of $400,00 as stated under 37 C.F.R. §1.17, as well as any additional fees required, or to credit any overpayment to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

10/17/2002 MDAMTE1 00000081 161445 10139730
02 FC:1252 400.00 CH

Patent Application
Attorney Docket No. PC11872A

Respectfully submitted,

Date: October 9, 2002

A. David Joran
Attorney for Applicant(s)
Reg. No. 37,858

Pfizer, Inc
Patent Department, 5th Floor
150 East 42nd Street
New York, NY 10017-5755
(212) 773-3381

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Patent Application
Attorney Docket No. PC11872A

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By _____
(Signature of person mailing)
A. David Joran
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle, et al.

APPLICATION NO.: 10/139,730 : Examiner:

FILING DATE: May 6, 2002 : Group Art Unit: 1614

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRA-CYCLO[10.3.1.02,11.04,9]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Commissioner for Patents
Washington, D.C. 20231

Sir:

PETITION FOR EXTENSION OF TIME PURSUANT TO 37 C.F.R. §1.136(a)

Pursuant to the provisions of 37 C.F.R. §1.136(a), it is requested that the term for response to the Examiner's Action in this application, mailed on June 10, 2002, and having an original period for response of two months, which expired on August 10, 2002, be extended by 2 month(s), such that it expires on October 10, 2002.

Authorization is hereby provided to charge the amount of $400,00 as stated under 37 C.F.R. §1.17, as well as any additional fees required, or to credit any overpayment to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

10/17/2002 MDAMTE1 00000081 161445 10139730
02 FC:1252 400.00 CH

Patent Application
Attorney Docket No. PC11872A

Respectfully submitted,

Date: October 9, 2002

A. David Joran
Attorney for Applicant(s)
Reg. No. 37,858

Pfizer, Inc
Patent Department, 5th Floor
150 East 42nd Street
New York, NY 10017-5755
(212) 773-3381

L4 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 2003:23533 CAPLUS
TI Pharmaceutical composition and method of modulating cholinergic function in a mammal
IN Coe, Jotham W.; Sands, Steven B.
PA Pfizer Inc., USA
SO U.S. Pat. Appl. Publ., 23 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2003008892	A1	20030109	US 2002-105605	20020325
WO 2003005998	A2	20030123	WO 2002-IB1767	20020521

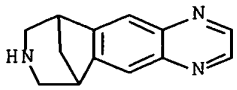
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-303957P P 20010709

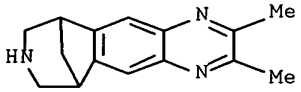
AB A compn. for modulating cholinergic function in a mammal comprises a nicotinic receptor partial agonist (NRPA) in combination with an anti-emetic/anti-nausea agent and a pharmaceutically acceptable carrier. The NRPA compd. and the anti-emetic/anti-nausea agent are present in amts. that render the compn. effective modulating cholinergic function or in the treatment of various disorders or conditions selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chem. dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alc., benzodiazepines, barbiturates, opioids or cocaine), headache, migraine, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome. The method of using these compns. is also disclosed.

IT **249296-44-4 357424-19-2**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. contg. nicotinic receptor partial agonist in combination with antiemetic for modulating cholinergic function)

RN 249296-44-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro- (9CI)(CA INDEX NAME)



RN 357424-19-2 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl- (9CI) (CA INDEX NAME)



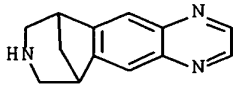
L4 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 2002:888737 CAPLUS
DN 137:375226
TI The citrate salt of 5, 8, 14-triazatetracyclo(10.3.1.02,11.04.9)-hexadeca-2.(11),3,5,7,9-pentane and pharmaceutical compositions thereof
IN Johnson, Philip James; Rose, Peter Robert; Wint, Lewin Theophilus; Williams, Glenn Robert
PA Pfizer Products Inc., USA
SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002092597	A1	20021121	WO 2002-IB1450	20020426

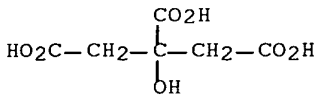
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-290863P P 20010514
AB The present invention is directed to the citrate salt of 5, 8, 14-triazatetracyclo[10.3.1.02.11.04.9]-hexadeca-2(11),3,5,7,9-pentane and pharmaceutical compns. thereof. The present invention is also directed to the various forms fo the citrate salt, particularly its hydrate and its anhyd./nearly anhyd. polymorph. The invention is also directed to processes for prepn. of these citrate salt forms.
IT **475478-66-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (citrate salt of azatetracyclohexadecapentaene and pharmaceutical compns. thereof)
RN 475478-66-1 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1), monohydrate (9CI) (CA INDEX NAME)

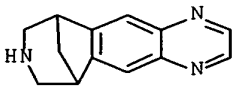
CM 1
CRN 249296-44-4
CMF C13 H13 N3



CM 2
CRN 77-92-9
CMF C6 H8 O7



IT **249296-44-4**
RL: RCT (Reactant); RACT (Reactant or reagent)
(citrate salt of azatetracyclohexadecapentaene and pharmaceutical compns. thereof)
RN 249296-44-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro- (9CI)(CA INDEX NAME)



RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

Appls

L4 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 2002:888559 CAPLUS
DN 137:375274
TI Preparation of pharmaceutical compositions of tartrate salts of 5,8,14-triazatetracyclo{10.3.1.02,11.04,9}-hexadeca-2(11),3,5,7,9-pentaene
IN Bogle, David Everett; Rose, Peter Robert; Williams, Glenn Robert
PA Pfizer Products Inc., USA
SO PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002092089	A1	20021121	WO 2002-IB1437	20020426

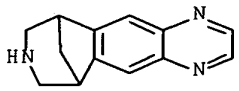
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-290861P P 20010514
AB The present invention is directed to the tartrate salts of 5,8,14-triazatetracyclo[10.3.1.02,11.04,9]-hexadeca-2(11),3,5,7,9-pentaen (I), and their pharmaceutical compns. The present invention in particular is directed to the L-tartrate salt, and further to the various polymorphs of the L-tartrate salt, including 2 distinct anhyd. polymorphs (referred to herein as Forms A and B) and a hydrate polymorph (referred to as Form C). In addn., the present invention is also directed to the D-tartrate salt of I and the various polymorphs as well as the DL-tartrate salt and its polymorphs, and the mesotartrate salt and its polymorphs. Thus, polymorphs of I L-tartrate salt were prepd. by the reaction of the drug base with L-tartaric acid in MeOH. The forms were characterized by x-ray diffraction, DSC and spectrometry.
IT **375815-87-5P**, CP 526555-18 **475470-33-8P**
475470-34-9P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); USES (Uses)
(pharmaceutical compns. contg. polymorphs of tartrate salts of triazatetracyclohexadecapentaene)
RN 375815-87-5 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 249296-44-4

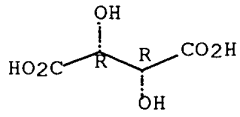
CMF C13 H13 N3



CM 2

CRN 87-69-4
CMF C4 H6 O6

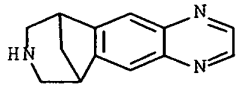
Absolute stereochemistry.



RN 475470-33-8 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-, (2R,3R)-2,3-dihydroxybutanedioate (1:1), monohydrate (9CI) (CA INDEX NAME)

CM 1

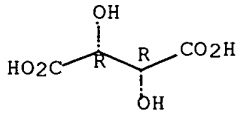
CRN 249296-44-4
CMF C13 H13 N3



CM 2

CRN 87-69-4
CMF C4 H6 O6

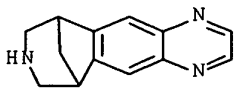
Absolute stereochemistry.



RN 475470-34-9 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-, 2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

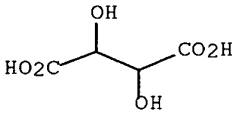
CM 1

CRN 249296-44-4
CMF C13 H13 N3

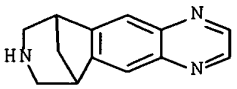


CM 2

CRN 526-83-0
CMF C4 H6 O6



IT **249296-44-4**, CP 526555
RL: RCT (Reactant); RACT (Reactant or reagent)
(pharmaceutical compns. contg. polymorphs of tartrate salts of triazatetracyclohexadecapentaene)
RN 249296-44-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-(9CI)(CA INDEX NAME)



RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

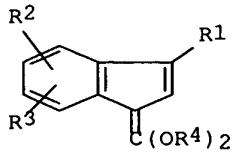
L4 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 2002:832750 CAPLUS
DN 137:337794
TI Process for the preparation of 1,3-substituted indenes and aryl-fused azapolycyclic compounds
IN Singer, Robert Alan; McKinley, Jason Daniel
PA Pfizer Products Inc., USA
SO PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002085843	A2	20021031	WO 2002-IB660	20020304

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-285131P P 20010420
OS MARPAT 137:337794
GI



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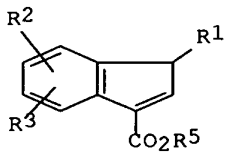
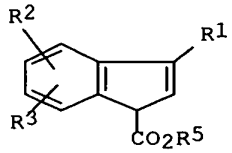
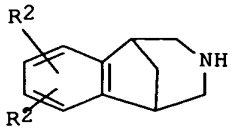


II



III



IV

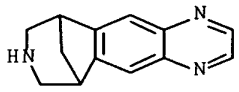
AB The 1,3-substituted indenes I-III [R1 = CN, alkoxycarbonyl, acyl, aryl, NO2, CF3, sulfonyl; R2, R3 = H, F, Cl, alkylthio, alkylsulfinyl, alkylsulfonyl, (un)substituted NH2, CO2H, CONH2, SO2NH2, alkoxy etc.; R4 = H, ammonium, alkali metal; R5 = alkyl, trialkylsilyl, SiPh3] were prepd. as intermediates for the benzoazabicyclooctanones IV which modulate cholinergic function. Thus, 2-BrC6H4CH2CN was treated with MeOCH:CHCO2Me to give 2-BrC6H4C(CN):CHCH2CO2Me which was cyclized to 3-(hydroxymethoxymethylene)-3H-indene-1-carbonitrile sodium salt. Reductive cyclization of the latter compd. gave 2,3,4,5-tetrahydro-1,5-methano-1H-benzazepin-2-one.

IT **249296-44-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of 1,3-substituted indenes as intermediates for aryl-fused

azapolycyclic compds. with cholinergic function)

RN 249296-44-4 CAPLUS

CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-(9CI)(CA INDEX NAME)

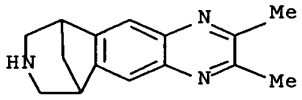


IT **230615-21-1P 230615-23-3P 357425-92-4P**

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of 1,3-substituted indenes as intermediates for aryl-fused azapolycyclic compds. with cholinergic function)

RN 230615-21-1 CAPLUS

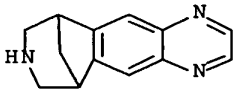
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 230615-23-3 CAPLUS

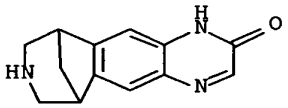
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 6,7,8,9-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 357425-92-4 CAPLUS

CN 6,10-Methano-2H-pyrazino[2,3-h][3]benzazepin-2-one, 1,6,7,8,9,10-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)

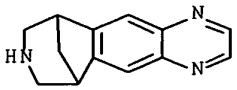


● HCl

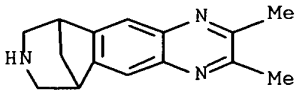
L4 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 2002:695763 CAPLUS
DN 137:210972
TI Use of GABAA inverse agonists in combination with nicotine receptor partial agonists, estrogen, selective estrogen modulators, or vitamin E for the treatment of cognitive disorders
IN Villalobos, Anabella
PA Pfizer Products Inc., USA
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002069948	A1	20020912	WO 2002-IB515	20020220
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2002193360	A1	20021219	US 2002-83743	20020226
PRAI	US 2001-272566P	P	20010301		

OS MARPAT 137:210972
AB A pharmaceutical compn. and method of treatment of diseases of cognitive dysfunction in a mammal comprising administration of a GABAA inverse agonist or a pharmaceutically acceptable salt thereof; and a nicotine receptor partial agonist, an estrogenic agent, selective estrogen receptor modulator or vitamin E or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier. The GABAA inverse agonist, and nicotine receptor partial agonist, estrogen, selective estrogen receptor modulator or vitamin E are present in amts. that render the compn. effective enhancing cognition or in the treatment of diseases of cognitive dysfunction including but not limited to Alzheimer's Disease (AD), mild cognitive impairment, age-related cognitive decline, vascular dementia, Parkinson's disease, Huntington's disease, memory impairment assocd. with depression or anxiety, schizophrenia, Down's syndrome, stroke, traumatic brain injury (TBI), AIDS assocd. dementia and attention deficit disorder. The method of using these compns. is also disclosed.
IT **249296-44-4 357424-19-2**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of GABAA inverse agonists in combination with nicotine receptor partial agonists or estrogen or selective estrogen modulators or vitamin E for treatment of cognitive disorders)
RN 249296-44-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro- (9CI)(CA INDEX NAME)



RN 357424-19-2 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl- (9CI) (CA INDEX NAME)

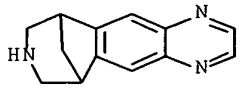


RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

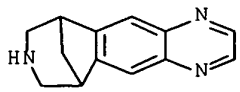
L4 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 2002:104621 CAPLUS
DN 136:145265
TI A pharmaceutical composition for the treatment of attention deficit hyperactivity disorder (ADHD) comprising a nicotine receptor partial agonist and anti-ADHD agent
IN Watsky, Eric Jacob; Coe, Jotham Wadsworth; Harrigan, Edmund Patrick; O'Neill, Brian Thomas; Sands, Steven Bradley
PA Pfizer Products Inc., USA
SO Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1177798	A2	20020206	EP 2001-306455	20010727
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	US 2002016334	A1	20020207	US 2001-865793	20010525
	BR 2001003169	A	20020528	BR 2001-3169	20010731
	JP 2002316949	A2	20021031	JP 2001-231554	20010731
PRAI	US 2000-221718P	P	20000731		

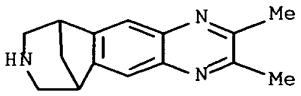
AB Pharmaceutical compns. are disclosed for the treatment of attention deficit hyperactivity disorder (ADHD). The pharmaceutical compns. are comprised of a therapeutically effective combination of a nicotine receptor partial agonist and an anti-ADHD agent and a pharmaceutically acceptable carrier. The method of using these compds. is also disclosed.
IT **249296-44-4 249296-44-4D**, isomers **357424-19-2 357424-19-2D**, isomers
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nicotine receptor partial agonist and anti-attention deficit hyperactivity disorder agent for pharmaceutical compn. for treatment of attention deficit hyperactivity disorder)
RN 249296-44-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro- (9CI) (CA INDEX NAME)



RN 249296-44-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro- (9CI)(CA INDEX NAME)

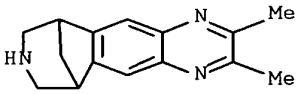


RN 357424-19-2 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl- (9CI) (CA INDEX NAME)



RN 357424-19-2 CAPLUS

CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl- (9CI) (CA INDEX NAME)



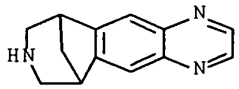
L4 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 2001:885334 CAPLUS
DN 136:658
TI A pharmaceutical composition for the treatment of obesity or to facilitate or promote weight loss, comprising a nicotine receptor partial agonist and an anti-obesity agent
IN Coe, Jotham W.; O'Neill, Brian T.; Sands, Steven B.; Dow, Robert L. B.; Harrigan, Edmund P.; Watsky, Eric J.
PA Pfizer Products Inc., USA
SO Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1159970	A2	20011205	EP 2001-304806	20010531
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	US 2002010192	A1	20020124	US 2001-850042	20010507
	BR 2001002211	A	20020305	BR 2001-2211	20010530
	JP 2002012558	A2	20020115	JP 2001-164010	20010531
PRAI	US 2000-208856P	P	20000602		

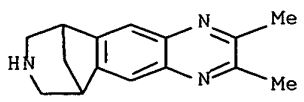
AB Pharmaceutical compns. are disclosed for the treatment of obesity, an overweight condition and compulsive overeating. The pharmaceutical compns. are comprised of a therapeutically effective combination of a nicotine receptor partial agonist and an anti-obesity agent or wt. loss facilitator or promoter, such as Xenical and Meridia, and a pharmaceutically acceptable carrier. The nicotine receptor partial agonist and an anti-obesity agent or wt. loss facilitator are administered substantially simultaneously. A method of treating a disorder or condition in which obesity or an overweight condition predominates, including type 2 diabetes mellitus, hypertension, dislipidemia, and increased mortality in a mammal comprises administering a compn. contg. nicotine receptor partial agonist and an anti-obesity agent.

IT **249296-44-4 357424-19-2**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising nicotine receptor partial agonist and antiobesity agent for treatment of obesity and related disorders)

RN 249296-44-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro- (9CI)(CA INDEX NAME)



RN 357424-19-2 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl- (9CI) (CA INDEX NAME)

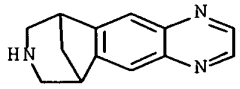


L4 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 2001:864711 CAPLUS
DN 136:11124
TI Reactive crystallization method to improve particle size
IN Am Ende, David Jon; Crawford, Thomas Charles; Weston, Neil Philip
PA Pfizer Products Inc., USA
SO Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1157726	A1	20011128	EP 2001-304422	20010518
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002028475	A2	20020129	JP 2001-153592	20010523
	US 2002016498	A1	20020207	US 2001-863492	20010523
	NO 2001002571	A	20011127	NO 2001-2571	20010525
	CN 1326803	A	20011219	CN 2001-119055	20010525
	BR 2001002129	A	20020521	BR 2001-2129	20010525
PRAI	US 2000-207629P	P	20000526		

AB This invention provides a method of conducting a simultaneous chem. reaction and controlled crystn. of the product employing impinging fluid jet streams contg. reactants capable of producing the product with desired particle size characteristics. An example is give for reaction and crystn. of ziprasidone to achieve the desired ziprasidone-HCl.H2O.

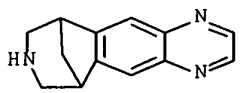
IT **249296-44-4**
RL: PRP (Properties); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(reactive crystn. method to improve particle size)
RN 249296-44-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro- (9CI)(CA INDEX NAME)



IT **375815-87-5P**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(reactive crystn. method to improve particle size)
RN 375815-87-5 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

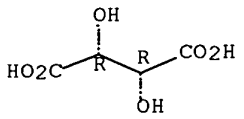
CRN 249296-44-4
CMF C13 H13 N3



CM 2
CRN 87-69-4

CMF C4 H6 O6

Absolute stereochemistry.



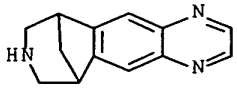
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 2001:798758 CAPLUS
DN 135:339282
TI Nicotine receptor partial agonist, cholinesterase inhibitor, and estrogenic agent composition for treatment of diseases of cognitive dysfunction in a mammal
IN Coe, Jotham Wadsworth; Sands, Steven Bradley; Harrigan, Edmund Patrick; O'Neill, Brian Thomas; Watsky, Eric Jacob
PA USA
SO U.S. Pat. Appl. Publ., 20 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2001036949	A1	20011101	US 2001-760966	20010116
WO 2001085145	A2	20011115	WO 2001-IB681	20010424
WO 2001085145	A3	20020613		

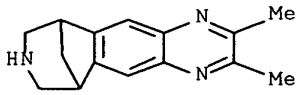
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 2000-202799P P 20000509
AB A pharmaceutical compn. and method of treatment of diseases of cognitive dysfunction in a mammal comprising administration of a nicotine receptor partial agonist or a pharmaceutically acceptable salt thereof; and an acetylcholinesterase inhibitor, butylcholinesterase inhibitor, an estrogenic agent, selective estrogen receptor modulator or muscarinic agonist or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier. The nicotine receptor partial agonist and acetylcholinesterase inhibitor, butylcholinesterase inhibitor, estrogen, selective estrogen receptor modulator or muscarinic agonist are present in amts. that render the compn. effective enhancing cognition or in the treatment of diseases of cognitive dysfunction including but not limited to Alzheimer's Disease, mild cognitive impairment, age-related cognitive decline, vascular dementia, Parkinson's disease dementia, Huntington's Disease, Stroke, TBI, AIDS assocd. dementia and schizophrenia. The method of using these compns. is also disclosed.
IT **249296-44-4 357424-19-2**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nicotine receptor partial agonist, cholinesterase inhibitor, and estrogenic agent compn. for treatment of diseases of cognitive dysfunction in a mammal)
RN 249296-44-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro- (9CI)(CA INDEX NAME)



RN 357424-19-2 CAPLUS

CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl- (9CI) (CA INDEX NAME)



L4 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 2001:762800 CAPLUS
DN 135:322726
TI A pharmaceutical composition containing a nicotine receptor agonist and an analgesic for treatment of acute, chronic pain and/or neuropathic pain and migraines
IN Coe, Jotham Wadsworth; Harrigan, Edmund Patrick; O'Neill, Brian Thomas; Sands, Steven Bradley; Watsky, Eric Jacob
PA Pfizer Products Inc., USA
SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001076576	A2	20011018	WO 2001-IB391	20010316
	WO 2001076576	A3	20020620		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2001036943	A1	20011101	US 2000-740307	20001218
	EP 1272218	A2	20030108	EP 2001-910097	20010316
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI	US 2000-195738P	P	20000407		
	WO 2001-IB391	W	20010316		

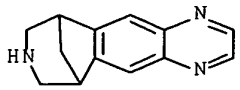
AB Oral, parenteral or transdermal compns. are disclosed for the treatment of acute, chronic and/or neuropathic pain. The pharmaceutical compns. are comprised of a therapeutically effective combination of a nicotine receptor partial agonist and an analgesic agent and a pharmaceutically acceptable carrier. The analgesic agent is selected from opioid analgesics, NMDA antagonists, substance P antagonists, COX 1 and COX 2 inhibitors, tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), capsaicin receptor agonists, anesthetic agents, benzodiazepines, skeletal muscle relaxants, migraine therapeutic agents, anticonvulsants, antihypertensives, antiarrhythmics, antihistamines, steroids, caffeine, N-type calcium channel antagonists and botulinum toxin. The method of using these compds. and a method of treating acute, chronic and/or neuropathic pain and migraine in a mammal including a human is also disclosed.

