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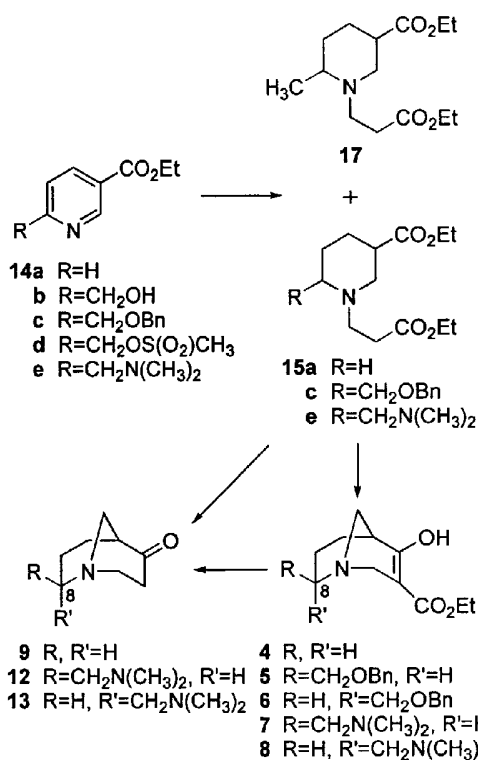
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[Continued on next page]

(54) Title: AZA-BRIDGED BICYCLIC AMINE DERIVATIVES FOR USE AS NOVEL CHOLINERGIC RECEPTOR LIGANDS

Synthesis of Aza-bridged [3.3.1]-Bicyclic Amines



(57) Abstract: The present invention discloses novel cholinergic receptor ligands. The present invention also relates to novel compounds and the synthesis of such compounds as substituted derivatives of aza-bridged bicyclic amines for use as muscarinic receptor ligands. The present invention also relates to methods of regulating function of certain cholinergic receptors, and hence acting as antagonists, agonists and partial agonists at certain specific cholinergic receptor subtypes. The present invention also relates to methods for treating disorders associated with cholinergic receptors.



SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/08 A61K31/529 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 07854 A (GYOGYSZERKUTATO INTEZET) 14 May 1992 (1992-05-14) page 4, line 12 -page 4, line 17; claims 1,2	19-52
A	claim 4	1-18
Y	EP 0 214 772 A (BEECHAM GROUP PLC) 18 March 1987 (1987-03-18) claims 1,14	19-52
A	claim 10	1-18
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

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Date of mailing of the international search report

26/03/2004

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International Application No.

PCT/US 03/24677

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KING F D ET AL: "SUBSTITUTED BENZAMIDES WITH CONFORMATIONALLY RESTRICTED SIDE CHAINS. 5. AZABICYCLOUX,Y,Z DERIVATIVES AS 5-HT4 RECEPTOR AGONISTS AND GASTRIC MOTILITY STIMULANTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 36, no. 6, 19 March 1993 (1993-03-19), pages 683-689, XP002073339 ISSN: 0022-2623 examples 5E,5F; table 1 ---	19-52
Y	ORLEK B. S. ET AL.: "Comparison of Azabicyclic Esters and Oxadiazoles as Ligands of the Muscarinic Receptor" J. MED. CHEM., vol. 34, 1991, pages 2726-2735, XP002260366 examples 4A,4B,4E,4F; table 1 ---	19-52
Y	EP 0 239 321 A (BEECHAM GROUP PLC) 30 September 1987 (1987-09-30) claims 1,11 ---	19-52
Y	EP 0 094 742 A (BEECHAM GROUP PLC) 23 November 1983 (1983-11-23) page 35, line 12 -page 35, line 21; claims 1,4; examples 8,9 ---	19-52
Y	EP 0 287 356 A (BEECHAM GROUP PLC) 19 October 1988 (1988-10-19) page 2, line 7 -page 2, line 9; claim 1; examples 1,2 ---	19-52
Y	EP 0 257 741 A (BEECHAM GROUP PLC) 2 March 1988 (1988-03-02) page 3, line 7 -page 3, line 9; claim 1; examples 1-4 ---	19-52
Y	WO 93 08191 A (WARNER LAMBERT CO) 29 April 1993 (1993-04-29) compounds of formula (IV) page 1, line 7 -page 1, line 10; claim 1 ---	19-52
Y	US 5 658 925 A (ABE SHINYA ET AL) 19 August 1997 (1997-08-19) column 5, line 1 -column 5, line 18; claims 1,6; examples 5,6,31-33 ---	19-52
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INTERNATIONAL SEARCH REPORT