IT **249296-44-4 357424-19-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)

(compns. contg. nicotine receptor agonist and analgesic for treatment of acute, chronic pain and/or neuropathic pain and migraines)

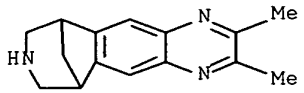
RN 249296-44-4 CAPLUS

CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-(9CI)(CA INDEX NAME)



RN 357424-19-2 CAPLUS

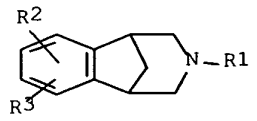
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl- (9CI) (CA INDEX NAME)



L4 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 2001:636053 CAPLUS
DN 135:210949
TI Preparation of aryl-fused azapolycyclic compounds as nicotine binding inhibitors
IN Brooks, Paige Roanne Palmer; Coe, Jotham Wadsworth
PA Pfizer Products Inc., USA
SO PCT Int. Appl., 110 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001062736	A1	20010830	WO 2001-IB153	20010208
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	BR 2001008610	A	20021119	BR 2001-8610	20010208
	EP 1259489	A1	20021127	EP 2001-953630	20010208
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	NO 2002004042	A	20021017	NO 2002-4042	20020823
PRAI	US 2000-514002	A	20000225		
	WO 2001-IB153	W	20010208		

OS MARPAT 135:210949
GI



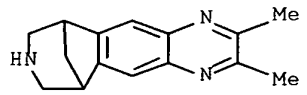
I

AB The invention discloses the prepn. of aryl-fused azapolycyclic compds., such as I [R1 = H, alkyl, unconjugated alkenyl, benzyl, X(CO)R13, CH2CH2O-alkyl; R2, R3 = H, alkenyl, alkynyl, hydroxy, nitro, amino, halo, cyano, SOqalkyl, (q = 0 - 2), alkylamino, CO2R4, CONR5R6, SO2NR7R8, COR13, X(CO)R13; R2 and R3, together with the carbons to which they are attached form a 4-7 membered monocyclic ring or a 10-14 membered bicyclic ring; R4-R8, R13 = H, alkyl or R5 and R6, or R7 and R8 together with nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, thiomorpholine; X = alkylene], and their pharmaceutically acceptable salts, as nicotine binding inhibitors (IC50

<
10 .mu.M) in the treatment of neurol. and psychol. disorders. Thus, aryl-fused azapolycyclic compd. I (R1-R3 = H) was prepd. via a multistep synthetic sequence starting from 2-fluorobromobenzene via a cycloaddn. with cyclopentadiene and an amination with triethylbenzylammonium chloride.

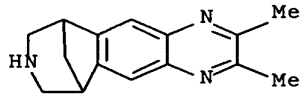
IT **357424-19-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of aryl-fused azapolycyclic compds. as nicotine binding inhibitors)

RN 357424-19-2 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl- (9CI) (CA INDEX NAME)



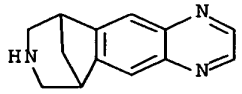
IT **230615-21-1P 230615-23-3P 249296-44-4P**
357424-07-8P 357424-21-6P 357424-81-8P
357425-48-0P 357425-92-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)(prepn. of aryl-fused azapolycyclic compds. as nicotine binding inhibitors)

RN 230615-21-1 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)



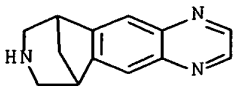
● HCl

RN 230615-23-3 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 6,7,8,9-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)

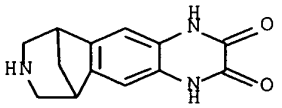


● HCl

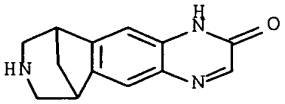
RN 249296-44-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-(9CI)(CA INDEX NAME)



RN 357424-07-8 CAPLUS
CN 6,10-Methano-1H-pyrazino[2,3-h][3]benzazepine-2,3-dione, 4,6,7,8,9,10-hexahydro- (9CI) (CA INDEX NAME)

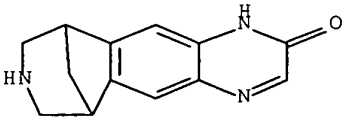


RN 357424-21-6 CAPLUS
CN 6,10-Methano-2H-pyrazino[2,3-h][3]benzazepin-2-one, 1,6,7,8,9,10-hexahydro-(9CI) (CA INDEX NAME)



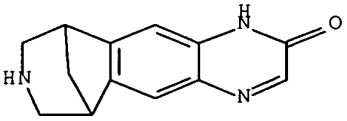
RN 357424-81-8 CAPLUS
CN 6,10-Methano-2H-pyrazino[2,3-h][3]benzazepin-2-one, 1,6,7,8,9,10-hexahydro-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).

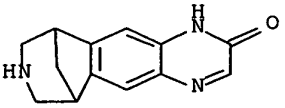


RN 357425-48-0 CAPLUS
CN 6,10-Methano-2H-pyrazino[2,3-h][3]benzazepin-2-one, 1,6,7,8,9,10-hexahydro-, (-)- (9CI) (CA INDEX NAME)

Rotation (-).



RN 357425-92-4 CAPLUS
CN 6,10-Methano-2H-pyrazino[2,3-h][3]benzazepin-2-one, 1,6,7,8,9,10-hexahydro-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

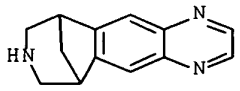
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 2001:152263 CAPLUS
DN 134:198095
TI Composition for the treatment and prevention of nicotine addiction containing a nicotine receptor agonist and an anti-depressant or anti-anxiety drug
IN Coe, Jotham Wadsworth; Harrigan, Edmund Patrick; O'neill, Brian Thomas; Sands, Steven Bradley
PA Pfizer Products Inc., USA
SO Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 1078637	A2	20010228	EP 2000-307254	20000823
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001072604	A2	20010321	JP 2000-254041	20000824
PRAI US 1999-151089P	P	19990827		

AB Pharmaceutical compns. are disclosed for the treatment of nicotine dependence or addiction, tobacco dependence or addiction, redn. of nicotine withdrawal symptoms or aiding in the cessation or lessening of tobacco use or substance abuse. The pharmaceutical compns. are comprised of a therapeutically effective combination of a nicotine receptor partial agonist and an anti-depressant or anxiolytic agent and a pharmaceutically acceptable carrier. The method of using these compds. is also disclosed.

IT **249296-44-4**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nicotine and other drug addiction treatment with compns. contg. nicotine receptor agonists and antidepressants or anxiolytic agents)
RN 249296-44-4 CAPLUS
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro- (9CI)
(CA INDEX NAME)



L4 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 1999:451282 CAPLUS
DN 131:102204
TI Preparation of 1,5-methano-3-benzazepines and analogs as nicotinic receptor ligands
IN Coe, Jotham Wadsworth; Brooks, Paige Roanne Palmer
PA Pfizer Products Inc., USA
SO PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9935131	A1	19990715	WO 1998-IB1813	19981113
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	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2316921	AA	19990715	CA 1998-2316921	19981113
	AU 9896416	A1	19990726	AU 1998-96416	19981113
	AU 753389	B2	20021017		
	BR 9814592	A	20001017	BR 1998-14592	19981113
	EP 1044189	A1	20001018	EP 1998-950274	19981113
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
	JP 2002500218	T2	20020108	JP 2000-527532	19981113
	ZA 9811911	A	20000629	ZA 1998-11911	19981229
	US 6410550	B1	20020625	US 1999-402010	19990928
	NO 2000003422	A	20000829	NO 2000-3422	20000630
	US 2002072525	A1	20020613	US 2002-75843	20020213
	US 2002072524	A1	20020613	US 2002-75348	20020214
	US 2002111350	A1	20020815	US 2002-127267	20020422
	US 2002132824	A1	20020919	US 2002-131278	20020423
PRAI	US 1997-70245P	P	19971231		
	WO 1998-IB1813	W	19981113		
	US 1999-402010	A3	19990928		

OS MARPAT 131:102204
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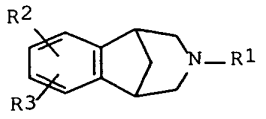


I

AB Title compds. [I; R1 = H, alk(en)yl, alkoxyethyl, oxoalkyl, etc.; R2,R3 =

H, halo, (di)(alkyl)amino, alkyl, etc.; R2R3 = atoms to complete a ring] were prepd. Thus, 2-FC6H4Br was cyclocondensed with cyclopentadiene and the product osmylated to give 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2,3-diol which was treated with NaIO4 and the product cyclocondensed with PhCH2NH2 to give, after deprotection, I (R1-R3 = H). Data for biol. activity of I were given.

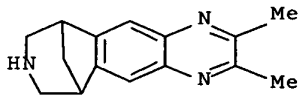
IT **230615-21-1P 230615-23-3P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of 1,5-methano-3-benzazepines and analogs as nicotinic receptor ligands)

RN 230615-21-1 CAPLUS

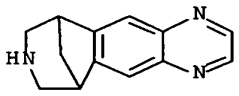
CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 7,8,9,10-tetrahydro-2,3-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 230615-23-3 CAPLUS

CN 6,10-Methano-6H-pyrazino[2,3-h][3]benzazepine, 6,7,8,9-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> d l1; d his; log y
L1 HAS NO ANSWERS
L1              STR
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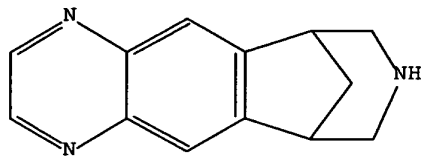


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Structure attributes must be viewed using STN Express query preparation.

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L2            0 S L1
L3           13 S L1 FUL

     FILE 'CAPLUS' ENTERED AT 18:47:21 ON 31 JAN 2003
L4           13 S L3

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L6            0 S L1 FUL

     FILE 'MARPAT' ENTERED AT 18:48:31 ON 31 JAN 2003
L7            0 S L1
L8            1 S L1 FUL
L9            0 S L8 NOT L4


COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               104.95     312.76

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
                                                   ENTRY    SESSION
CA SUBSCRIBER PRICE                                0.00      -8.46

STN INTERNATIONAL LOGOFF AT 18:49:31 ON 31 JAN 2003
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/139,730	05/06/2002	David E. Bogle	PC11872A	5317

7590 02/05/2003

Paul H. Ginsburg
Pfizer Inc
Patent Department (150/05/49)
150 East 42nd Street
New York, NY 10017-5612

EXAMINER	
KIFLE, BRUCK	

ART UNIT	PAPER NUMBER
1624	9

DATE MAILED: 02/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/139,730	Bogle et al.
Examiner	**Art Unit**
Bruck Kifle, Ph.D.	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 6, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-66* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1-37 and 41-66 are rejected under 35 U.S.C. 102(e) as being anticipated by Am Ende et al. (US 2002/0016498). The claims read on the salt and process taught in Example 5 (see page 4).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coe et al. (WO 99/35131). The reference teaches a generic group of salts of the instant compound including the tartaric acid salt (See page 10, lines 12-16). The claims differ from the reference by

reciting a specific salt of the reference. However, it would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the salts from the genus taught by the reference, including the tartrate salt instantly claimed, because the skilled chemist would have the reasonable expectation that any of the salts of the genus would have similar properties and, thus, the same use as taught for the genus as a whole. One of ordinary skill in the art would have been motivated to select the claimed salt from the genus in the reference since such salts would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. v. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

Claim Rejections - 35 USC § 112

Claim 39 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling as a method of treating nicotine dependency, addiction and withdrawal, does not reasonably provide enablement for treatment of all of the diseases recited in claim 39.

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: The method of use claims are drawn in part to the treatment of ALS, sleep disorders, Parkinson's disease, multiple sclerosis, chemical dependencies and addictions, etc.

2) The state of the prior art: There are no known compounds which have been demonstrated to treat all of the diseases recited in claim 39. For example, the notion that a compound could be effective against chemical addiction in general is absolutely contrary to our current understanding of how chemical dependencies operate. There is not, and probably never will be, a pharmacological treatment for "drug addiction" generally. That is because "drug addiction" is not a single disease or cluster of related disorders, but in fact, a collection with relatively little in common. Addiction to barbiturates, alcohol, cocaine, opiates, amphetamines, benzodiazepines, nicotine, etc. all involve different parts of the CNS system; different receptors in the body. For example, cocaine binds at the dopamine reuptake transmitter. Heroin addiction, for example, arises from binding at the opiate receptors, cigarette addiction from some interaction at the nicotinic acid receptors, many tranquilizers involve the benzodiazepine receptor, alcohol involves yet another system, etc. All attempts to find an pharmaceutical to treat chemical addictions generally have thus failed.

Disorders that are "opposites" such as sleeplessness and narcolepsy are embraced by a sleep disorder. A drug for one cannot be used to treat the other.

AD patients are treated using acetylcholinesterase inhibitors (albeit not effectively), a property that the instant compounds are not disclosed to have. Parkinson's disease is treated using dopamine antagonists, etc.

The skill in this art is low relative to the difficulty of the task of treating any and all of these diseases.

3) The predictability or lack thereof in the art: There is no evidence of record which would enable the skilled artisan that all of these diseases can be treated using a single drug.

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present to direct one to treat a potential host with the disorders cited.

6) The breadth of the claims: The claims are drawn to disorders that are not related and whose treatment using a single drug is unknown.

7) The quantity of experimentation need would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

Claim 39 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Regarding claim 39, the phrases "e.g." or "including but not limited to" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruck Kifle whose telephone number is (703) 305-4484.

The fax phone number for this Group is (703) 308-4556 or (703) 305-3592. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

February 3, 2003

Bruck Kifle
Primary Examiner
Art Unit 1624

Notice of References Cited	Application/Control No. 10/139,730	Applicant(s)/Patent Under Reexam Bogle et al.	
	Examiner Bruck Kifle, Ph.D.	Art Unit 1624	Page 1 of 1

U.S. PATENT DOCUMENTS

		Document Number Country Code-Number-Kind Code	Date MM-YYYY[1]	Name	Classification[2]	
	A	2002/16498	2/2002	Am Ende et al.	562	400
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

		Document Number Country Code-Number-Kind Code	Date MM-YYYY[1]	Country	Name	Classification[2]	
	N						
	O						
	P						
	Q						
	R						
	S						
	T						

NON-PATENT DOCUMENTS

		Include, as applicable: Author, Title, Date, Publisher, Edition or Volume, Pertinent Pages
	U	
	V	
	W	
	X	

* A copy of this reference is not being furnished with this Office action. See MPEP § 707.05(a). [1] Dates in MM-YYYY format are publication dates. [2] Classifications may be U.S. or foreign.

INFORMATION DISCLOSURE CITATION *(Use several sheets if necessary)*	ATTY. DOCKET NO. PC11872A	SERIAL NO. 10/139,730
	APPLICANT D. Bogle	
	FILING DATE 05/06/02	GROUP 1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER							DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER								DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
B.K.	WO	9	9	3	5	1	3	1	07/15/99	PCT	—			
B.K.		1	0	7	8	6	3	7	08/23/00	EP	—			

OTHER DOCUMENTS (*Including Author, Title, Date, Pertinent Pages, Etc.*)

EXAMINER Bruce Kisliuk DATE CONSIDERED 2/3/03

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Conforms with FORM PTO-FB-A820 INFORMATION DISCLOSURE

INFORMATION DISCLOSURE CITATION LIST.DOT, 3/99

Patent Application
Attorney Docket No.PC11872A

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3/17/03

I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231 on this 11th day of February, 2003.

By _____
(Signature of person mailing)
A. David Joran
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle, et. al.

APPLICATION NO.: 10/139,730 : Examiner:

FILING DATE: May 6, 2002 : Group Art Unit: 1614

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRA-CYCLO[10.3.1.02,11.04,9]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Commissioner for Patents
Washington, D.C. 20231

Sir:

INFORMATION DISCLOSURE STATEMENT
PURSUANT TO 37 C.F.R. § 1.97 ET SEQ.

Applicant(s) herein make(s) available to the U.S. Patent and Trademark Office a copy of PTO-FB-A820 which lists the references cited by the applicant(s), copies of which are enclosed.

The Examiner is requested to consider carefully the complete text of these references in connection with the examination of the above-identified application in accord with 37 C.F.R. § 1.104(a). It is believed the Examiner will concur with applicant's belief that the subject matter presently claimed is neither anticipated nor rendered obvious by the foregoing references.

It is requested that the references listed on the attached form PTO-FB-A820 be included in the "References Cited" portion of any patent issuing from this application (M.P.E.P. § 1302.12).

Please charge all appropriate fees to cover this submission to Pfizer Deposit Account No. 16-1445.

A prompt and favorable response is earnestly solicited.

Respectfully submitted,

Date: Feb 11, 2003

A. David Joran
Attorney for Applicant(s)
Reg. No. 37,858

Pfizer Inc
Patent Department, 5th Floor
150 East 42nd Street
New York, NY 10017-5755
(212)733 -3381

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 1st day of July, 2003.

By _____
(Signature of person mailing)

A. David Joran (Reg. No. 37,858)
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle, et al.

APPLICATION NO.: 10/139,730

FILING DATE: May 6, 2002

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Examiner: Kifle, Bruck

Group Art Unit: 1624

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT

This amendment is submitted in response to the Action issued February 5, 2003 in connection with the above-identified application. A response is due July 5, 2003, with a 2-month extension of time. A Petition for Extension is being filed concurrently herewith. Accordingly, this Amendment is being timely filed.

Please amend the subject application as follows.

IN THE CLAIMS (37 CFR §1.121 Revised)

1. (cancelled)

2. (cancelled)

3. (cancelled)

4. (currently amended) [A compound according to claim 3] The anhydrous L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene characterized substantially by at least one of the following powder x-ray diffraction pattern peaks expressed in terms of 2θ as measured with copper radiation chosen from: 6.1, 16.8 and 21.9.

5. (currently amended) A compound according to claim [3] 4 characterized substantially by the following principal powder x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ	d-value (Å)
6.1	14.5
12.2	7.2
13.0	6.8
14.7	6.0
16.8	5.3
19.4	4.6
21.9	4.1
24.6	3.6

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6. (original) A compound according to claim 5 characterized in that it has a onset of melt of about 223 °C.

7. (original) A compound according to claim 5 characterized substantially by solid state ^{13}C NMR resonance peaks at 178.4, 145.1, and 122.9 ppm.

8. (original) A compound according to claim 5 characterized substantially by solid state ^{13}C NMR resonance peaks at 178.4, 149.3, 147.4, 145.1, and 122.9 ppm.

9. (currently amended) A compound according to claim [3] 4 characterized substantially by at least one powder x-ray diffraction pattern peaks in terms of 2θ measured with copper radiation chosen from: 5.9 and 21.8.

10. (currently amended) A compound according to claim [3] 4 characterized substantially by the principal powder x-ray diffraction pattern peaks in terms of 2θ and d-spacings measured with copper radiation:

Angle 2θ	d-value (Å)
5.9	15.0
12.8	6.9
14.4	6.1
15.3	5.8
16.9	5.2
17.2	5.2
21.8	4.1
23.8	3.7
25.1	3.5

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11. (original) A compound according to claim 10 characterized in having an onset of melting of about 215 °C.

12. (original) A compound according to claim 10 characterized substantially by the solid state ^{13}C NMR principal resonance peaks at: 179.2, 178.0, 144.4, 124.8 and 122.5 ppm.

13. (original) A compound according to claim 10 characterized substantially by the solid state ^{13}C NMR principal resonance peaks: 179.2, 178.0, 147.4, 145.2, 144.4, 124.8 and 122.5 ppm.

14. (original) A compound according to claim 10 characterized by the single crystal structure of Figure 8A.

15. (original) A compound according to claim 10 that forms orthorhombic crystals belonging to the P2(1)2(1)2(1) space group.

16. (currently amended) [A compound according to claim 2 which is a] The L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene hydrate.

17. (original) A compound according to claim 16 where the hydrate is a monohydrate.

18. (original) A compound according to claim 16 characterized substantially by at least one of the powder x-ray diffraction pattern peaks in terms of 2θ as measured with copper radiation chosen from: 11.8, 16.5, 23.1 and 26.5.

19. (original) A compound according to claim 16 characterized substantially by the principal powder x-ray diffraction pattern peaks in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
5.9	15.1
11.8	7.5
16.5	5.4
21.2	4.2
23.1	3.8
23.8	3.7
26.5	3.4

B1

20. (original) A compound according to claim 16 characterized by the single crystal structure of Figure 8B.

21. (original) A compound according to claim 16 that forms monoclinic crystals belonging to the P2(1) space group.

22. (original) A compound according to claim 16 characterized in having an onset of solid-solid transition at about 73 °C and an onset of melting transition at about 220 °C.

23. (original) A compound according to claim 16 characterized substantially by solid state ^{13}C NMR principal resonance peaks: 179.0, 176.1, 147.5 and 144.5 ppm.

24. (original) A compound according to claim 16 characterized substantially by solid state ^{13}C NMR principal resonance peaks: 179.0, 176.1, 147.5, 144.5 and 124.6 ppm.

25. (cancelled)

26. (cancelled)

27. (currently amended) [A compound according to claim 26] The anhydrous D,L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene characterized substantially by a powder x-ray diffraction pattern peaks expressed in terms of 2θ as measured with copper radiation at: 6.0.

28. (currently amended) A compound according to claim [26] 27 characterized substantially by the following principal powder x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
6.0	14.6
11.9	7.4
15.0	5.9
17.1	5.2
22.1	4.0
24.5	3.6

29. (currently amended) A compound according to claim [26] 27 characterized in that it has a onset of melt of about 212 °C.

30. (currently amended) [A compound according to claim 25 which is a] The D,L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene hydrate.

31. (original) A compound according to claim 30 characterized substantially by the powder x-ray diffraction pattern peaks in terms of 2θ as measured with copper radiation at: 6.2 and 25.1.

32. (original) A compound according to claim 30 characterized substantially by the principal powder x-ray diffraction pattern peaks in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
6.2	14.2
12.0	7.4
15.2	5.8
18.1	4.9
24.0	3.7
25.1	3.5

33. (original) A compound according to claim 30 characterized by having an onset of a solid-solid transition at about 131 °C and an onset of melting transition at about 217 °C.

34. (cancelled)

35. (cancelled)

36. (cancelled)

37. (cancelled)

38. (currently amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to any of claims [1, 2,] 4, 9, 18, 27, or 31[, 34 or 37].

39. (currently amended) A method of treating [~~inflammatory bowel disease (including but not limited to~~] ulcerative colitis, pyoderma gangrenosum and Crohn's disease[~~)~~], irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, [~~amyotrophic lateral sclerosis (ALS),~~] cognitive dysfunction, drug/toxin-induced cognitive impairment [~~(e.g.,~~] from alcohol, barbiturates, vitamin deficiencies, recreational drugs, lead, arsenic, mercury[~~),~~] disease-induced cognitive impairment [~~(e.g.,~~] arising from [~~Alzheimer's disease (senile dementia),~~] vascular dementia, [~~Parkinson's disease, multiple sclerosis,~~] AIDS, encephalitis, trauma, renal and hepatic encephalopathy, hypothyroidism, Pick's disease, Korsakoff's syndrome and frontal and subcortical dementia[~~),~~]; hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions [~~(e.g.~~], dependencies on, or addictions to nicotine [~~(and/~~]or tobacco products[~~)~~], alcohol, benzodiazepines, barbiturates, opioids or cocaine[~~),~~]; headache, migraine, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome compris[~~es~~]ing administering to a subject in need of treatment a therapeutically effective amount of a compound according to any of claims [1, 2,] 4, 9, 18, 27, or 31[, 34 or 37].

40. (currently amended) A method of treatment for nicotine dependency, addiction and withdrawal comprising the administration of a compound according to any of claims [1, 2,] 4, 9, 18, 27, or 31[, 34 or 37]. to a subject in need thereof.

41. (original) A process for the preparation of a compound according to claim 4 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with between about 1 and about 2 equivalents of L-tartaric acid; and

(ii) collecting the crystals formed.

42. (original) A process according to claim 41 wherein 1.1 equivalents of L-tartaric acid are employed and the tartaric acid is added to a solution containing the free base.

43. (original) A process according to claim 41 wherein the contacting step is allowed to proceed above 45 °C.

44. (original) A process according to claim 41 wherein the contacting step is allowed to proceed for less than 2 hours.

45. (original) A process according to claim 41 wherein the suitable solvent is selected from the group consisting of an (C_1-C_6)alkyl alcohol, an (C_1-C_6)alkyl ketone, an (C_1-C_6)alkyl ether, acetonitrile and an (C_1-C_6)alkyl ester.

46. (original) A process according to claim 41 wherein the suitable solvent is ethanol or methanol.

47. (original) A process for the preparation of a compound according to claim 9 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with between about 1 and about 2.3 equivalents of L-tartaric acid; and

(ii) collecting the crystals formed.

48. (original) A process according to claim 47 wherein 1.1 equivalents of L-tartaric acid are employed and the free base in solution is added to a solution containing L-tartaric acid.

49. (original) A process according to claim 47 wherein the contact step is allowed to proceed for at least 2 hours.

50. (original) A process according to claim 47 wherein the contact step is allowed to proceed for at least 12 hours.

51. (original) A process according to claim 47 wherein the suitable solvent is selected from the group consisting of an (C_1-C_6)alkyl alcohol, an (C_1-C_6)alkyl ketone, an (C_1-C_6)alkyl ether, acetonitrile and an (C_1-C_6)alkyl ester.

52. (original) A process according to claim 47 wherein the suitable solvent is methanol or ethanol.

53. (original) A process according to claim 47 wherein the suitable solvent is methanol.

54. (original) A process for the preparation of a compound according to claim 18 comprising the steps of

(i) contacting an anhydrous L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene with water; and

(ii) collecting the crystals formed.

55. (original) A process according to claim 54 wherein the contacting of step (i) comprises exposing the anhydrous L-tartrate salt to greater than 70% humidity.

56. (original) A process according to claim 54 wherein the contacting of step (i) comprises slurrying the anhydrous L-tartrate salt with water.

57. (original) A process according to claim 54 wherein step (i) comprises the addition of an organic solvent.

58. (original) A process according to claim 54 wherein step (i) comprises the addition of methanol, ethanol or acetonitrile.

59. (original) A process for the preparation of a compound according to claim 27 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of D,L-tartaric acid; and

(ii) collecting the crystals formed.

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60. (original) A process according to claim 59 wherein about 2.2 equivalents of D,L-tartaric acid is employed and the free base in solution is added to a solution containing D,L-tartaric acid.

61. (original) A process according to claim 59 wherein the contact step is allowed to proceed for at least 24 hours.

62. (original) A process according to claim 59 wherein the suitable solvent is anhydrous ethanol.

63. (original) A process for the preparation of a compound according to claim 31 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of D,L-tartaric acid; and

(ii) collecting the crystals formed.

64. (original) A process according to claim 63 wherein about 2.2 equivalents of D,L-tartaric acid is employed and the free base in solution is added to a solution containing D,L-tartaric acid.

65. (original) A process according to claim 63 wherein the contact step is allowed to proceed for at least 24 hours.

66. (original) A process according to claim 63 wherein the suitable solvent is 20% aqueous ethanol.

REMARKS

Claims 4-24, 27-33 and 38-66 are now pending in the application. Claim 4, 5, 9, 10, 16, 27-30, and 38-40 are currently amended. Claims 1-3, 25, 26 and 34-37 have been cancelled without prejudice. A copy of the claims now pending in the application showing changes made to currently amended claims in accord with 37 CFR §1.121, as revised, has been provided hereinabove.

No new matter has been introduced by virtue of the amendments made herein. Accordingly, applicants respectfully request their entry. In view of the amendments made herein and the remarks below, applicants respectfully request reconsideration and withdrawal of the rejection set forth in the February 5, 2003 office action.

Rejection under 35 USC §102(e)

The Examiner rejected claims 1-37 and 41-66 under 35 USC §102(e) as being anticipated by Am Ende et al. (US 2002/0016498). The Examiner stated: "The claims read on the salt and process taught in Example 5." In response, without conceding the correctness of the stated ground for rejection, but in order to expedite the prosecution of the subject application, applicants have cancelled claims 1-3 and amended claim 4 to incorporate the limitations of claims 1-3 therein; amended claims 5, 9 and 10 to depend from claim 4; amended claim 16 to be independent and to incorporate the limitations of claims 1 and 2; cancelled claim 25 and 26 and amended claim 27 to be independent and to incorporate the limitations of claims 1, 25 and 26 therein; amended claim 30 to be independent and to incorporate the limitations of claims 1 and 25; cancelled claims 34-37 without prejudice and, amended claims 38, 39 and 40 to correct dependency in view of the cancellation of claims 1, 2, 34 and 37.

Applicants respectfully submit that Am Ende et al. disclose generically only the reactive crystallization of the anhydrous tartrate salt in Example 5, but do not teach or suggest the specific anhydrous tartrate salt having the x-ray diffraction features recited in claims 4-15, as amended herein. Applicants further submit that Am Ende et al. do not teach or suggest a hydrate tartrate salt as recited in claims 16-24, and *a fortiori*, a salt having the x-ray diffraction features recited in claims 18-21, or having the physical properties recited in claims 22-24.

Regarding claims 27-33, applicants respectfully submit that Am Ende et al. do not teach or suggest the specific D,L-tartrate salt or anhydrous form thereof claimed in the subject application having the x-ray diffraction features recited in claim 27 or the specific hydrate DL-tartrate of claim 30, as the cited reference only teaches the anhydrous L-salt and no suggestion is provided therein to prepare either the anhydrous or hydrate form of the D,L-tartrate salt, or that such a procedure would succeed as disclosed.

Claims 41-46 claim a process for preparing the compound of claim 4, *i.e.*, the anhydrous L-tartrate salt, using the specific process steps recited in claim 41. This process differs from the jet impingement process of Am Ende et al., which uses methanol and ethyl acetate as solvents,

as set forth in Example 5 of the cited reference. The different crystallization conditions of the cited reference are not disclosed to afford the polymorphic forms produced by the process of the subject application.

Claims 47-53 and 54-58 claim processes for forming L-tartrate salts having the x-ray diffraction parameters recited in claims 9 and 18, respectively. Am Ende et al. only disclose a process for preparing an L-tartrate form of controlled size not having the specific x-ray diffraction parameters disclosed in the subject invention.

Claims 59-62 and 63-66 claim processes for preparing a D,L-tartrate crystal form having the specific x-ray diffraction parameters recited in claims 27 and 31, respectively. These processes differ from that used by Am Ende et al. to prepare the L-tartrate salt disclosed there.

Accordingly, applicants respectfully submit that Am Ende et al. do not anticipate pending claims 4-24, 27-33 and 38-66 under 35 USC §102(e) and respectfully request withdrawal of the rejection.

Rejection under 35 USC §103(a)

The Examiner rejected claims 1 - 66 under USC §103(a) as unpatentable over Coe et al. (WO99/35131) which "...teaches a generic group of salts of the instant compound including the tartaric acid salt." The Examiner concedes that "[t]he claims differ from the reference by reciting a specific salt" but states "it would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the salts from the genus taught by the reference, including the citrate salt instantly claimed, because the skilled chemist would have the reasonable expectation that any of the salts of the genus would have similar properties and, thus, the same use as taught for the genus as a whole. One of ordinary skill in the art would have been motivated to select the claimed salt from the genus in the reference since such salts would have been suggested by the reference as a whole."

In response, without conceding the correctness of the stated ground for rejection, but in order to expedite the prosecution of the subject application, applicants have cancelled claims 1-3 and amended claim 4 to incorporate the limitations of claims 1-3 therein; amended claims 5, 9 and 10 to depend from claim 4; amended claim 16 to be independent and to incorporate the limitations of claims 1 and 2, respectively; cancelled claims 25 and 26 and amended claim 27 to be independent and to incorporate the limitations of claims 1, 25 and 26 therein; amended claim 30 to be independent and to incorporate the limitations of claims 1 and 25; cancelled claims 34-37 without prejudice and, amended claims 38, 39 and 40 to correct dependency in view of the cancellation of claims 1, 2, 34 and 37.

As noted in response to the rejection under 35 U.S.C. §102(e), applicants respectfully submit that Am Ende et al. disclose generically only the reactive crystallization of the anhydrous tartrate salt in Example 5, but do not teach or suggest the specific anhydrous tartrate salt having

the x-ray diffraction features recited in claims 4-15, as amended herein. Applicants further submit that Am Ende et al. do not teach or suggest a hydrate tartrate salt as recited in claims 16-24, and *a fortiori*, a salt having the x-ray diffraction features recited in claims 18-21, or having the physical properties recited in claims 22-24. There being no motivation to prepare the specific salts of claims 16-24, applicants submit that claims 16-24 are not obvious over Am Ende et al.

Regarding claims 27-33, applicants respectfully submit that Am Ende et al. do not teach or suggest the specific D,L-tartrate salt or anhydrous form thereof claimed in the subject application having the x-ray diffraction features recited in claim 27 or the specific hydrate DL-tartrate of claim 30, as the cited reference only teaches the anhydrous L-salt and no suggestion is provided therein to prepare such either the anhydrous or hydrate form of the D,L-tartrate salt, or that such a procedure would succeed as disclosed. Thus, in the absence of a suggestion or motivation to modify the prior art, claims 27-33 are not obvious over the cited reference.

Claims 41-46 claim a process for preparing the compound of claim 4, *i.e.,* the anhydrous L-tartrate salt, using the specific process steps recited in claim 41. This process differs from the jet impingement process of Am Ende et al., which uses methanol and ethyl acetate as solvents, as set forth in Example 5 of the cited reference. The different crystallization conditions of the cited reference are not disclosed to afford the polymorphic forms produced by the process of the subject application. Accordingly, in the absence of a suggestion or motivation to modify the prior art, Am Ende et al. do not render obvious the processes set forth in claims 41-46.

Claims 47-53 and 54-58 claim processes for forming L-tartrate salts having the x-ray diffraction parameters recited in claims 9 and 18, respectively. Am Ende et al. only disclose a process for preparing an L-tartrate form of controlled size not having the specific x-ray diffraction parameters disclosed in the subject invention. Thus, Am Ende et al. provide no suggestion or motivation to prepare the L-tartrate salt form according to claims 47-53 and 54-58, which are therefore not obvious in view of Am Ende et al.

Claims 59-62 and 63-66 claim processes for preparing a D,L-tartrate crystal form having the specific x-ray diffraction parameters recited in claims 27 and 31, respectively. These processes differ from that used by Am Ende et al. to prepare the L-tartrate salt disclosed there. Thus, Am Ende et al. provide no suggestion or motivation to prepare the D,L-tartrate salt form according to claims 59-62 and 63-66, which are thus not rendered obvious over Am Ende et al.

Accordingly, applicants respectfully submit that Am Ende et al. do not render pending claims 4-24, 27-33 and 38-66 obvious under 35 USC § 103(a) over the cited reference, and respectfully request withdrawal of the rejection.

Rejection under 35 USC §112, first paragraph

The Examiner rejected claim 39 under 35 USC §112, first paragraph, "because the specification, while being enabling as a method of treating nicotine dependency, addiction and

withdrawal, does not reasonably provide enablement for treatment of all of the diseases recited in claim 39."

Applicants respectfully note that the instant specification at pages 34-35 provides sufficient guidance to one of ordinary skill in the art in using the compounds of the present invention in a range of dosage forms and doses. In addition, applicants respectfully submit that, contrary to the Examiner's assertions, an undue amount of experimentation would not be required of one of ordinary skill in the art of pharmaceutical development since such an individual is experienced, and the guidance given in the instant specification is adequate given the state of testing methods and test analysis that have existed and have been commonly practiced in the art for years and at the time of filing. However, without prejudice to applicants' rights, and in the interests of facilitating prosecution, applicants have amended claim 39 by deletion of the phrases "sleep disorders", "amyotrophic lateral sclerosis (ALS)", "Alzheimer's disease (senile dementia)", "Parkinson's disease" and "multiple sclerosis". Applicants respectfully submit that claim 39, as amended, is patentable under 35 USC §112, first paragraph, and respectfully request withdrawal of the rejection.

Rejection under 35 USC §112, second paragraph

The Examiner rejected claim 39 under 35 USC §112, second paragraph, for indefiniteness due to the phrases "e.g." and "including but not limited to". Without prejudice, and in the interests of facilitating prosecution, claim 39 has been amended by deletion of these phrases. In addition, punctuation has been inserted, the connective term "and/or" has been replaced with "or" and the term "comprises" has been replaced with "comprising" in the interests of retaining clarity. Applicants respectfully submit claim 39, as amended, is patentable under 35 USC §112, second paragraph, and respectfully request withdrawal of the rejection.

In view of the amendments set forth herein and remarks above, applicants respectfully submit that the pending claims are fully allowable, and solicits the issuance of a notice to such effect. If a telephone interview is deemed to be helpful to expedite the prosecution of the subject application, the Examiner is invited to contact applicants' undersigned attorney at the telephone number provided.

The Commissioner is hereby authorized to charge any fees required under 37 C.F.R. §§1.16 and 1.17 or to credit any overpayment to Deposit Account No. 16-1445.

Date: July 1, 2003

A. David Joran
Attorney for Applicant(s)
Reg. No. 37,858

Pfizer Inc
Patent Department
150 East 42nd Street – 5th Floor
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Patent Application
Attorney Docket No. PC11872A

#1624

I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 1st day of July 2003.

#11

By _____
(Signature of person mailing)
A. David Joran
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle, et al.

APPLICATION NO.: 10/139,730 — Examiner: Kifle, Bruck

FILING DATE: May 6, 2002 — Group Art Unit: 1624

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA. 22313-1450

Sir:

PETITION FOR EXTENSION OF TIME PURSUANT TO 37 C.F.R. §1.136(a)

Pursuant to the provisions of 37 C.F.R. §1.136(a), it is requested that the term for response to the Examiner's Action in this application, mailed on February 5, 2003, and having an original period for response of 3 months, which expired on May 5, 2003, be extended by two month(s), such that it expires on July 5, 2003.

Authorization is hereby provided to charge the amount of $410.00, as stated under 37 C.F.R. §1.17, as well as any additional fees required, or to credit any overpayment to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

07/09/2003 DEMMANU1 00000070 161445 10139730
01 FC:1252 410.00 DA

Respectfully submitted,

Date: July 1, 2003

A. David Joran
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Patent Application
Attorney Docket No. PC11872A

#1624

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07/09/2003 DEMMANU1 00000070 161445 10139730
01 FC:1252 410.00 DA

Respectfully submitted,

Date: July 1, 2003

A. David Joran
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/139,730	05/06/2002	David E. Bogle	PC11872A	5317

7590 09/24/2003

Paul H. Ginsburg
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EXAMINER	
KIFLE, BRUCK	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/24/2003 13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/139,730	BOGLE ET AL.	
	Examiner	Art Unit	
	Bruck Kifle, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-24,27-33 and 38-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39* is/are rejected.

7)☒ Claim(s) *4-24,27-33 and 38-66* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicant's amendments and remarks filed 7/7/03 have been received and reviewed. Claims 4-24, 27-33 and 38-66 are now pending in this application.

Duplicate Claiming

Claims 4-24, 27-33 and 38-66 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim 41. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 4-15; 16-24; 27-29 and 30-33 are all drawn to **one compound** each. These four compounds have the data given in the specification. These claims cannot be narrowed because the same compound is being claimed different ways. An example of such claiming is:

Claim 1. A claim drawn to benzene.

Claim 2. A claim according to claim 1, wherein the benzene has six carbons.

Claim 3. A claim according to claim 1, wherein the benzene has six hydrogens.

Claim 4. A claim according to claim 1, wherein the benzene has six carbons and six hydrogens.

All of these claims are drawn to the same compound and are duplicate sets of claims similar to claims 4-15; 16-24; 27-29 and 30-33 of the instant claims. Claims 38-40 depend from claims 4, 9, 18, 27 or 31. However, claim 4 and 9 are the same compound. See also process claims 41-46 and 47-53 drawn to a process of making the same compound the same way.

The point is, the claims are all drawn to the 4 compounds.