International Publication No

PCT/US 03/24677

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	STERNBACH L. H. ET AL.: "Antispasmodics I: Bicyclic Basic Alcohols" J. AM. CHEM. SOC., vol. 74, 1952, pages 2215-2218, XP002260367 synthesis of XVI starting from XIV ---	1-18
Y	STERNBACH L. H. ET AL.: "Antispasmodics II: Esters of Basic Bicyclic Alcohols" J. AM. CHEM. SOC., vol. 74, 1952, pages 2219-2221, XP002260368 compounds IIIa and IIIb table 1 -----	1-52

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/24677

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.1

Although claims 32-49 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition. Although claims 50-52 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/24677

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9207854	A	14-05-1992	HU 59922 A2	28-07-1992
			AU 645377 B2	13-01-1994
			AU 8911391 A	26-05-1992
			CA 2093417 A1	06-05-1992
			CZ 9300752 A3	16-02-1994
			EP 0556342 A1	25-08-1993
			FI 932034 A	05-05-1993
			WO 9207854 A1	14-05-1992
			JP 6505706 T	30-06-1994
EP 0214772	A	18-03-1987	EP 0214772 A1	18-03-1987
			JP 62059278 A	14-03-1987
			US 4798829 A	17-01-1989
EP 0239321	A	30-09-1987	AU 600476 B2	16-08-1990
			AU 7044287 A	24-09-1987
			CA 1308104 C	29-09-1992
			DE 3786187 D1	22-07-1993
			DE 3786187 T2	14-10-1993
			DK 145287 A	23-09-1987
			EP 0239321 A2	30-09-1987
			ES 2058107 T3	01-11-1994
			HK 1004548 A1	27-11-1998
			IE 60166 B1	15-06-1994
			JP 2079924 C	09-08-1996
			JP 7107062 B	15-11-1995
			JP 62270583 A	24-11-1987
			NZ 219719 A	27-03-1990
			PT 84535 A , B	01-04-1987
			US 4800225 A	24-01-1989
			ZA 8702057 A	30-12-1987
EP 0094742	A	23-11-1983	AU 563225 B2	02-07-1987
			AU 1343483 A	20-10-1983
			CA 1223873 A1	07-07-1987
			DE 3381772 D1	06-09-1990
			EP 0094742 A2	23-11-1983
			ES 8406485 A1	01-11-1984
			IE 56226 B1	22-05-1991
			JP 1932774 C	26-05-1995
			JP 6047591 B	22-06-1994
			JP 58188885 A	04-11-1983
			JP 2014108 C	02-02-1996
			JP 5194513 A	03-08-1993
			JP 7014934 B	22-02-1995
			NZ 203861 A	11-07-1986
			US 4857647 A	15-08-1989
			US 4612319 A	16-09-1986
			US 4697019 A	29-09-1987
			ZA 8302549 A	28-09-1988
EP 0287356	A	19-10-1988	AT 133415 T	15-02-1996
			AU 614513 B2	05-09-1991
			AU 1455788 A	27-10-1988
			DE 3854932 D1	07-03-1996
			DE 3854932 T2	13-06-1996
			DK 202388 A	16-10-1988
			EP 0287356 A2	19-10-1988

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Publication No

PCT/US 03/24677

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0287356 A		JP 2651695 B2	10-09-1997
		JP 63290878 A	28-11-1988
		NZ 224237 A	26-04-1991
		PT 87231 A	01-05-1988
		US 4971975 A	20-11-1990
		US 5132316 A	21-07-1992
		ZA 8802589 A	22-02-1989
EP 0257741 A	02-03-1988	AU 599990 B2	02-08-1990
		AU 7469487 A	07-01-1988
		DK 324387 A	28-12-1987
		EP 0257741 A2	02-03-1988
		JP 63039879 A	20-02-1988
		NZ 220840 A	28-08-1990
		PT 85173 A , B	01-07-1987
		US 4870081 A	26-09-1989
		ZA 8704626 A	31-08-1988
WO 9308191 A	29-04-1993	AU 2782792 A	21-05-1993
		MX 9205892 A1	01-04-1993
		PT 100959 A	29-10-1993
		US 5318978 A	07-06-1994
		WO 9308191 A1	29-04-1993
		US 5464842 A	07-11-1995
		ZA 9207924 A	14-04-1994
US 5658925 A	19-08-1997	JP 3235913 B2	04-12-2001
		JP 7041463 A	10-02-1995
		US 5723472 A	03-03-1998
		US 5861418 A	19-01-1999
		CA 2128493 A1	31-01-1995
		DE 69429147 D1	03-01-2002
		DE 69429147 T2	18-07-2002
		DK 645391 T3	21-05-2002
		EP 0645391 A2	29-03-1995
		ES 2163417 T3	01-02-2002
		US 5512579 A	30-04-1996
		US 5677311 A	14-10-1997