Claim Rejections - 35 USC § 112

Claim 39 is again rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling as a method of treating nicotine dependency, addiction and withdrawal, does not reasonably provide enablement for treatment of all of the diseases recited in claim 39. The basis of this rejection is the same as given in the previous office action and is incorporated herein fully by reference. There are no known compounds which have been demonstrated to treat all of the diseases recited in claim 39. For example, the notion that a compound could be effective against chemical addiction in general is absolutely contrary to our current understanding of how chemical dependencies operate. There is not, and probably never will be, a pharmacological treatment for "drug addiction" generally. That is because "drug addiction" is not a single disease or cluster of related disorders, but in fact, a collection with relatively little in common. Addiction to barbiturates, alcohol, cocaine, opiates, amphetamines, benzodiazepines, nicotine, etc. all involve different parts of the CNS system; different receptors in the body. For example, cocaine binds at the dopamine reuptake transmitter. Heroin addiction, for example, arises from binding at the opiate receptors, cigarette addiction from some interaction at the nicotinic acid receptors, many tranquilizers involve the benzodiazepine receptor, alcohol involves yet another system, etc. All attempts to find an pharmaceutical to treat chemical addictions generally have thus failed.

Disorders that are "opposites" such as sleeplessness and narcolepsy are embraced by a sleep disorder. A drug for one cannot be used to treat the other.

The skill in this art is low relative to the difficulty of the task of treating any and all of these diseases.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruck Kifle, Ph.D. whose telephone number is 703-305-4484. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund J. Shah can be reached on 703-308-4716. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Bruck Kifle, Ph.D.
Primary Examiner
Art Unit 1624

BK
September 19, 2003

#10

INFORMATION DISCLOSURE CITATION *(Use several sheets if necessary)*	ATTY. DOCKET NO. PC11872A	SERIAL NO. 10/139,730
	APPLICANT David E. Bogle, et. al.	
	FILING DATE May 6, 2002	GROUP 1614

FEB 14 2003 PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER								DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
B.K.	US	3	4	7	1	5	0	3	10/7/69	John R. Carson	260	294.7	

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FOREIGN PATENT DOCUMENTS

DOCUMENT NUMBER									DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
													YES	NO
B.K.	EP	1	0	7	8	6	3	7	2/28/01	EUROPE ~~PCT~~	—			
B.K.	WO	9	9	3	5	1	3	1	7/15/99	PCT	—			

OTHER DOCUMENTS (*Including Author, Title, Date, Pertinent Pages, Etc.*)

B.K.			Paul H. Mazzochi, et. al., "Synthesis and Pharmacological Activity of 2,3,4,5-Tetrahydro-1,5-Methano-1H-3-Benzazepines", J. Med. Chem., Vol. 22, No. 4, 1979, pp 455-457, XP002090422

EXAMINER Bruce K. [illegible] DATE CONSIDERED 9/12/03

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Conforms with FORM PTO-FB-A820 INFORMATION DISCLOSURE

INFORMATION DISCLOSURE CITATION LIST.DOT, 3/99

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By _____
(Signature of person mailing)

A. David Joran (Reg. No. 37,858)
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle et al.

APPLICATION NO.: 10/139,730

FILING DATE: May 6, 2002

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Examiner: Kifle, Bruck

Group Art Unit: 1624

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT IN RESPONSE TO SEPTEMBER 24, 2003 OFFICE ACTION

This amendment is submitted in response to the Office Action issued September 24, 2003 in connection with the above-identified application. A response is due March 24, 2004, with a three-month extension of time, a petition for which is submitted herewith. Accordingly, this Amendment is being timely filed.

Please amend the subject application as follows.

IN THE CLAIMS:

1. (reinstated) The tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

2. (reinstated) A compound according to claim 1 which is the L-tartrate salt.

3. (reinstated) A compound according to claim 2 which is anhydrous.

4. (currently amended) A compound according to claim 3 [[~~The anhydrous L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$] hexadeca-2(11),3,5,7,9-pentaene~~]] characterized substantially by at least one of the following powder x-ray diffraction pattern peaks expressed in terms of 2θ as measured with copper radiation chosen from: 6.1, 16.8 and 21.9.

5. (currently amended) A compound according to claim [[4]] 3 characterized substantially by the following principal powder x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ	d-value (Å)
6.1	14.5
12.2	7.2
13.0	6.8
14.7	6.0
16.8	5.3
19.4	4.6
21.9	4.1
24.6	3.6

6. (original) A compound according to claim 5 characterized in that it has a onset of melt of about 223 °C.

7. (original) A compound according to claim 5 characterized substantially by solid state ^{13}C NMR resonance peaks at 178.4, 145.1, and 122.9 ppm.

8. (original) A compound according to claim 5 characterized substantially by solid state ^{13}C NMR resonance peaks at 178.4, 149.3, 147.4, 145.1, and 122.9 ppm.

9. (currently amended) A compound according to claim [[4]] 3 characterized substantially by at least one powder x-ray diffraction pattern peaks in terms of 2θ measured with copper radiation chosen from: 5.9 and 21.8.

10. (currently amended) A compound according to claim [[4]] 3 characterized substantially by the principal powder x-ray diffraction pattern peaks in terms of 2θ and d-spacings measured with copper radiation:

Angle 2θ	d-value (Å)
5.9	15.0
12.8	6.9
14.4	6.1
15.3	5.8
16.9	5.2
17.2	5.2
21.8	4.1
23.8	3.7
25.1	3.5

11. (original) A compound according to claim 10 characterized in having an onset of melting of about 215 °C.

12. (original) A compound according to claim 10 characterized substantially by the solid state ^{13}C NMR principal resonance peaks at: 179.2, 178.0, 144.4, 124.8 and 122.5 ppm.

13. (original) A compound according to claim 10 characterized substantially by the solid state ^{13}C NMR principal resonance peaks: 179.2, 178.0, 147.4, 145.2, 144.4, 124.8 and 122.5 ppm.

14. (original) A compound according to claim 10 characterized by the single crystal structure of Figure 8A.

15. (original) A compound according to claim 10 that forms orthorhombic crystals belonging to the P2(1)2(1)2(1) space group.

16. (currently amended) The L-tartrate salt of [[~~5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene~~]] claim 2 that is a hydrate.

17. (original) A compound according to claim 16 where the hydrate is a monohydrate.

18. (original) A compound according to claim 16 characterized substantially by at least one of the powder x-ray diffraction pattern peaks in terms of 2θ as measured with copper radiation chosen from: 11.8, 16.5, 23.1 and 26.5.

19. (original) A compound according to claim 16 characterized substantially by the principal powder x-ray diffraction pattern peaks in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
5.9	15.1
11.8	7.5
16.5	5.4
21.2	4.2
23.1	3.8
23.8	3.7
26.5	3.4

20. (original) A compound according to claim 16 characterized by the single crystal structure of Figure 8B.

21. (original) A compound according to claim 16 that forms monoclinic crystals belonging to the P2(1) space group.

22. (original) A compound according to claim 16 characterized in having an onset of solid-solid transition at about 73 °C and an onset of melting transition at about 220 °C.

23. (original) A compound according to claim 16 characterized substantially by solid state ^{13}C NMR principal resonance peaks: 179.0, 176.1, 147.5 and 144.5 ppm.

24. (original) A compound according to claim 16 characterized substantially by solid state ^{13}C NMR principal resonance peaks: 179.0, 176.1, 147.5, 144.5 and 124.6 ppm.

25. (reinstated) A compound according to claim 1 which is the D,L-tartrate salt.

26. (reinstated) A compound according to claim 25 which is anhydrous.

27. (currently amended) [[~~The anhydrous~~]] A D,L-tartrate salt of [[~~5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene~~]] claim 26 characterized substantially by a powder x-ray diffraction pattern peaks expressed in terms of 2θ as measured with copper radiation at: 6.0.

28. (currently amended) A compound according to claim [[27]] 26 characterized substantially by the following principal powder x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
6.0	14.6
11.9	7.4
15.0	5.9
17.1	5.2
22.1	4.0
24.5	3.6

29. (currently amended) A compound according to claim [[27]] 26 characterized in that it has a onset of melt of about 212 °C.

30. (currently amended) [[~~The~~]] A D,L-tartrate salt of claim 25 [[~~5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene~~]] which is a hydrate.

31. (original) A compound according to claim 30 characterized substantially by the powder x-ray diffraction pattern peaks in terms of 2θ as measured with copper radiation at: 6.2 and 25.1.

32. (original) A compound according to claim 30 characterized substantially by the principal powder x-ray diffraction pattern peaks in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
6.2	14.2
12.0	7.4
15.2	5.8
18.1	4.9
24.0	3.7
25.1	3.5

33. (original) A compound according to claim 30 characterized by having an onset of a solid-solid transition at about 131 °C and an onset of melting transition at about 217 °C.

34. (reinstated) A compound according to claim 1 which is the D-tartrate salt.

35. (reinstated) A compound according to claim 34 which is anhydrous.

36. (reinstated) A compound according to claim 34 which is a hydrate.

37. (reinstated) A compound according to claim 1 which is the meso-tartrate salt.

38. (currently amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to any of claims 1, 2, 4, 9, 18, 27, [[or]] 31, 34 or 37.

39. (currently amended) A method of treating ulcerative colitis, pyoderma gangrenosum and Crohn's disease, irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, ~~[sleep disorders,]~~ jet lag, cognitive dysfunction, drug/toxin-induced cognitive impairment from alcohol, barbiturates, vitamin deficiencies, recreational drugs, lead, arsenic, mercury, disease-induced cognitive impairment arising from vascular dementia, AIDS, encephalitis, trauma, renal and hepatic encephalopathy, hypothyroidism, Pick's disease, Korsakoff's syndrome and frontal and subcortical dementia; hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions, dependencies on, or addictions to nicotine or tobacco products, alcohol, benzodiazepines, barbiturates, opioids or cocaine; headache, migraine, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome comprising administering to a subject in need of treatment a therapeutically effective amount of a compound according to any of claims 1, 2, 4, 9, 18, 27, [[or]] 31, 34 or 37.

40. (currently amended) A method of treatment for nicotine dependency, addiction and withdrawal comprising the administration of a compound according to any of claims 1, 2, 4, 9, 18, 27, [[or]] 31, 34 or 37 to a subject in need thereof.

41. (original) A process for the preparation of a compound according to claim 4 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with between about 1 and about 2 equivalents of L-tartaric acid; and

(ii) collecting the crystals formed.

42. (original) A process according to claim 41 wherein 1.1 equivalents of L-tartaric acid are employed and the tartaric acid is added to a solution containing the free base.

43. (original) A process according to claim 41 wherein the contacting step is allowed to proceed above 45 °C.

44. (original) A process according to claim 41 wherein the contacting step is allowed to proceed for less than 2 hours.

45. (original) A process according to claim 41 wherein the suitable solvent is selected from the group consisting of an (C_1-C_6)alkyl alcohol, an (C_1-C_6)alkyl ketone, an (C_1-C_6)alkyl ether, acetonitrile and an (C_1-C_6)alkyl ester.

46. (original) A process according to claim 41 wherein the suitable solvent is ethanol or methanol.

47. (original) A process for the preparation of a compound according to claim 9 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with between about 1 and about 2.3 equivalents of L-tartaric acid; and

(ii) collecting the crystals formed.

48. (original) A process according to claim 47 wherein 1.1 equivalents of L-tartaric acid are employed and the free base in solution is added to a solution containing L-tartaric acid.

49. (original) A process according to claim 47 wherein the contact step is allowed to proceed for at least 2 hours.

50. (original) A process according to claim 47 wherein the contact step is allowed to proceed for at least 12 hours.

51. (original) A process according to claim 47 wherein the suitable solvent is selected from the group consisting of an (C_1-C_6)alkyl alcohol, an (C_1-C_6)alkyl ketone, an (C_1-C_6)alkyl ether, acetonitrile and an (C_1-C_6)alkyl ester.

52. (original) A process according to claim 47 wherein the suitable solvent is methanol or ethanol.

53. (original) A process according to claim 47 wherein the suitable solvent is methanol.

54. (original) A process for the preparation of a compound according to claim 18 comprising the steps of

(i) contacting an anhydrous L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene with water; and

(ii) collecting the crystals formed.

55. (original) A process according to claim 54 wherein the contacting of step (i) comprises exposing the anhydrous L-tartrate salt to greater than 70% humidity.

56. (original) A process according to claim 54 wherein the contacting of step (i) comprises slurrying the anhydrous L-tartrate salt with water.

57. (original) A process according to claim 54 wherein step (i) comprises the addition of an organic solvent.

58. (original) A process according to claim 54 wherein step (i) comprises the addition of methanol, ethanol or acetonitrile.

59. (original) A process for the preparation of a compound according to claim 27 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of D,L-tartaric acid; and

(ii) collecting the crystals formed.

60. (original) A process according to claim 59 wherein about 2.2 equivalents of D,L-tartaric acid is employed and the free base in solution is added to a solution containing D,L-tartaric acid.

61. (original) A process according to claim 59 wherein the contact step is allowed to proceed for at least 24 hours.

62. (original) A process according to claim 59 wherein the suitable solvent is anhydrous ethanol.

63. (original) A process for the preparation of a compound according to claim 31 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of D,L-tartaric acid; and

(ii) collecting the crystals formed.

64. (original) A process according to claim 63 wherein about 2.2 equivalents of D,L-tartaric acid is employed and the free base in solution is added to a solution containing D,L-tartaric acid.

65. (original) A process according to claim 63 wherein the contact step is allowed to proceed for at least 24 hours.

66. (original) A process according to claim 63 wherein the suitable solvent is 20% aqueous ethanol.

REMARKS

Claims 1-66 are now pending in the application. Claims 1-3, 25, 26 and 34-37 previously canceled without prejudice have been reinstated. Claims 4, 5, 9, 10, 16, 27-30 and 38-40 are currently amended. Claims 6-8, 11-15, 17-24, 31-33 and 41-66 are original. The claims now pending in the application showing changes made in the present amendment are set forth above.

No new matter has been introduced by virtue of the amendments made herein. Accordingly, applicants respectfully request their entry. In view of the amendments made herein, the remarks below, and appended declarations under 37 CFR 1.132 the applicants respectfully request reconsideration and withdrawal of the rejection set forth in the September 24, 2003 Office Action and the Office Action of February 5, 2003.

Submission of Declarations Under 37 CFR 1.132

The Examiner had earlier rejected claims 1-37 and 41-46 under 35 USC §102(e) as being anticipated by Am Ende et al (US 2002/0016498 now US 6,558,435 B2). In response, the applicants respectfully refer the Examiner to MPEP (Rev. 1, Feb. 2003) section 716.10 "Attribution" and to the appended declarations submitted by the applicants under 37 CFR 1.132. The appended declarations recite that the present applicants are:

the inventors of the tartrate salt used by Am Ende et al,

that they are the inventors of all the tartrate salts disclosed in the present application,

that the present inventors supplied the sample of tartrate salt used by Am Ende et al. in development of the process of US 6,558,435 B2,

that the applicants and the patentees of US 6,558,435 B2 were all employed by Pfizer, Inc., to which both the present application and the aforementioned patent are assigned, at the time the present invention was made, and

that the earlier disclosure of the (L) - tartrate salt in US Patent 6,558,435 B2, was not made in order to claim the (L) - tartrate salt as the invention of the patentees, but merely as an example of the claimed process of reactive crystallization.

In addition, declarations under 37 CFR 1.132 by the Patentees of US 6,558,435 B2 are appended. The appended Patentee declarations recite:

that the Patentees are not and make no claim to being inventors of the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, or any other tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene claimed in application, no. 10/139,730,

that the Patentees received a sample of the (L)-tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, to assist in

development of the reactive crystallization method described in US 6,558,435, from the above named applicants who at the time the invention disclosed in the present application was made, were co-workers at Pfizer, Inc., the assignee of the aforesaid patent and the present application No. 10/139,730, and

that the Patentees absolutely disclaim any inference that they are co-inventors of the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene or any other tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene claimed in application, no. 10/139,730.

In view of the above applicant and patentee declarations, the applicants have reinstated claims 1 - 3, 25, 26 and 34-37 previously canceled without prejudice, in order to more completely claim their invention. In addition, currently amended claims 4, 5, 9, 10, 16, 27-30, 38-40 were restored to their original dependency. Applicants submit that in view of the appended declarations under 37 CFR 1.132, the now pending reinstated, currently amended and original claims 1-37 and 41-66 are not anticipated by Am Ende et al. under 35 USC §102(e) and respectfully request withdrawal of the rejection.

Applicants further submit that their earlier response (submitted July 1, 2003) to the rejection of claims 1-66 under 35 USC §103(a) applies to the now pending reinstated, currently amended and original claims, and respectfully request withdrawal of the rejection.

Objection for Duplicate Claiming

Claims 4-24, 27-33 and 38-66 were objected to under 37 C.F.R. §1.75 as allegedly being a substantial duplicate of claim 41. Applicants submit that claim 4 refers to the anhydrous L-tartrate salt, whereas claim 27 refers to the anhydrous DL-tartrate salt, and claim 38 is a pharmaceutical composition, while claim 41 is a process claim. Applicants respectfully submit that a claim from one statutory class cannot be a substantial duplicate of a claim from a different statutory class, and therefore, request clarification of the Examiner's objection.

The applicants further submit that the original dependency has been restored to the pending claims and note that the pending claims clearly refer to specific crystal structures of L, DL, D and meso tartaric acid salts depicted as either anhydrous or hydrated that are specifically characterized by physical parameters and that all these forms are described in the specification in detail.

The Examiner asserts that when two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper *after allowing one claim* to object to the other as being a substantial duplicate of the allowed claim. The applicants submit that the Examiner's assertion is based on actual allowance of a claim, but the instant office action does not contain any notice of such allowance. The

Examiner cited three groups of claims with each group allegedly drawn to one compound per group, as follows: claims 4-15, claims 16-24, and claims 27-29 and 30-33, but failed to formally allow a claim in any group. Applicants respectfully submit that the present objection of duplicate claiming is impermissible until a claim is allowed.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner again rejected claim 39 under 35 U.S.C. § 112, first paragraph, on the ground that the specification allegedly does not reasonably provide enablement for treatment of all of the diseases recited in claim 39. However, the Examiner concedes that the instant specification is enabling as to a method of treating nicotine dependency, addiction and withdrawal. Applicants submit that those skilled in the art would understand that the underlying factors causing the recited diseases and disorders are interrelated.

Applicants submit that the Examiner's assertion that "[a]ddiction to barbiturates, alcohol, cocaine, opiates, amphetamines, benzodiazepines, nicotine, etc., all involve different parts of the CNS system [and] different receptors in the body" does not reflect the state of knowledge in the art prior to and at the time of filing of the provisional application (May 14, 2001) which is the basis of the instant application. As an example, applicants respectfully refer the Examiner to the publication "Alcohol Preference: Association With Reduced Striatal Nicotinic Receptors" by Y. Tizabi et al., which appeared in *Alcohol & Alcoholism,* **2001,** Vol. 36, No. 4, 318-322, and was accepted for publication February 24, 2001, as well as the references cited therein. Based on their experiments, the authors state: "The data suggest a link between striatal nicotinic receptors and alcohol preference." Applicants submit that the subject specification provides reasonable enablement for treatment of the diseases and disorders recited in claim 39 based on the state of knowledge at the time the provisional application was filed. However, in the interests of facilitating prosecution and without conceding the correctness of the Examiner's position, applicants have amended claim 39, without prejudice, by deletion of the term "sleep disorders".

Applicants respectfully submit claim 39 as currently amended is patentable under 35 U.S.C. §112, first paragraph, and respectfully request withdrawal of the rejection.

In view of the amendments set forth herein and remarks above, the applicant respectfully submits that the pending claims are fully allowable, and solicits the issuance of a notice to such effect. If a telephone interview is deemed to be helpful to expedite the prosecution of the subject application, the Examiner is invited to contact applicant's undersigned attorney at the telephone number provided.

The Commissioner is hereby authorized to charge any fees required under 37 C.F.R. §§1.16 and 1.17 or to credit any overpayment to Deposit Account No. 16-1445.

Date: March 23, 2004

A. David Joran
Attorney for Applicant(s)
Reg. No. 37,858

Pfizer Inc
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle, Peter R. Rose, Glenn R. Williams

Examiner: Kifle, Bruck

APPLICATION NO.: 10/139,730

Group Art Unit: 1624

FILING DATE: May 6, 2002

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 CFR 1.132

OF NEIL P. WESTON

I, Neil P. Weston, declare as follows:

1. that as a Patentee of United States Patent 6,558,435 B2, formerly United States Patent Application, publication number US 2002/0016498 A1, I am not and make no claim to being an inventor of the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, or any other tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene claimed in application, no. 10/139,730.

2. that the Patentees received a sample of the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, to assist in development of the reactive crystallization method described in US 6,558,435, from the above named applicants who at the time the invention disclosed in the present application was made, were co-workers at Pfizer, Inc., the assignee of the aforesaid patent and the present application No. 10/139,730.

3. that as a Patentee of US Patent 6,558,435 B2, I absolutely disclaim any inference that I am a co-inventor of the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene or any other tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene claimed in application, no. 10/139,730.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these

statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date 16/2/04

Neil P. Weston

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle, Peter R. Rose, Glenn R. Williams

Examiner: Kifle, Bruck

APPLICATION NO.: 10/139,730

Group Art Unit: 1624

FILING DATE: May 6, 2002

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 CFR 1.132
OF DAVID J. AM ENDE

I, David J. Am Ende, declare as follows:

1. that as a Patentee of United States Patent 6,558,435 B2, formerly United States Patent Application, publication number US 2002/0016498 A1, I am not and make no claim to being an inventor of the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, or any other tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene claimed in application, no. 10/139,730.

2. that the Patentees received a sample of the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, to assist in development of the reactive crystallization method described in US 6,558,435, from the above named applicants who at the time the invention disclosed in the present application was made, were co-workers at Pfizer, Inc., the assignee of the aforesaid patent and the present application No. 10/139,730.

3. that as a Patentee of US Patent 6,558,435 B2, I absolutely disclaim any inference that I am a co-inventor of the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene or any other tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene claimed in application, no. 10/139,730.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these

statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date 12-22-2003

David J. Am Ende

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle, Peter R. Rose, Glenn R. Williams

APPLICATION NO.: 10/139,730

FILING DATE: May 6, 2002

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Examiner: Kifle, Bruck

Group Art Unit: 1624

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 CFR 1.132
OF THOMAS C. CRAWFORD

I, Thomas C. Crawford, declare as follows:

1. that as a Patentee of United States Patent 6,558,435 B2, formerly United States Patent Application, publication number US 2002/0016498 A1, I am not and make no claim to being an inventor of the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, or any other tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene claimed in application, no. 10/139,730.

2. that the Patentees received a sample of the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, to assist in development of the reactive crystallization method described in US 6,558,435, from the above named applicants who at the time the invention disclosed in the present application was made, were co-workers at Pfizer, Inc., the assignee of the aforesaid patent and the present application No. 10/139,730.

3. that as a Patentee of US Patent 6,558,435 B2, I absolutely disclaim any inference that I am a co-inventor of the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene or any other tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene claimed in application, no. 10/139,730.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date 19 January 2004

Thomas C. Crawford

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle, Peter R. Rose, Glenn R. Williams

Examiner: Kifle, Bruck

APPLICATION NO.: 10/139,730

Group Art Unit: 1624

FILING DATE: May 6, 2002

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 CFR 1.132 OF DAVID E. BOGLE

I, David E. Bogle, declare as follows:

1. that the invention set forth in the United States Patent Application, publication number US 2002/0016498 A1, now United States Patent 6,558,435 B2, specifically the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, which was cited by the Examiner under 35 USC 102(e) as anticipating claims of the present application, no. 10/139,730, is the joint invention of the above named applicants who are also the joint inventors of the (D), (D,L) and meso tartrate salts of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene disclosed in the present application.

2. that the earlier disclosure of the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in US Patent 6,558,435 B2, was not made in order to claim the (L) - tartrate salt as the invention of the patentees, but merely as an example of the claimed process of reactive crystallization.

3. that the present inventors and patentees of US 6,558,435 B2 were all employed by Pfizer Inc. at the time the present invention was made and that the aforesaid patent and the instant application are both assigned to Pfizer Inc.

4. that the present inventors provided the patentees with the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene for use in development of the reactive crystallization process claimed in the patent.

5. that the present inventors reiterate their previous declaration that they are the joint inventors of the triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene tartrate salts as disclosed in the present application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date 19 Dec. 2003

David E. Bogle

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle, Peter R. Rose, Glenn R. Williams

APPLICATION NO.: 10/139,730

FILING DATE: May 6, 2002

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Examiner: Kifle, Bruck

Group Art Unit: 1624

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 CFR 1.132 OF PETER R. ROSE

I, Peter R. Rose, declare as follows:

1. that the invention set forth in the United States Patent Application, publication number US 2002/0016498 A1, now United States Patent 6,558,435 B2, specifically the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, which was cited by the Examiner under 35 USC 102(e) as anticipating claims of the present application, no. 10/139,730, is the joint invention of the above named applicants who are also the joint inventors of the (D), (D,L) and meso tartrate salts of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene disclosed in the present application.

2. that the earlier disclosure of the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in US Patent 6,558,435 B2, was not made in order to claim the (L) - tartrate salt as the invention of the patentees, but merely as an example of the claimed process of reactive crystallization.

3. that the present inventors and patentees of US 6,558,435 B2 were all employed by Pfizer Inc. at the time the present invention was made and that the aforesaid patent and the instant application are both assigned to Pfizer Inc.

4. that the present inventors provided the patentees with the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene for use in development of the reactive crystallization process claimed in the patent.

5. that the present inventors reiterate their previous declaration that they are the joint inventors of the triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene tartrate salts as disclosed in the present application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date 12/17/03

Peter R. Rose

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle, Peter R. Rose, Glenn R. Williams

APPLICATION NO.: 10/139,730

FILING DATE: May 6, 2002

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Examiner: Kifle, Bruck

Group Art Unit: 1624

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 CFR 1.132 OF GLENN R. WILLIAMS

I, Glenn R. Williams, declare as follows:

1. that the invention set forth in the United States Patent Application, publication number US 2002/0016498 A1, now United States Patent 6,558,435 B2, specifically the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, which was cited by the Examiner under 35 USC 102(e) as anticipating claims of the present application, no. 10/139,730, is the joint invention of the above named applicants who are also the joint inventors of the (D), (D,L) and meso tartrate salts of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene disclosed in the present application.

2. that the earlier disclosure of the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in US Patent 6,558,435 B2, was not made in order to claim the (L) - tartrate salt as the invention of the patentees, but merely as an example of the claimed process of reactive crystallization.

3. that the present inventors and patentees of US 6,558,435 B2 were all employed by Pfizer Inc. at the time the present invention was made and that the aforesaid patent and the instant application are both assigned to Pfizer Inc.

4. that the present inventors provided the patentees with the (L) - tartrate salt of triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene for use in development of the reactive crystallization process claimed in the patent.

5. that the present inventors reiterate their previous declaration that they are the joint inventors of the triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene tartrate salts as disclosed in the present application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date 01/21/2004

Glenn R. Williams

1624

Patent Application
Attorney Docket No.PC11872A

I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 23rd day of March 2004.

By _____
(Signature of person mailing)
A. David Joran
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle et al.

APPLICATION NO.: 10/139,730 : Examiner: Kifle, Bruck

FILING DATE: May 6, 2002 : Group Art Unit: 1624

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.0 ^{2,11} 0 ^{4,9}]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA. 22313-1450

Sir:

PETITION FOR EXTENSION OF TIME PURSUANT TO 37 C.F.R. §1.136(a)

Pursuant to the provisions of 37 C.F.R. §1.136(a), it is requested that the term for response to the Examiner's Action in this application, mailed on September 24, 2003, and having an original period for response of 3 months, which expired on December 24, 2003, be extended by 3 months month(s), such that it expires on March 24, 2004

Authorization is hereby provided to charge the amount of $950.00, as stated under 37 C.F.R. §1.17, as well as any additional fees required, or to credit any overpayment to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

03/26/2004 WABDELR1 00000013 161445 10139730
01 FC:1253 950.00 DA

Respectfully submitted,

Date: Mar. 23, 2004

A. David Joran
Attorney for Applicant(s)
Reg. No. 37,858

Pfizer, Inc
Patent Department, 5th Floor
150 East 42nd Street
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(212) 733-3381

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/139,730	05/06/2002	David E. Bogle	PC11872A	5317

7590 04/14/2004

Paul H. Ginsburg
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EXAMINER	
KIFLE, BRUCK	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 04/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
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www.uspto.gov

Paper No.

Notice of Non-Compliant Amendment (37 CFR 1.121)

The amendment document filed on 03/25/04 is considered non-compliant because it has failed to meet the requirements of 37 CFR 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611*, Jun. 30, 2003). In order for the amendment document to be compliant, correction of the following item(s) is required. **Only the corrected section of the non-compliant amendment document must be resubmitted (in its entirety), e.g., the entire "Amendments to the claims" section of applicant's amendment document must be re-submitted.** 37 CFR 1.121(h).

THE FOLLOWING CHECKED (X) ITEM(S) CAUSE THE AMENDMENT DOCUMENT TO BE NON-COMPLIANT:

☐ 1. Amendments to the specification:
- ☐ A. Amended paragraph(s) do not include markings.
- ☐ B. New paragraph(s) should not be underlined.
- ☐ C. Other_____

☐ 2. Abstract:
- ☐ A. Not presented on a separate sheet. 37 CFR 1.72.
- ☐ B. Other_____

☐ 3. Amendments to the drawings: _____

☐ 4. Amendments to the claims:
- ☐ A. A complete listing of all of the claims is not present.
- ☐ B. The listing of claims does not include the text of all claims (including withdrawn claims)
- ☑ C. Each claim has not been provided with the proper status identifier, and as such, the individual status of each claim cannot be identified.
- ☐ D. The claims of this amendment paper have not been presented in ascending numerical order.
- ☑ E. Other: Only the following status identifiers must be presented in parentheses after the claim number for each claim; (original), (currently amended), (canceled), (withdrawn), (new), (previously presented), and (not entered). **(reinstated)** is not a status identifier that the PTO recognizes. Also, claims 1-3 should be submitted as the next available claim numbers, for example: Claim 1 would be submitted as Claim 67 (new), Claim 2 as Claim 68 (new) ect.

For further explanation of the amendment format required by 37 CFR 1.121, see MPEP Sec. 714 and the USPTO website at http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/officeflyer.pdf.

If the non-compliant amendment is a **PRELIMINARY AMENDMENT,** applicant is given ONE MONTH from the mail date of this letter to supply the corrected section which complies with 37 CFR 1.121. Failure to comply with 37 CFR 1.121 will result in non-entry of the preliminary amendment and examination on the merits will commence without consideration of the proposed changes in the preliminary amendment(s). This notice is not an action under 35 U.S.C. 132, and **this ONE MONTH time limit is not extendable**.

If the non-compliant amendment is a reply to a **NON-FINAL OFFICE ACTION (including a submission for an RCE),** and since the amendment appears to be a *bona fide* attempt to be a reply (37 CFR 1.135(c)), applicant is given a TIME PERIOD of ONE MONTH from the mailing of this notice within which to re-submit the corrected section which complies with 37 CFR 1.121 in order to avoid abandonment. **EXTENSIONS OF THIS TIME PERIOD ARE AVAILABLE UNDER 37 CFR 1.136(a).**

If the amendment is a reply to a **FINAL REJECTION,** this form may be an attachment to an Advisory Action. **The period for response to a final rejection continues to run from the date set in the final rejection**, and is not affected by the non-compliant

status of the amendment.

__Daveina B. Williams_____	(571) 272-0568_____
Legal Instruments Examiner (LIE)	Telephone No.

1624

I hereby certify that this correspondence is being deposited as first-class mail with the United States Postal Service, and is addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 26th day of April 2004.

By _____
(Signature of person mailing)
A. David Joran (Reg. No. 37,858)
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle et al.

APPLICATION NO.: 10/139,730

FILING DATE: May 6, 2002

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Examiner: Kifle, Bruck

Group Art Unit: 1624

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

AMENDMENT

This amendment is submitted in response to the Notice of Non-Compliant Amendment (37 CFR 1.121) issued April 14, 2004 in connection with the above-identified application. A response is due May 14, 2004. Accordingly, this Amendment is being timely filed.

Please amend the subject application as follows.

IN THE CLAIMS:

1- 3 (canceled)

67.(new) The tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

68. (new) A compound according to claim 67 which is the L-tartrate salt.

69. (new) A compound according to claim 68 which is anhydrous.

4. (currently amended) A compound according to claim 69 [[~~The anhydrous L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$] hexadeca-2(11),3,5,7,9-pentaene~~]] characterized substantially by at least one of the following powder x-ray diffraction pattern peaks expressed in terms of 2θ as measured with copper radiation chosen from: 6.1, 16.8 and 21.9.

5. (currently amended) A compound according to claim [[4]] 69 characterized substantially by the following principal powder x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ	d-value (Å)
6.1	14.5
12.2	7.2
13.0	6.8
14.7	6.0
16.8	5.3
19.4	4.6
21.9	4.1
24.6	3.6

6. (original) A compound according to claim 5 characterized in that it has a onset of melt of about 223 °C.

7. (original) A compound according to claim 5 characterized substantially by solid state ^{13}C NMR resonance peaks at 178.4, 145.1, and 122.9 ppm.

8. (original) A compound according to claim 5 characterized substantially by solid state ^{13}C NMR resonance peaks at 178.4, 149.3, 147.4, 145.1, and 122.9 ppm.

9. (currently amended) A compound according to claim [[4]] 69 characterized substantially by at least one powder x-ray diffraction pattern peaks in terms of 2θ measured with copper radiation chosen from: 5.9 and 21.8.

10. (currently amended) A compound according to claim [[4]] 69 characterized substantially by the principal powder x-ray diffraction pattern peaks in terms of 2θ and d-spacings measured with copper radiation:

Angle 2θ	d-value (Å)
5.9	15.0
12.8	6.9
14.4	6.1
15.3	5.8
16.9	5.2
17.2	5.2
21.8	4.1
23.8	3.7
25.1	3.5

11. (original) A compound according to claim 10 characterized in having an onset of melting of about 215 ºC.

12. (original) A compound according to claim 10 characterized substantially by the solid state ^{13}C NMR principal resonance peaks at: 179.2, 178.0, 144.4, 124.8 and 122.5 ppm.

13. (original) A compound according to claim 10 characterized substantially by the solid state ^{13}C NMR principal resonance peaks: 179.2, 178.0, 147.4, 145.2, 144.4, 124.8 and 122.5 ppm.

14. (original) A compound according to claim 10 characterized by the single crystal structure of Figure 8A.

15. (original) A compound according to claim 10 that forms orthorhombic crystals belonging to the P2(1)2(1)2(1) space group.

16. (currently amended) The L-tartrate salt of [[~~5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene~~]] claim 68 that is a hydrate.

17. (original) A compound according to claim 16 where the hydrate is a monohydrate.

18. (original) A compound according to claim 16 characterized substantially by at least one of the powder x-ray diffraction pattern peaks in terms of 2θ as measured with copper radiation chosen from: 11.8, 16.5, 23.1 and 26.5.

19. (original) A compound according to claim 16 characterized substantially by the principal powder x-ray diffraction pattern peaks in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
5.9	15.1
11.8	7.5
16.5	5.4
21.2	4.2
23.1	3.8
23.8	3.7
26.5	3.4

20. (original) A compound according to claim 16 characterized by the single crystal structure of Figure 8B.

21. (original) A compound according to claim 16 that forms monoclinic crystals belonging to the P2(1) space group.

22. (original) A compound according to claim 16 characterized in having an onset of solid-solid transition at about 73 °C and an onset of melting transition at about 220 °C.

23. (original) A compound according to claim 16 characterized substantially by solid state ^{13}C NMR principal resonance peaks: 179.0, 176.1, 147.5 and 144.5 ppm.

24. (original) A compound according to claim 16 characterized substantially by solid state ^{13}C NMR principal resonance peaks: 179.0, 176.1, 147.5, 144.5 and 124.6 ppm.

25 - 26 (canceled)

70. (new) A compound according to claim 67 which is the D,L-tartrate salt.

71. (new) A compound according to claim 70 which is anhydrous.

27. (currently amended) [[~~The anhydrous~~]] A D,L-tartrate salt of [[~~5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene~~]] claim 71 characterized substantially by a powder x-ray diffraction pattern peaks expressed in terms of 2θ as measured with copper radiation at: 6.0.

28. (currently amended) A compound according to claim [[27]] 71 characterized substantially by the following principal powder x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
6.0	14.6
11.9	7.4
15.0	5.9
17.1	5.2
22.1	4.0
24.5	3.6

29. (currently amended) A compound according to claim [[27]] 71 characterized in that it has a onset of melt of about 212 °C.

30. (currently amended) [[~~The~~]] A D,L-tartrate salt of claim 70 [[~~5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene~~]] which is a hydrate.

31. (original) A compound according to claim 30 characterized substantially by the powder x-ray diffraction pattern peaks in terms of 2θ as measured with copper radiation at: 6.2 and 25.1.

32. (original) A compound according to claim 30 characterized substantially by the principal powder x-ray diffraction pattern peaks in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
6.2	14.2
12.0	7.4
15.2	5.8
18.1	4.9
24.0	3.7
25.1	3.5

33. (original) A compound according to claim 30 characterized by having an onset of a solid-solid transition at about 131 °C and an onset of melting transition at about 217 °C.

34 - 37 (canceled)

72. (new) A compound according to claim 1 which is the D-tartrate salt.

73. (new) A compound according to claim 34 which is anhydrous.

74. (new) A compound according to claim 34 which is a hydrate.

75. (new) A compound according to claim 1 which is the meso-tartrate salt.

38. (currently amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to any of claims 67, 68, 4, 9, 18, 27, [[or]] 31, 72 or 75.

39. (currently amended) A method of treating ulcerative colitis, pyoderma gangrenosum and Crohn's disease, irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, ~~[sleep disorders,]~~ jet lag, cognitive dysfunction, drug/toxin-induced cognitive impairment from alcohol, barbiturates, vitamin deficiencies, recreational drugs, lead, arsenic, mercury, disease-induced cognitive impairment arising from vascular dementia, AIDS, encephalitis, trauma, renal and hepatic encephalopathy, hypothyroidism, Pick's disease, Korsakoff's syndrome and frontal and subcortical dementia; hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions, dependencies on, or addictions to nicotine or tobacco products, alcohol, benzodiazepines, barbiturates, opioids or cocaine; headache, migraine, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome comprising administering to a subject in need of treatment a therapeutically effective amount of a compound according to any of claims 67, 68, 4, 9, 18, 27, [[or]] 31, 72 or 75.

40. (currently amended) A method of treatment for nicotine dependency, addiction and withdrawal comprising the administration of a compound according to any of claims 67, 68, 4, 9, 18, 27, [[or]] 31, 72 or 75 to a subject in need thereof.

41. (original) A process for the preparation of a compound according to claim 4 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with between about 1 and about 2 equivalents of L-tartaric acid; and

(ii) collecting the crystals formed.

42. (original) A process according to claim 41 wherein 1.1 equivalents of L-tartaric acid are employed and the tartaric acid is added to a solution containing the free base.

43. (original) A process according to claim 41 wherein the contacting step is allowed to proceed above 45 °C.

44. (original) A process according to claim 41 wherein the contacting step is allowed to proceed for less than 2 hours.

45. (original) A process according to claim 41 wherein the suitable solvent is selected from the group consisting of an (C_1-C_6)alkyl alcohol, an (C_1-C_6)alkyl ketone, an (C_1-C_6)alkyl ether, acetonitrile and an (C_1-C_6)alkyl ester.

46. (original) A process according to claim 41 wherein the suitable solvent is ethanol or methanol.

47. (original) A process for the preparation of a compound according to claim 9 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with between about 1 and about 2.3 equivalents of L-tartaric acid; and

(ii) collecting the crystals formed.

48. (original) A process according to claim 47 wherein 1.1 equivalents of L-tartaric acid are employed and the free base in solution is added to a solution containing L-tartaric acid.

49. (original) A process according to claim 47 wherein the contact step is allowed to proceed for at least 2 hours.

50. (original) A process according to claim 47 wherein the contact step is allowed to proceed for at least 12 hours.

51. (original) A process according to claim 47 wherein the suitable solvent is selected from the group consisting of an (C_1-C_6)alkyl alcohol, an (C_1-C_6)alkyl ketone, an (C_1-C_6)alkyl ether, acetonitrile and an (C_1-C_6)alkyl ester.

52. (original) A process according to claim 47 wherein the suitable solvent is methanol or ethanol.

53. (original) A process according to claim 47 wherein the suitable solvent is methanol.

54. (original) A process for the preparation of a compound according to claim 18 comprising the steps of

(i) contacting an anhydrous L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene with water; and

(ii) collecting the crystals formed.

55. (original) A process according to claim 54 wherein the contacting of step (i) comprises exposing the anhydrous L-tartrate salt to greater than 70% humidity.

56. (original) A process according to claim 54 wherein the contacting of step (i) comprises slurrying the anhydrous L-tartrate salt with water.

57. (original) A process according to claim 54 wherein step (i) comprises the addition of an organic solvent.

58. (original) A process according to claim 54 wherein step (i) comprises the addition of methanol, ethanol or acetonitrile.

59. (original) A process for the preparation of a compound according to claim 27 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of D,L-tartaric acid; and

(ii) collecting the crystals formed.

60. (original) A process according to claim 59 wherein about 2.2 equivalents of D,L-tartaric acid is employed and the free base in solution is added to a solution containing D,L-tartaric acid.

61. (original) A process according to claim 59 wherein the contact step is allowed to proceed for at least 24 hours.

62. (original) A process according to claim 59 wherein the suitable solvent is anhydrous ethanol.

63. (original) A process for the preparation of a compound according to claim 31 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of D,L-tartaric acid; and

(ii) collecting the crystals formed.

64. (original) A process according to claim 63 wherein about 2.2 equivalents of D,L-tartaric acid is employed and the free base in solution is added to a solution containing D,L-tartaric acid.

65. (original) A process according to claim 63 wherein the contact step is allowed to proceed for at least 24 hours.

66. (original) A process according to claim 63 wherein the suitable solvent is 20% aqueous ethanol.

REMARKS

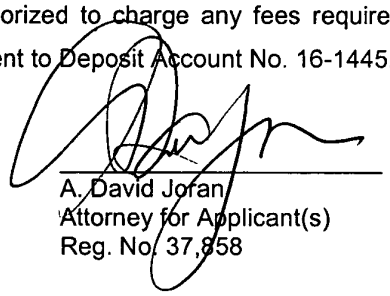
Without prejudice and in the interests of facilitating prosecution, applicants have amended the claims in accord with the Notice of Non-Compliant Amendment. Claims 1, 2 and 3 which had been identified as "reinstated" have been renumbered as claims 67, 68 and 69 and identified as "new". Claims 1, 2 and 3 are identified as "canceled". Claims 25, 26 which were previously identified as "reinstated" have been renumbered as claims 70 and 71 and identified as "new". Claims 25 and 26 are identified as "canceled". Claims 34, 35, 36 and 37 which had been identified as "reinstated" have been renumbered as claims 72, 73, 74 and 75 and identified as "new". Claims 34, 35, 36 and 37 are identified as "canceled". Dependent claims have been amended to reflect the number of the "new" claim corresponding to the claim previously identified as "reinstated".

No new matter has been introduced by virtue of the amendments made herein. In view of the amendments made herein, applicants respectfully submit that the above amendments to the claims are compliant with 37 CFR 1.121. Accordingly, applicants respectfully request their entry.

In view of the amendments set forth herein and remarks above, applicants respectfully submit that the pending claims are fully allowable, and solicit the issuance of a notice to such effect. If a telephone interview is deemed to be helpful to expedite the prosecution of the subject application, the Examiner is invited to contact applicants' undersigned attorney at the telephone number provided.

The Commissioner is hereby authorized to charge any fees required under 37 C.F.R. §§1.16 and 1.17 or to credit any overpayment to Deposit Account No. 16-1445.

Date: April 26, 2004



A. David Joran
Attorney for Applicant(s)
Reg. No. 37,858

Pfizer Inc
Patent Department
150 East 42nd Street – 5th Floor
New York, NY 10017-5755
(212) 733-3381

1624

I hereby certify that this correspondence is being deposited as first-class mail with the United States Postal Service, and is addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 26th day of April 2004.

By _____
(Signature of person mailing)
A. David Joran (Reg. No. 37,858)
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle et al. :

APPLICATION NO.: 10/139,730 :

FILING DATE: May 6, 2002 :

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF :

Examiner: Kifle, Bruck

Group Art Unit: 1624

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

AMENDMENT

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Please amend the subject application as follows.

REMARKS

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No new matter has been introduced by virtue of the amendments made herein. In view of the amendments made herein, applicants respectfully submit that the above amendments to the claims are compliant with 37 CFR 1.121. Accordingly, applicants respectfully request their entry.

In view of the amendments set forth herein and remarks above, applicants respectfully submit that the pending claims are fully allowable, and solicit the issuance of a notice to such effect. If a telephone interview is deemed to be helpful to expedite the prosecution of the subject application, the Examiner is invited to contact applicants' undersigned attorney at the telephone number provided.

The Commissioner is hereby authorized to charge any fees required under 37 C.F.R. §§1.16 and 1.17 or to credit any overpayment to Deposit Account No. 16-1445.

Date: April 26, 2004

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/139,730	05/06/2002	David E. Bogle	PC11872A	5317

7590 05/05/2004

Paul H. Ginsburg
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New York, NY 10017-5612

EXAMINER	
KIFLE, BRUCK	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

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Paper No.

Notice of Non-Compliant Amendment (37 CFR 1.121)

The amendment document filed on 4/28/04 is considered non-compliant because it has failed to meet the requirements of 37 CFR 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611*, Jun. 30, 2003). In order for the amendment document to be compliant, correction of the following item(s) is required. **Only the corrected section of the non-compliant amendment document must be resubmitted (in its entirety), e.g., the entire "Amendments to the claims" section of applicant's amendment document must be re-submitted.** 37 CFR 1.121(h).

THE FOLLOWING CHECKED (X) ITEM(S) CAUSE THE AMENDMENT DOCUMENT TO BE NON-COMPLIANT:

☐ 1. Amendments to the specification:
- ☐ A. Amended paragraph(s) do not include markings.
- ☐ B. New paragraph(s) should not be underlined.
- ☐ C. Other_____

☐ 2. Abstract:
- ☐ A. Not presented on a separate sheet. 37 CFR 1.72.
- ☐ B. Other_____

☐ 3. Amendments to the drawings: _____

☒ 4. Amendments to the claims:
- ☐ A. A complete listing of all of the claims is not present.
- ☐ B. The listing of claims does not include the text of all claims (including withdrawn claims)
- ☐ C. Each claim has not been provided with the proper status identifier, and as such, the individual status of each claim cannot be identified.
- ☒ D. The claims of this amendment paper have not been presented in ascending numerical order.
- ☐ E. Other: _____

For further explanation of the amendment format required by 37 CFR 1.121, see MPEP Sec. 714 and the USPTO website at http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/officeflyer.pdf .

If the non-compliant amendment is a **PRELIMINARY AMENDMENT,** applicant is given ONE MONTH from the mail date of this letter to supply the corrected section which complies with 37 CFR 1.121. Failure to comply with 37 CFR 1.121 will result in non-entry of the preliminary amendment and examination on the merits will commence without consideration of the proposed changes in the preliminary amendment(s). This notice is not an action under 35 U.S.C. 132, and **this ONE MONTH time limit is not extendable.**

If the non-compliant amendment is a reply to a **NON-FINAL OFFICE ACTION (including a submission for an RCE),** and since the amendment appears to be a *bona fide* attempt to be a reply (37 CFR 1.135(c)), applicant is given a TIME PERIOD of ONE MONTH from the mailing of this notice within which to re-submit the corrected section which complies with 37 CFR 1.121 in order to avoid abandonment. **EXTENSIONS OF THIS TIME PERIOD ARE AVAILABLE UNDER 37 CFR 1.136(a).**

If the amendment is a reply to a **FINAL REJECTION,** this form may be an attachment to an Advisory Action. **The period for response to a final rejection continues to run from the date set in the final rejection**, and is not affected by the non-compliant status of the amendment.

Gloria J. Hammell — 571-272-0561

Legal Instruments Examiner (LIE) — Telephone No.

Rev. 10/03

1624
IFW

I hereby certify that this correspondence is being deposited as first-class mail with the U.S. Postal Service with sufficient postage and is addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 21st day of May 2004.

(Signature of person transmitting)

A. David Joran (Reg. No. 37,858)
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle, et al

APPLICATION NO.: 10/139,730

FILING DATE: May 6, 2002

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Examiner: Kifle, Bruck

Group Art Unit: 1624

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT

This amendment is submitted in response to the Notice of Non-Compliant Amendment issued May 5, 2004 in connection with the above-identified application. A response is due June 5, 2004. Accordingly, this amendment is being timely filed. As required under 37 CFR 1.121 the claims are listed in ascending numerical order in the amendments to the claims section presented herein. No other changes have been made

Please substitute the following amendments to the claims section for the amendments to the claims submitted in the amendment document filed April 28, 2004.

IN THE CLAIMS:

1- 3 (canceled)

4. (currently amended) A compound according to claim 69 [[~~The anhydrous L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene~~]] characterized substantially by at least one of the following powder x-ray diffraction pattern peaks expressed in terms of 2θ as measured with copper radiation chosen from: 6.1, 16.8 and 21.9.

5. (currently amended) A compound according to claim [[4]] 69 characterized substantially by the following principal powder x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ	d-value (Å)
6.1	14.5
12.2	7.2
13.0	6.8
14.7	6.0
16.8	5.3
19.4	4.6
21.9	4.1
24.6	3.6

6. (original) A compound according to claim 5 characterized in that it has a onset of melt of about 223 °C.

7. (original) A compound according to claim 5 characterized substantially by solid state ^{13}C NMR resonance peaks at 178.4, 145.1, and 122.9 ppm.

8. (original) A compound according to claim 5 characterized substantially by solid state ^{13}C NMR resonance peaks at 178.4, 149.3, 147.4, 145.1, and 122.9 ppm.

9. (currently amended) A compound according to claim [[4]] 69 characterized substantially by at least one powder x-ray diffraction pattern peaks in terms of 2θ measured with copper radiation chosen from: 5.9 and 21.8.

10. (currently amended) A compound according to claim [[4]] 69 characterized substantially by the principal powder x-ray diffraction pattern peaks in terms of 2θ and d-spacings measured with copper radiation:

Angle 2θ	d-value (Å)
5.9	15.0
12.8	6.9
14.4	6.1
15.3	5.8
16.9	5.2
17.2	5.2
21.8	4.1
23.8	3.7
25.1	3.5

11. (original) A compound according to claim 10 characterized in having an onset of melting of about 215 °C.

12. (original) A compound according to claim 10 characterized substantially by the solid state ^{13}C NMR principal resonance peaks at: 179.2, 178.0, 144.4, 124.8 and 122.5 ppm.

13. (original) A compound according to claim 10 characterized substantially by the solid state ^{13}C NMR principal resonance peaks: 179.2, 178.0, 147.4, 145.2, 144.4, 124.8 and 122.5 ppm.

14. (original) A compound according to claim 10 characterized by the single crystal structure of Figure 8A.

15. (original) A compound according to claim 10 that forms orthorhombic crystals belonging to the P2(1)2(1)2(1) space group.

16. (currently amended) The L-tartrate salt of [[~~5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene~~]] claim 68 that is a hydrate.

17. (original) A compound according to claim 16 where the hydrate is a monohydrate.

18. (original) A compound according to claim 16 characterized substantially by at least one of the powder x-ray diffraction pattern peaks in terms of 2θ as measured with copper radiation chosen from: 11.8, 16.5, 23.1 and 26.5.

19. (original) A compound according to claim 16 characterized substantially by the principal powder x-ray diffraction pattern peaks in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
5.9	15.1
11.8	7.5
16.5	5.4
21.2	4.2
23.1	3.8
23.8	3.7
26.5	3.4

20. (original) A compound according to claim 16 characterized by the single crystal structure of Figure 8B.

21. (original) A compound according to claim 16 that forms monoclinic crystals belonging to the P2(1) space group.

22. (original) A compound according to claim 16 characterized in having an onset of solid-solid transition at about 73 °C and an onset of melting transition at about 220 °C.

23. (original) A compound according to claim 16 characterized substantially by solid state ^{13}C NMR principal resonance peaks: 179.0, 176.1, 147.5 and 144.5 ppm.

24. (original) A compound according to claim 16 characterized substantially by solid state ^{13}C NMR principal resonance peaks: 179.0, 176.1, 147.5, 144.5 and 124.6 ppm.

25 - 26 (canceled)

27. (currently amended) [[~~The anhydrous~~]] A D,L-tartrate salt of [[~~5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene~~]] claim 71 characterized substantially by a powder x-ray diffraction pattern peaks expressed in terms of 2θ as measured with copper radiation at: 6.0.

28. (currently amended) A compound according to claim [[27]] 71 characterized substantially by the following principal powder x-ray diffraction pattern peaks expressed in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
6.0	14.6
11.9	7.4
15.0	5.9
17.1	5.2
22.1	4.0
24.5	3.6

29. (currently amended) A compound according to claim [[27]] 71 characterized in that it has a onset of melt of about 212 °C.

30. (currently amended) [[~~The~~]] A D,L-tartrate salt of claim 70 [[~~5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene~~]] which is a hydrate.

31. (original) A compound according to claim 30 characterized substantially by the powder x-ray diffraction pattern peaks in terms of 2θ as measured with copper radiation at: 6.2 and 25.1.

32. (original) A compound according to claim 30 characterized substantially by the principal powder x-ray diffraction pattern peaks in terms of 2θ and d-spacings as measured with copper radiation:

Angle 2θ (± 0.2)	d-value (Å) (± 0.2)
6.2	14.2
12.0	7.4
15.2	5.8
18.1	4.9
24.0	3.7
25.1	3.5

33. (original) A compound according to claim 30 characterized by having an onset of a solid-solid transition at about 131 °C and an onset of melting transition at about 217 °C.

34 - 37 (canceled)

38. (currently amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to any of claims 67, 68, 4, 9, 18, 27, [[or]] 31, 72 or 75.

39. (currently amended) A method of treating ulcerative colitis, pyoderma gangrenosum and Crohn's disease, irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, ~~[sleep disorders,]~~ jet lag, cognitive dysfunction, drug/toxin-induced cognitive impairment from alcohol, barbiturates, vitamin deficiencies, recreational drugs, lead, arsenic, mercury, disease-induced cognitive impairment arising from vascular dementia, AIDS, encephalitis, trauma, renal and hepatic encephalopathy, hypothyroidism, Pick's disease, Korsakoff's syndrome and frontal and subcortical dementia; hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions, dependencies on, or addictions to nicotine or tobacco products, alcohol, benzodiazepines, barbiturates, opioids or cocaine; headache, migraine, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome comprising administering to a subject in need of treatment a therapeutically effective amount of a compound according to any of claims 67, 68, 4, 9, 18, 27, [[or]] 31, 72 or 75.

40. (currently amended) A method of treatment for nicotine dependency, addiction and withdrawal comprising the administration of a compound according to any of claims 67, 68, 4, 9, 18, 27, [[or]] 31, 72 or 75 to a subject in need thereof.

41. (original) A process for the preparation of a compound according to claim 4 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with between about 1 and about 2 equivalents of L-tartaric acid; and

(ii) collecting the crystals formed.

42. (original) A process according to claim 41 wherein 1.1 equivalents of L-tartaric acid are employed and the tartaric acid is added to a solution containing the free base.

43. (original) A process according to claim 41 wherein the contacting step is allowed to proceed above 45 °C.

44. (original) A process according to claim 41 wherein the contacting step is allowed to proceed for less than 2 hours.

45. (original) A process according to claim 41 wherein the suitable solvent is selected from the group consisting of an (C_1-C_6)alkyl alcohol, an (C_1-C_6)alkyl ketone, an (C_1-C_6)alkyl ether, acetonitrile and an (C_1-C_6)alkyl ester.

46. (original) A process according to claim 41 wherein the suitable solvent is ethanol or methanol.

47. (original) A process for the preparation of a compound according to claim 9 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with between about 1 and about 2.3 equivalents of L-tartaric acid; and

(ii) collecting the crystals formed.

48. (original) A process according to claim 47 wherein 1.1 equivalents of L-tartaric acid are employed and the free base in solution is added to a solution containing L-tartaric acid.

49. (original) A process according to claim 47 wherein the contact step is allowed to proceed for at least 2 hours.

50. (original) A process according to claim 47 wherein the contact step is allowed to proceed for at least 12 hours.

51. (original) A process according to claim 47 wherein the suitable solvent is selected from the group consisting of an (C_1-C_6)alkyl alcohol, an (C_1-C_6)alkyl ketone, an (C_1-C_6)alkyl ether, acetonitrile and an (C_1-C_6)alkyl ester.

52. (original) A process according to claim 47 wherein the suitable solvent is methanol or ethanol.

53. (original) A process according to claim 47 wherein the suitable solvent is methanol.

54. (original) A process for the preparation of a compound according to claim 18 comprising the steps of

(i) contacting an anhydrous L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene with water; and

(ii) collecting the crystals formed.

55. (original) A process according to claim 54 wherein the contacting of step (i) comprises exposing the anhydrous L-tartrate salt to greater than 70% humidity.

56. (original) A process according to claim 54 wherein the contacting of step (i) comprises slurrying the anhydrous L-tartrate salt with water.

57. (original) A process according to claim 54 wherein step (i) comprises the addition of an organic solvent.

58. (original) A process according to claim 54 wherein step (i) comprises the addition of methanol, ethanol or acetonitrile.

59. (original) A process for the preparation of a compound according to claim 27 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of D,L-tartaric acid; and

(ii) collecting the crystals formed.

60. (original) A process according to claim 59 wherein about 2.2 equivalents of D,L-tartaric acid is employed and the free base in solution is added to a solution containing D,L-tartaric acid.

61. (original) A process according to claim 59 wherein the contact step is allowed to proceed for at least 24 hours.

62. (original) A process according to claim 59 wherein the suitable solvent is anhydrous ethanol.

63. (original) A process for the preparation of a compound according to claim 31 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of D,L-tartaric acid; and

(ii) collecting the crystals formed.

64. (original) A process according to claim 63 wherein about 2.2 equivalents of D,L-tartaric acid is employed and the free base in solution is added to a solution containing D,L-tartaric acid.

65. (original) A process according to claim 63 wherein the contact step is allowed to proceed for at least 24 hours.

66. (original) A process according to claim 63 wherein the suitable solvent is 20% aqueous ethanol.

67.(new) The tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

68. (new) A compound according to claim 67 which is the L-tartrate salt.

69. (new) A compound according to claim 68 which is anhydrous.

70. (new) A compound according to claim 67 which is the D,L-tartrate salt.

71. (new) A compound according to claim 70 which is anhydrous.

72. (new) A compound according to claim 1 which is the D-tartrate salt.

73. (new) A compound according to claim 34 which is anhydrous.

74. (new) A compound according to claim 34 which is a hydrate.

75. (new) A compound according to claim 1 which is the meso-tartrate salt.

REMARKS

No new matter has been introduced by virtue of the amendments made herein. In view of the amendments made herein, applicants respectfully submit that the above amendments to the claims are compliant with 37 CFR 1.121. Accordingly, applicants respectfully request their entry.

In view of the amendments set forth herein and remarks above, the applicant respectfully submits that the pending claims are fully allowable, and solicits the issuance of a notice to such effect. If a telephone interview is deemed to be helpful to expedite the prosecution of the subject application, the Examiner is invited to contact applicant's undersigned attorney at the telephone number provided.

The Commissioner is hereby authorized to charge any fees required under 37 C.F.R. §§1.16 and 1.17 or to credit any overpayment to Deposit Account No. 16-1445.

Date: May 21, 2004

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/139,730	05/06/2002	David E. Bogle	PC11872A	5317

7590 08/19/2004

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EXAMINER	
KIFLE, BRUCK	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 08/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/139,730	BOGLE ET AL.	
	Examiner	Art Unit	
	Bruck Kifle, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-24, 27-33 and 38-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38 and 67-70* is/are rejected.

7)☒ Claim(s) *4-24, 27-33, 39-66 and 71-75* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's amendments and remarks filed 3/25/04, 4/28/04 and 5/24/04 have been received and reviewed. According to the claim set filed on 5/24/04, claims 4-24, 27-33 and 38-75 are now pending in this application.

Claims 72-75 are objected to and have not been examined because they depend on canceled claims. Applicants need to correct claim dependencies of claims 38-40 as well.

The presentation of the instant claims is confusing. Applicants are requested to rewrite these claims in consecutive order for ease of examination and to avoid errors when the patent issues.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 67-70 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coe et al. (WO 99/35131). The reference teaches a list of salts of the instant compound including the tartaric acid salt (See page 10, lines 12-16). The claims differ from the reference by reciting a specific salt of the reference. The basis of this rejection is the same as given in the previous office action and is incorporated herein fully by reference.

Claim Rejections - 35 USC § 112

Claim 39 is again rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling as a method of treating nicotine dependency, addiction and withdrawal, does not reasonably provide enablement for treatment of all of the diseases recited in claim 39. The basis of this rejection is the same as given in the previous office action and is incorporated herein fully by reference. There are no known compounds which have been

demonstrated to treat all of the diseases recited in claim 39. For example, the notion that a compound could be effective against chemical addiction in general is absolutely contrary to our current understanding of how chemical dependencies operate. There is not, and probably never will be, a pharmacological treatment for "chemical dependencies" generally. That is because "chemical dependencies" is not a single disease or cluster of related disorders, but in fact, a collection with relatively little in common. Addiction to barbiturates, alcohol, cocaine, opiates, amphetamines, benzodiazepines, nicotine, etc. all involve different parts of the CNS system; different receptors in the body. For example, cocaine binds at the dopamine reuptake transmitter. Heroin addiction, for example, arises from binding at the opiate receptors, cigarette addiction from some interaction at the nicotinic acid receptors, many tranquilizers involve the benzodiazepine receptor, alcohol involves yet another system, etc. All attempts to find a pharmaceutical to treat chemical addictions generally have thus failed.

AIDS, vitamin deficiencies, encephalitis, etc. are not known to be treated by modulating cholinergic function.

The skill in this art is low relative to the difficulty of the task of treating any and all of these diseases.

Duplicate Claims

Claims 4-8, 9-15, 18-24, 27-29 and 31-33 are objected to under 37 CFR 1.75 as being a substantial duplicate of each other. That is, claims 4-8 are drawn to the same compound; claims 9-15 are the same compound; claims 18-24 are the same compound; claims 27-29 are the same compound; claims 31-33 are drawn to the same compound. See also the corresponding method and process claims.

When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruck Kifle, Ph.D. whose telephone number is 571-272-0668. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund J. Shah can be reached on 571-272-0674. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Bruck Kifle, Ph.D.
Primary Examiner
Art Unit 1624

BK
August 18, 2004

Search Notes

Application No.	Applicant(s)	
10/139,730	BOGLE ET AL.	
Examiner	**Art Unit**	
Bruck Kifle, Ph.D.	1624	

SEARCHED			
Class	Subclass	Date	Examiner
514	252.1 255.04	8/17/2004	BK
544	343	8/17/2004	BK

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR

AMENDMENT AFTER FINAL
EXPEDITED PROCEDURE
GROUP ART UNIT 1624

Patent Application 10/139,730
Attorney Docket No. PC11872A

I hereby certify that this correspondence is being transmitted by facsimile transmission (to Fax No. 703-872-9306) and is directed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 19th day of November 2004.

By _____
(Signature of person transmitting)

A. David Joran (Reg. No. 37,858)
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle, et al	:	Examiner: Kifle, Bruck
APPLICATION NO.: 10/139,730	:	Group Art Unit: 1624
FILING DATE: May 6, 2002	:	
TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF	:	

Commissioner for Patents
Box AF
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

AMENDMENT IN RESPONSE TO AUGUST 19, 2004 OFFICE ACTION

This amendment is submitted in response to the Office Action issued August 19, 2004, in connection with the above-identified application. A response is due November 19, 2004. Accordingly, this amendment is being timely filed.

Please amend the subject application as follows:

IN THE CLAIMS:

1-15 (canceled)

16. (previously presented) The L-tartrate salt of claim 68 that is a hydrate.

17. (original) A compound according to claim 16 where the hydrate is a monohydrate.

18-29. (canceled)

30. (previously presented) A D,L-tartrate salt of claim 70 which is a hydrate.

31-37. (canceled)

38. (currently amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to any of claims 67, 68, [[4, 9, 18, 27, 31,]] 72 or 75.

39. (canceled)

40. (currently amended) A method of treatment for nicotine dependency, addiction and withdrawal comprising the administration of a compound according to any of claims 67, 68, [[4, 9, 18, 27, 31,]] 72 or 75 to a subject in need thereof.

41. (original) A process for the preparation of a compound according to claim 4 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with between about 1 and about 2 equivalents of L-tartaric acid; and

(ii) collecting the crystals formed.

42. (original) A process according to claim 41 wherein 1.1 equivalents of L-tartaric acid are employed and the tartaric acid is added to a solution containing the free base.

43. (original) A process according to claim 41 wherein the contacting step is allowed to proceed above 45 °C.

44. (original) A process according to claim 41 wherein the contacting step is allowed to proceed for less than 2 hours.

45. (original) A process according to claim 41 wherein the suitable solvent is selected from the group consisting of an (C_1-C_6)alkyl alcohol, an (C_1-C_6)alkyl ketone, an (C_1-C_6)alkyl ether, acetonitrile and an (C_1-C_6)alkyl ester.

46. (original) A process according to claim 41 wherein the suitable solvent is ethanol or methanol.

47. (original) A process for the preparation of a compound according to claim 9 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with between about 1 and about 2.3 equivalents of L-tartaric acid; and

(ii) collecting the crystals formed.

48. (original) A process according to claim 47 wherein 1.1 equivalents of L-tartaric acid are employed and the free base in solution is added to a solution containing L-tartaric acid.

49. (original) A process according to claim 47 wherein the contact step is allowed to proceed for at least 2 hours.

50. (original) A process according to claim 47 wherein the contact step is allowed to proceed for at least 12 hours.

51. (original) A process according to claim 47 wherein the suitable solvent is selected from the group consisting of an (C_1-C_6)alkyl alcohol, an (C_1-C_6)alkyl ketone, an (C_1-C_6)alkyl ether, acetonitrile and an (C_1-C_6)alkyl ester.

52. (original) A process according to claim 47 wherein the suitable solvent is methanol or ethanol.

53. (original) A process according to claim 47 wherein the suitable solvent is methanol.

54. (original) A process for the preparation of a compound according to claim 18 comprising the steps of

(i) contacting an anhydrous L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene with water; and

(ii) collecting the crystals formed.

55. (original) A process according to claim 54 wherein the contacting of step (i) comprises exposing the anhydrous L-tartrate salt to greater than 70% humidity.

56. (original) A process according to claim 54 wherein the contacting of step (i) comprises slurrying the anhydrous L-tartrate salt with water.

57. (original) A process according to claim 54 wherein step (i) comprises the addition of an organic solvent.

58. (original) A process according to claim 54 wherein step (i) comprises the addition of methanol, ethanol or acetonitrile.

59. (original) A process for the preparation of a compound according to claim 27 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of D,L-tartaric acid; and

(ii) collecting the crystals formed.

60. (original) A process according to claim 59 wherein about 2.2 equivalents of D,L-tartaric acid is employed and the free base in solution is added to a solution containing D,L-tartaric acid.

61. (original) A process according to claim 59 wherein the contact step is allowed to proceed for at least 24 hours.

62. (original) A process according to claim 59 wherein the suitable solvent is anhydrous ethanol.

63. (original) A process for the preparation of a compound according to claim 31 comprising the steps of

(i) contacting 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene in a suitable solvent with about 1 to about 2.3 equivalents of D,L-tartaric acid; and

(ii) collecting the crystals formed.

64. (original) A process according to claim 63 wherein about 2.2 equivalents of D,L-tartaric acid is employed and the free base in solution is added to a solution containing D,L-tartaric acid.

65. (original) A process according to claim 63 wherein the contact step is allowed to proceed for at least 24 hours.

66. (original) A process according to claim 63 wherein the suitable solvent is 20% aqueous ethanol.

67. (previously presented) The tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

68. (previously presented) A compound according to claim 67 which is the L-tartrate salt.

69. (previously presented) A compound according to claim 68 which is anhydrous.

70. (previously presented) A compound according to claim 67 which is the D,L-tartrate salt.

71. (previously presented) A compound according to claim 70 which is anhydrous.

72. (currently amended) A compound according to claim [[1]] 67 which is the D-tartrate salt.

73. (currently amended) A compound according to claim [[34]] 72 which is anhydrous.

74. (currently amended) A compound according to claim [[34]] 72 which is a hydrate.

75. (currently amended) A compound according to claim [[1]] 67 which is the meso-tartrate salt.

REMARKS

Claims 4-24, 27-33, and 38-75 are now pending in the application. Claims 4-15, 18-24, 27-29, 31-33 and 39 have been cancelled herein without prejudice. No new matter has been introduced by virtue of the amendments made herein. No added burden is imposed on the Examiner to engage in a further search, and it is submitted that the amendments herein are made merely to expedite the prosecution of the subject application and to place the application in condition for allowance. Accordingly, applicants respectfully request entry of the present amendments. In view of the remarks below and the amendments made herein, applicants respectfully request reconsideration of the grounds for objection and rejection set forth in the outstanding Office Action.

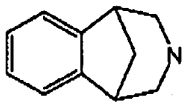
Objection to Claim Dependencies

Claims 38-40 and 72-75 were objected to because they depend on cancelled claims. The Examiner also requested the applicants to rewrite the claims in consecutive order.

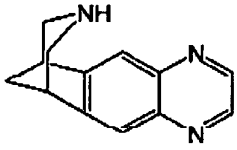
In response, applicants have cancelled claim 39, without prejudice, amended claims 38, 40 and 72-75 to reflect the proper dependencies, and rewritten the claims in the required ascending order. Applicants respectfully submit that the claims are now in consecutive order and all of the claim dependencies are now proper.

Rejection under 35 U.S.C. § 103 (a)

The Examiner rejected claims 38 and 67-70 under 35 U.S.C. §103 (a) as being allegedly unpatentable over Coe *et al.* (WO 99/35131). The Examiner alleges that the '131 reference teaches a generic list of salts, including the tartaric acid salt among many others of a compound of the following structure as well as numerous related structures:



In contrast, the claimed invention relates to tartrate salts and polymorphs of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene, which has the following structure:



Coe *et al.* do not suggest or disclose specific tartrate salts and polymorphs of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene. Moreover, Coe *et al.* do not suggest or

disclose picking and choosing from the myriad of possible substituents disclosed in the generic structures in Coe et al. necessary to arrive at the specific tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene. In addition, Coe *et al.* do not motivate one skilled in the art to pick and choose from the myriad of possible substituents disclosed in the generic structures in Coe et al. necessary to arrive at the specific tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

Moreover, Coe *et al.* is further removed from the claimed invention by not suggesting or disclosing any specific polymorphs of tartrate salts. Claims 67-70 of the claimed invention all relate to specific polymorphs of the tartrate salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene. It is not easy to isolate and identify polymorphs of a particular compound. Isolating polymorphs is important for determining the optimal polymorph for further development in industry, all of which would not be obvious to one skilled in the art. The identification of polymorphs, therefore, plays an important role in the progress of science. Thus, in the absence of a teaching or suggestion in the art to select the specific polymorphs of the claimed tartrate salts, applicants respectfully contend that the Examiner has failed to provide a *prima facie* case of obviousness.

In the alternative, without conceding the lack of a *prima facie* basis for the rejection, but assuming for the sake of argument that such basis is indeed absent, applicants point out that the claimed tartrate salts possess unexpected and significant superior properties when compared with the closest prior art. As set forth in the Declaration of Peter R. Rose under 35 C.F.R. §1.132, submitted herewith, the claimed anhydrous and hydrate tartrate salts of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene are significantly and surprisingly less hygroscopic that the corresponding hydrochloride salt. Specifically, the L-tartrate salt, Form B, and the monohydrate, Form B, both picked up less than 0.5% of water content by weight under conditions of 90% humidity, whereas the hydrochloride salt gained 64% of water by weight. As noted by the declarant, such a difference in hygroscopicity is important in the development of pharmaceutical products for several reasons, including its impact on the *in vivo* activity of the drug and the ability to stably maintain the drug under typical manufacturing and storage conditions. In the absence of extensive experimentation, this unexpected decrease in hygroscopicity of the claimed tartrate salts is unobvious to the worker of skill in the art.

Accordingly, applicants respectfully submit that claims 38 and 67-70 are patentable under 35 U.S.C. §103(a), and respectfully request withdrawal of this rejection.

Rejection under 35 U.S.C. §112, First Paragraph

The Examiner rejected claim 39 under 35 U.S.C. §112, first paragraph, on the ground that the specification does not reasonable provide enablement for treatment of all of the diseases recited in claim 39. However, the Examiner concedes that the instant specification is enabling as to a method of treating nicotine dependency, addiction, and withdrawal.

In response, in order to expedite the prosecution of the subject application, and without prejudice, applicants have cancelled claim 39. Accordingly, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Objection for Duplicate Claiming

Claims 4-8, 9-15, 18-24, 27-29 and 31-33 were objected to under 37 C.F.R. §1.75 as allegedly being substantial duplicates of each other. Each set of these five sets of claims relate to a particular polymorph.

Notwithstanding applicants' previously stated position that the Examiner cannot reject any claims, alleging duplicate claims, prior to the allowance of one of these claims and that, at most, the Examiner can give a duplicate claim warning before the allowance of these claims (MPEP §706.03(k)), applicants have canceled the allegedly duplicative claims without prejudice to their right to pursue them in a future continuation application and merely in order to expedite the prosecution of the subject application.

For the record, applicants point out that although the physical characteristics of the tartrate salts in each of the five sets of claims mentioned above can be characteristic of a single polymorph, this does not necessarily mean that the physical characteristics in each individual claim set are representative of only one type of polymorph. Multiple polymorphs may be possible for each salt form. It is also generally known in the art that different anhydrous polymorphs can coexist together, as well as anhydrous and hemihydrous polymorphs. Because of the transformations that naturally occur between different polymorphs, and because of the possible coexistence of different polymorphs, a specific physical characteristic, as recited in each of the individual claims, does not by itself necessarily represent only one specific polymorph. The structural claim elements recited in the claims objected to merely refer to a single polymorph. Accordingly, applicants respectfully submit that claims 4-8, 9-15, 18-24, 27-29 and 31-33 are not substantial duplicates of each other.

In view of the amendments set forth herein and remarks above, applicants respectfully submit that the pending claims are fully allowable, and solicit the issuance of a Notice to such effect. If a telephone interview is deemed to be helpful to expedite the prosecution of the subject application, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number provided.

The Commissioner is hereby authorized to charge any fees required under 37 C.F.R. §§1.16 and 1.17 or to credit any overpayment to Deposit Account No. 16-1445.

Respectfully submitted,

Date: November 19, 2004

A. David Joran
Attorney for Applicant(s)
Reg. No. 37,888

Pfizer Inc
Patent Department
150 East 42nd Street – 5th Floor
New York, NY 10017-5755
(212) 733-3381

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: David E. Bogle et al.

APPLICATION NO.: 10/139,730

FILING DATE: May 6, 2002

TITLE: TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Examiner: Kifle, Bruck

Group Art Unit: 1624

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

DECLARATION OF PETER R. ROSE UNDER 37 CFR §1.132

I, Peter R. Rose, declare as follows:

1. I am a Principal Scientist employed with Pfizer Global Research and Development in Groton, Connecticut.
2. I have extensive training in the science of chemistry, and specifically in structural chemistry, and the research and development of pharmaceutically useful crystalline forms for application in clinical medicine. In particular, I have significant experience in the field of crystallization development of small molecules. I am an author or co-author of numerous research publications in the field, and an inventor or co-inventor of patents directed to various crystalline forms of novel pharmaceutical substances.
3. I am aware of the above named patent application which is directed to an invention of present and former colleagues of mine in Pfizer Global Research and Development, and I understand the technical issues surrounding the preparation of the stable salts of the present invention.
4. I have compared the tartrate salt claimed in this application with the hydrochloride salt of the prior art, and have found that the tartrate salt produces superior and unexpected results when compared with the

hydrochloride salt of 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene.

5. As is known in the art, hygroscopicity is a key factor which determines whether a substance can be used in a dosage form such as tablets. Specifically, hygroscopicity is an undesirable feature for a substance which is intended to be formulated in tablets because it produces adverse effects in manufacturing, storage and use such as:
   - Changes of drug activity. The activity of a drug substance will change with the humidity, thereby making it difficult or impossible in the manufacturing process to keep the activity of the substance in each tablet within a prescribed standard.
   - Chemical deterioration in storage. Hygroscopic materials tend to be chemically unstable causing loss of activity in storage.
   - Manufacturing problems due to poor flow. The flow properties of hygroscopic materials change with increasing water content resulting in sticking and clumping.
   - Physical deterioration in storage. As tablets absorb water, they expand resulting in fracture.

6. The following results were obtained in a comparison of the hygroscopicity of the tartrate salt Form B; anhydrous and Form C, hydrate versus the hydrochloride salt at 90% relative humidity:

Amount Of Water Pick Up At 90% Relative Humidity As % Increase Of Initial Weight		
L-TARTRATE SALT (Form B; anhydrous	L-TARTRATE SALT (Form C; monohydrate	HYDROCHLORIDE SALT
<0.5%	<0.5%	64%

7. The low hygroscopicity of the tartrate salt Form B; anhydrous and Form C, hydrate compared to the high hygroscopicity of the hydrochloride is unexpected. The low hygroscopicity of the tartrate salt Form B, anhydrous

makes it suitable for use in tablets while the hydrochloride salt is not suitable for tablets due to its high hygroscopicity.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 16 November 2004

Peter R. Rose

10/739730

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number: RD-18572A

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	66	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	90 minus 20=	* 70
INDEPENDENT CLAIMS	1 minus 3 =	* 0
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	370.00	OR	BASIC FEE	740.00
X$ 9=		OR	X$18=	1260
X42=		OR	X84=	
+140=		OR	+280=	280
TOTAL		OR	TOTAL	

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 90	Minus	** 90	= 0
Independent	* 1	Minus	*** 3	= 0
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 68	Minus	** 90	= 0
Independent	* 4	Minus	*** 3	= 1
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	86.00
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	86.00

PL

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 92	Minus	** 90	= 2
Independent	* 1	Minus	*** 4	= 0
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

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NOTICE OF ALLOWANCE AND FEE(S) DUE

7590 12/03/2004

Paul H. Ginsburg
Pfizer Inc
Patent Department (150/05/49)
150 East 42nd Street
New York, NY 10017-5612

EXAMINER	
KIFLE, BRUCK	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 12/03/2004

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/139,730	05/06/2002	David E. Bogle	PC11872A	5317

TITLE OF INVENTION: TARTRATE SALTS OF 5,8, 14-TRIAZATERACYCLO[10.3.1.02,11 04.9]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1370	$300	$1670	03/03/2005

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 11/04) Approved for use through 04/30/2007.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (703) 746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

7590 12/03/2004

Paul H. Ginsburg
Pfizer Inc
Patent Department (150/05/49)
150 East 42nd Street
New York, NY 10017-5612

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (703) 746-4000, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/139,730	05/06/2002	David E. Bogle	PC11872A	5317

TITLE OF INVENTION: TARTRATE SALTS OF 5,8, 14-TRIAZATERACYCLO[10.3.1.02,11 04.9]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1370	$300	$1670	03/03/2005

EXAMINER	ART UNIT	CLASS-SUBCLASS
KIFLE, BRUCK	1624	514-252100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are enclosed:

☐ Issue Fee

☐ Publication Fee (No small entity discount permitted)

☐ Advance Order - # of Copies _____

4b. Payment of Fee(s):

☐ A check in the amount of the fee(s) is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.
NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/139,730	05/06/2002	David E. Bogle	PC11872A	5317

7590 12/03/2004

Paul H. Ginsburg
Pfizer Inc
Patent Department (150/05/49)
150 East 42nd Street
New York, NY 10017-5612

EXAMINER	
KIFLE, BRUCK	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 12/03/2004

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (703) 305-1383. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

PTOL-85 (Rev. 11/04) Approved for use through 04/30/2007.

Notice of Allowability	Application No.	Applicant(s)	
	10/139,730	BOGLE ET AL.	
	Examiner	Art Unit	
	Bruck Kifle, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *papers filed 11/19/04*.

2. ☒ The allowed claim(s) is/are *16, 17, 30, 38, 40-75*.

3. ☐ The drawings filed on _____ are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *12/01/04* .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

Bruck Kifle, Ph.D.
Primary Examiner
Art Unit: 1624

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Mr. David Joran on December 1, 2004.

The application has been amended as follows:

i) In claim 41, first line, replace "claim 4" by "claim 67".

ii) In claim 47, first line, replace "claim 9" by "claim 67".

iii) In claim 54, first line, replace "claim 18" by "claim 16".

iv) In claim 59, first line, replace "claim 27" by "claim 71".

v) In claim 63, first line, replace "claim 31" by "claim 30".

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruck Kifle, Ph.D. whose telephone number is 571-272-0668. The examiner can normally be reached Tuesdays to Fridays between 8:30 AM and 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund J. Shah can be reached on 571-272-0674. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bruck Kifle, Ph.D.
Primary Examiner
Art Unit 1624

BK
December 1, 2004

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	10/139,730	BOGLE ET AL.	
	Examiner	Art Unit	
	Bruck Kifle, Ph.D.	1624	

All Participants:

(1) *Bruck Kifle, Ph.D.*.

(2) *Mr. David Joran*.

Status of Application: _____

(3) _____.

(4) _____.

Date of Interview: *1 December 2004*

Time: *2:30 PM*

Type of Interview:
- ☒ Telephonic
- ☐ Video Conference
- ☐ Personal (Copy given to: ☐ Applicant ☐ Applicant's representative)

Exhibit Shown or Demonstrated: ☐ Yes ☐ No
If Yes, provide a brief description: .

Part I.

Rejection(s) discussed:

Claims discussed:
41, 47, 54, 59 and 63

Prior art documents discussed:

Part II.

SUBSTANCE OF INTERVIEW DESCRIBING THE GENERAL NATURE OF WHAT WAS DISCUSSED:
Claims 41, 47, 54, 69 and 63 depend on deleted claims. Mr. Joran agreed to have appropriate corrections to be done by Examiners amendment.

Part III.

☒ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview directly resulted in the allowance of the application. The examiner will provide a written summary of the substance of the interview in the Notice of Allowability.

☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview did not result in resolution of all issues. A brief summary by the examiner appears in Part II above.

(Examiner/SPE Signature) (Applicant/Applicant's Representative Signature – if appropriate)

Attachment A

ALLOWANCE HOT LIST

Appl. No. 10/139,730 Prepared by P. Stanback
Examiner-TC Kifle Date 12/2/04

JACKET:

(YES) NO Primary Examiner box complete.
(YES) NO Issuing Classification complete.

PTO-892/1449:

(YES) NO Examiner's initials or cross-through lines supplied for each item cited by applicant.
(YES) NO Date(s) supplied/complete on all PTO-1449/892 sheets. (Month and year required.)

SPEC:

(YES) NO Brief Description of Drawings includes description of each figure in drawings.
(YES) NO Continuing data is mentioned in 1st paragraph. (Can be an insert.)

CLAIMS:

(YES) NO Claims listed on Notice of Allowability match allowed claims and/or index of claims.
(YES) NO Claims correctly numbered in index.
(No duplicate or missing claim numbers.)
(No incorrect dependencies.)

CRFE:
YES NO If necessary (biological sequence listing).

NOTICE OF ALLOWABILITY:

YES NO Either Box No. 3 (drawings accepted) or Box No. 8 (corrected drawing request) has been checked.

Issue Classification	Application No.	Applicant(s)	
	10/139,730	BOGLE ET AL.	
	Examiner	Art Unit	
	Bruck Kifle, Ph.D.	1624	

ISSUE CLASSIFICATION

ORIGINAL					CROSS REFERENCE(S)						
CLASS				SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					
514				252.1	514	255.04					
INTERNATIONAL CLASSIFICATION					544	343					
C	0	7	D	241/36							
A	6	1	K	31/50							
A	6	1	K	31/495							
				/							
				/							

(Assistant Examiner) (Date)

(Legal Instruments Examiner) 12/2/04 (Date)

Bruck Kifle 12/01/04

(Primary Examiner) (Date)

Total Claims Allowed: 40

O.G. Print Claim(s)	O.G. Print Fig.
1	--

☐ **Claims renumbered in the same order as presented by applicant** ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		31	35	61		91		121		151		181
	2		32	36	62		92		122		152		182
	3		33	37	63		93		123		153		183
	4		34	38	64		94		124		154		184
	5		35	39	65		95		125		155		185
	6		36	40	66		96		126		156		186
	7		37	1	67		97		127		157		187
	8	13	38	2	68		98		128		158		188
	9		39	3	69		99		129		159		189
	10	14	40	4	70		100		130		160		190
	11	15	41	5	71		101		131		161		191
	12	16	42	6	72		102		132		162		192
	13	17	43	7	73		103		133		163		193
	14	18	44	8	74		104		134		164		194
	15	19	45	9	75		105		135		165		195
10	16	20	46		76		106		136		166		196
11	17	21	47		77		107		137		167		197
	18	22	48		78		108		138		168		198
	19	23	49		79		109		139		169		199
	20	24	50		80		110		140		170		200
	21	25	51		81		111		141		171		201
	22	26	52		82		112		142		172		202
	23	27	53		83		113		143		173		203
	24	28	54		84		114		144		174		204
	25	29	55		85		115		145		175		205
	26	30	56		86		116		146		176		206
	27	31	57		87		117		147		177		207
	28	32	58		88		118		148		178		208
	29	33	59		89		119		149		179		209
12	30	34	60		90		120		150		180		210

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
Washington, DC 20231
www.uspto.gov

CONFIRMATION NO. 5317

Bib Data Sheet

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/139,730	05/06/2002 RULE	514	1614	PC11872A

APPLICANTS

David E. Bogle, Jewett City, CT;
Peter R. Rose, Ledyard, CT;
Glenn R. Williams, East Aurora, NY;

**** CONTINUING DATA ***************************

This appln claims benefit of 60/290,861 05/14/2001

**** FOREIGN APPLICATIONS *********************

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 06/10/2002

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☑ no	CT	20	66	1
35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance				
Verified and Acknowledged Examiner's Signature	Initials D.K.			

ADDRESS

Paul H. Ginsburg
Pfizer Inc
Patent Department (150/05/49)
150 East 42nd Street
New York ,NY 10017-5612

TITLE

Tartrate salts of 5,8, 14-triazateracyclo[10.3.1.02,11 04.9]-hexadeca-2(11),3,5,7,9-pentaene and pharmaceutical compositions thereof

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
2410	No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Search Notes

Application No.	Applicant(s)	
10/139,730	BOGLE ET AL.	
Examiner	**Art Unit**	
Bruck Kifle, Ph.D.	1624	

SEARCHED			
Class	Subclass	Date	Examiner
514	252.1 255.04	11/30/04	BK
544	343	11/30/2004	BK

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
514	**252.1**	**11/04/04**	**BK**
514	255.04	11/4/2004	BK
544	343	11/4/2004	BK

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR

PART B - FEE(S) TRANSMITTAL

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7590 12/03/2004

Paul H. Ginsburg
Pfizer Inc
Patent Department (150/05/49)
150 East 42nd Street
New York, NY 10017-5612

03/07/2005 DEMMANU2 00000078 161445 10139730

01 FC:1501 1400.00 DA
02 FC:1504 300.00 DA

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (703) 746-4000, on the date indicated below.

A. David Joran	(Depositor's name)
	(Signature)
February 28, 2005	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/139,730	05/06/2002	David E. Bogle	PC11872A	5317

TITLE OF INVENTION: TARTRATE SALTS OF 5,8, 14-TRIAZATERACYCLO[10.3.1.02,11 04.9]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1370	$300	$1670	03/03/2005

EXAMINER	ART UNIT	CLASS-SUBCLASS
KIFLE, BRUCK	1624	514-252100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
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2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Peter C. Richardson
2 Lorraine B. Ling
3 A. David Joran

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Pfizer Inc New York, NY

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are enclosed:
- ☒ Issue Fee
- ☒ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s):
- ☐ A check in the amount of the fee(s) is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☒ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number 16-1445 16-1445 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
- ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.
NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date February 28, 2005

Typed or printed name A. David Joran Registration No. 37,858

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

AO 120 (Rev. 3/04)

TO:	Commissioner of Trademarks P.O. Box 1451 Alexandria, VA 22313-1451 ATTN: TTAB	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court **Southern District of New York** on the following ✔ Patents or Trademarks:

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
10 cv 6463	8/30/10	500 Pearl Street New York, NY 10007

PLAINTIFF	DEFENDANT
PFizer Inc., Pfizer Products Inc. C.P. Pharmaceuticals International C.V.	Mylan Inc. Mylan Pharmaceuticals Inc.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	7,265.119	9/04/2007	Pfizer Inc.
2	6,890,927	5/10/2005	" "
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
Ruby J. Krajick		8/30/2010

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

PTO/SB/81A (12-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT - POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Patent Number	6,890,927
Issue Date	May 10, 2005
First Named Inventor	David E. Bogle
Title	Tartrate Salts of 5,8,14-Triazateracyclo [10.3.1.02,11 04.9]-Hexadeca-2
Attorney Docket Number	PC11872A

I hereby revoke all previous powers of attorney given in the above-identified patent.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 28523

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified patent to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Inventor, having ownership of the patent.

OR

☒ Patent owner.

Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Inventor or Patent Owner

Signature		Date	21 December 2010
Name	Roy F. Waldron	Telephone	212-733-5086
Title and Company	Senior Vice President and Associate General Counsel, Pfizer Inc.; Attorney-in-Fact, Pfizer Products Inc.		

NOTE: Signatures of all the inventors or patent owners of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

PTO/SB/96 (04-09)
Approved for use through 05/31/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Pfizer Inc. and Pfizer Products Inc.

Application No./Patent No.: 10/139,730 /6,890,927 Filed/Issue Date: May 06, 2002/May 10, 2005

Titled: TARTRATE SALTS OF 5,8, 14-TRIAZATERACYCLO[10.3.1.02,11 04.9]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Pfizer Inc. and Pfizer Products Inc. , a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: see attached To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel 013694, Frame 0400, or for which a copy thereof is attached.

2. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

_____ 21 December 2010
Signature Date

Roy F. Waldron Sr VP-Assoc. GC, Pfizer Inc.
Printed or Typed Name Atty-in-Fact, PPI
Title

Attachment Sheet for Statement Under 37 CFR 3.73(b)

Patent No.: 6,890,927
Issued: May 10, 2005
Titled: TARTRATE SALTS OF 5,8, 14-TRIAZATERACYCLO[10.3.1.02,11 04.9]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF

ASSIGNMENT 1
From:
David E. Bogle
Peter R. Rose
Glenn R. Williams

To:
Pfizer Inc.
Pfizer Products Inc.

Reel/Frame: 013694/0400

Electronic Acknowledgement Receipt

EFS ID:	9083380
Application Number:	10139730
International Application Number:	
Confirmation Number:	5317
Title of Invention:	TARTRATE SALTS OF 5,8, 14-TRIAZATERACYCLO[10.3.1.02,11 04.9]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF
First Named Inventor/Applicant Name:	David E. Bogle
Correspondence Address:	Paul H. Ginsburg Pfizer Inc Patent Department (150/05/49) 150 East 42nd Street New York NY 10017-5612 US 2125732369 -
Filer:	Mary Jane Hosley
Filer Authorized By:	
Attorney Docket Number:	PC11872A
Receipt Date:	21-DEC-2010
Filing Date:	06-MAY-2002
Time Stamp:	12:12:43
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		PC11872A-POA-AddressChng.PDF	122780 caae775bdeec7081798a5e148c1d017c415db887	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Power of Attorney	1	1
	Assignee showing of ownership per 37 CFR 3.73(b).	2	3

Warnings:	
Information:	
Total Files Size (in bytes):	122780

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/139,730	05/06/2002	David E. Bogle	PC11872A

CONFIRMATION NO. 5317

28523
PFIZER INC.
PATENT DEPARTMENT
Bld 114 M/S 9114
EASTERN POINT ROAD
GROTON, CT 06340

POA ACCEPTANCE LETTER

OC000000045160640

Date Mailed: 12/29/2010

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/21/2010.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/vvan/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/139,730	05/06/2002	David E. Bogle	PC11872A

CONFIRMATION NO. 5317

Paul H. Ginsburg
Pfizer Inc
Patent Department (150/05/49)
150 East 42nd Street
New York, NY 10017-5612

POWER OF ATTORNEY NOTICE

OC000000045160596

Date Mailed: 12/29/2010

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/21/2010.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/vvan/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

AO 120 (Rev. 3/04)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Southern District of New York on the following X Patents or Trademarks:

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:10-CV-6463	8/30/2010	Southern District of New York

PLAINTIFF	DEFENDANT
Pfizer. Inc., et al	Mylan Inc., et al

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	7,265,119		See Attached List
2	6,890,927		
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1			
2			
3			
4			
5			

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
Attached: COPY OF NOTICE OF DISMISSAL.

CLERK	(BY) DEPUTY CLERK	DATE
Ruby Krajick		12/22/2010

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

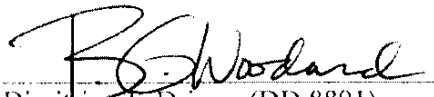
PFIZER INC., PFIZER PRODUCTS INC., and C.P. PHARMACEUTICALS INTERNATIONAL C.V., Plaintiffs, v. MYLAN INC. and MYLAN PHARMACEUTICALS INC., Defendants.	Civil Action No. 10-6463 Judge William H. Pauley

PFIZER INC., PFIZER PRODUCTS INC., AND C.P. PHARMACEUTICALS INTERNATIONAL C.V.'S NOTICE OF DISMISSAL WITHOUT PREJUDICE

PLEASE TAKE NOTICE that, pursuant to Fed. R. Civ. P. 41(a)(1)(A)(i), Plaintiffs Pfizer Inc., Pfizer Products Inc., and C.P. Pharmaceuticals International C.V. (collectively, "Pfizer") hereby voluntarily dismiss this action without prejudice as to Defendants Mylan Inc. and Mylan Pharmaceuticals Inc. (collectively, "Mylan"). Mylan has not filed a responsive pleading to Pfizer's Complaint.

Dated: December 21, 2010

Respectfully submitted,



Dimitrios T. Drivas (DD 8891)
Jeffrey J. Oelke (JO 2534)
Adam Gahtan (AG 8802)
Brendan G. Woodard (BW 6194)

R. Gregory Parker (RP 2121)
WHITE & CASE LLP
1155 Avenue of the Americas
New York, New York 10036

Attorneys for Plaintiffs Pfizer Inc., Pfizer Products Inc., and C.P. Pharmaceuticals International C.V.

(12) **United States Patent**
Bogle et al.

(10) **Patent No.: US 7,265,119 B2**
(45) **Date of Patent: Sep. 4, 2007**

(54) **TARTRATE SALTS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.0^{2,11}.0^{4,9}]-HEXADECA-2(11),3,5,7,9-PENTAENE AND PHARMACEUTICAL COMPOSITIONS THEREOF**

(75) Inventors: **David E. Bogle**, Jewett City, CT (US); **Glenn R. Williams**, Oaksville (CA); **Peter R. Rose**, Ledyard, CT (US)

(73) Assignee: **Pfizer Inc**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 105 days.

(21) Appl. No.: **11/069,724**

(22) Filed: **Feb. 28, 2005**

(65) **Prior Publication Data**

US 2005/0148591 A1 Jul. 7, 2005

Related U.S. Application Data

(63) Continuation of application No. 10/139,730, filed on May 6, 2002, now Pat. No. 6,890,927.

(60) Provisional application No. 60/290,861, filed on May 14, 2001.

(51) **Int. Cl.**
C07D 241/36 (2006.01)
A61K 31/50 (2006.01)
A61K 31/495 (2006.01)

(52) **U.S. Cl.** **514/250**; 544/343

(58) **Field of Classification Search** 544/343; 514/250

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,471,503 A 10/1969 Carson

FOREIGN PATENT DOCUMENTS

EP	1078637	2/2001
WO	WO 9935131	7/1999

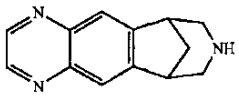
OTHER PUBLICATIONS

Paul H. Mazzochi, et al., "Synthesis and Pharmacological Activity of 2,3,4,5-Tetrahydro-1,5-Methano-1H-3-Benzazepines", J. Med. Chem., vol. 22, No. 4, 1979, pp. 455-457, XP002090422.

Primary Examiner—Bruck Kifle
(74) *Attorney, Agent, or Firm*—Steve T. Zelson; A. David Joran

(57) **ABSTRACT**

The present invention is directed to the tartrate salts of 5,8,14-triazatetracyclo[10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene:



and pharmaceutical compositions thereof. The present invention in particular is directed to the L-tartrate salt, and further to the various polymorphs of the L-tartrate salt, including two distinct anhydrous polymorphs (referred to herein as Forms A and B) and a hydrate polymorph (referred to herein as Form C). In addition, the present invention is also directed to the D-tartrate salt of 5,8,14-triazatetracyclo [10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene and the various polymorphs thereof; as well as the D,L-tartrate salt thereof and its polymorphs, and the meso-tartrate salt thereof and its polymorphs.

15 Claims, 20 Drawing Sheets

AO 120 (Rev. 3/04)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Southern District of New York on the following X Patents or Trademarks:

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:10-CV-6464	8/30/2010	Southern District of New York

PLAINTIFF	DEFENDANT
Pfizer. Inc., et al	Apoxtex Inc., et al

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	7,265,119		See Attached List
2	6,890,927		
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
Attached: COPY OF NOTICE OF DISMISSAL.

CLERK	(BY) DEPUTY CLERK	DATE
Ruby Krajick		12/22/2010

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

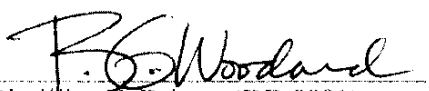
PFIZER INC., PFIZER PRODUCTS INC., and C.P. PHARMACEUTICALS INTERNATIONAL C.V., Plaintiffs, v. APOTEX INC. and APOTEX CORP., Defendants.	Civil Action No. 10-6464 Judge William H. Pauley

PFIZER INC., PFIZER PRODUCTS INC., AND C.P. PHARMACEUTICALS INTERNATIONAL C.V.'S NOTICE OF DISMISSAL WITHOUT PREJUDICE

PLEASE TAKE NOTICE that, pursuant to Fed. R. Civ. P. 41(a)(1)(A)(i), Plaintiffs Pfizer Inc., Pfizer Products Inc., and C.P. Pharmaceuticals International C.V. (collectively, "Pfizer") hereby voluntarily dismiss this action without prejudice as to Defendants Apotex Inc. and Apotex Corp. (collectively, "Apotex"). Apotex has not filed a responsive pleading to Pfizer's Complaint.

Dated: December 21, 2010

Respectfully submitted,



Dimitrios T. Drivas (DD 8891)
Jeffrey J. Oelke (JO 2534)
Adam Gahtan (AG 8802)
Brendan G. Woodard (BW 6194)

R. Gregory Parker (RP 2121)
WHITE & CASE LLP
1155 Avenue of the Americas
New York, New York 10036

Attorneys for Plaintiffs Pfizer Inc., Pfizer Products Inc., and C.P. Pharmaceuticals International C.V.

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Southern District of New York on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
19-cv-00615-WHP	1/22/2019	Southern District of New York

PLAINTIFF	DEFENDANT
Par Pharmaceutical Inc	Pfizer Inc., et al.,

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,890,927	5/10/2005	Pfizer Inc. and Pfizer Products Inc.
2	7,265,119	9/4/2007	Pfizer Inc.
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 See Attached Sheet		See Attached Sheet
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
COPY ATTACHED: Notice of Voluntary Dismissal

CLERK	(BY) DEPUTY CLERK	DATE
Ruby J. Krajick	s/K.Mango	3/18/2019

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

IN THE UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF NEW YORK

PAR PHARMACEUTICAL, INC., Plaintiff v. PFIZER INC., PFIZER PRODUCTS INC., and C.P. PHARMACEUTICALS INTERNATIONAL C.V., Defendants	)	**NOTICE OF VOLUNTARY DISMISSAL PURSUANT TO F.R.C.P. 41(a)(1)(A)(i)** Case No.: 1:19-cv-00615-WHP

NOTICE OF VOLUNTARY DISMISSAL PURSUANT TO F.R.C.P. 41(a)(1)(A)(i)

Pursuant to F.R.C.P. 41(a)(1)(A)(i) of the Federal Rules of Civil Procedure, the Plaintiff Par Pharmaceutical, Inc. and or their counsel(s), hereby give notice that the above-captioned action is voluntarily dismissed, with prejudice against the Defendants Pfizer Inc., Pfizer Products Inc., and C.P. Pharmaceuticals International C.V.

Dated: 3/15/19

David H. Silverstein (No. DS4242)
AXINN, VELTROP & HARKRIDER LLP
114 West 47th Street, 22nd Floor
New York, NY 10036

Of Counsel:
Aziz Burgy (pro hac vice to be submitted)
AXINN, VELTROP & HARKRIDER LLP
950 F Street, NW, 7th Floor
Washington, DC 20004

Attorneys for Plaintiff Par Pharmaceutical, Inc.

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the Southern District of New York on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
19-cv-6607	7/16/2019	for the Southern District of New York

PLAINTIFF	DEFENDANT
Ajanta Pharma Limited	Pfizer Inc., et al.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,890,927	5/10/2005	Pfizer Inc. and Pfizer Products Inc.
2	7,265,119	9/4/2007	Pfizer Inc.
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
Decision

CLERK	(BY) DEPUTY CLERK	DATE
Ruby J. Krajick	Yadira Fuschillo	10/4/2019

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

AJANTA PHARMA LTD.,	:	
Plaintiff,	:	
-v-	:	19-CV-6607 (JMF)
PFIZER INC. et al.,	:	ORDER OF DISMISSAL
Defendants.	:	

JESSE M. FURMAN, United States District Judge:

The Court having been advised at the initial pretrial conference on October 3, 2019, that all claims asserted herein have been settled in principle, it is ORDERED that the above-entitled action be and is hereby DISMISSED and discontinued without costs, and without prejudice to the right to reopen the action **within thirty days** of the date of this Order if the settlement is not consummated.

To be clear, any application to reopen **must** be filed **by the aforementioned deadline**; any application to reopen filed thereafter may be denied solely on that basis. Further, if the parties wish for the Court to retain jurisdiction for the purposes of enforcing any settlement agreement, they **must** submit the settlement agreement to the Court by the same deadline to be "so ordered" by the Court. Per Paragraph 4(B) of the Court's Individual Rules and Practices for Civil Cases, unless the Court orders otherwise, the Court will not retain jurisdiction to enforce a settlement agreement unless it is made part of the public record.

Any pending motions are moot. All conferences are canceled. The Clerk of Court is directed to close the case.

SO ORDERED.

Dated: October 3, 2019
New York, New York

JESSE M. FURMAN
United States District Judge

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	1/31/2020	for the District of Delaware

PLAINTIFF	DEFENDANT
PFIZER INC., PFIZER PRODUCTS INC., PF PRISM C.V. and C.P. PHARMACEUTICALS INTERNATIONAL C.V.	VIWIT PHARMACEUTICAL CO., LTD.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,410,550 B1	6/25/2002	Pfizer Inc.
2	6,890,927 B2	5/10/2005	Pfizer Inc.
3	7,265,119 B2	9/4/2007	Pfizer Inc.
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above---entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1---Upon initiation of action, mail this copy to Director Copy 3---Upon termination of action, mail this copy to Director
Copy 2---Upon filing document adding patent(s), mail this copy to Director Copy 4---Case file copy