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(54) **QUINUCLIDINE DERIVATIVES AND THEIR USE AS MUSCARINIC M3 RECEPTOR LIGANDS**

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C07D 453/04	(2006.01)
A61K 31/345	(2006.01)
A61K 31/435	(2006.01)
A61P 1/00	(2006.01)
A61P 1/04	(2006.01)
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A61K 9/00	(2006.01)
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A61P 1/12	(2006.01)
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A61P 11/02	(2006.01)
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CPC A61K 31/4745; A61K 31/56; A61K 45/06; A61K 47/26; A61K 9/0073; A61K 31/439; A61K 9/0075; C07D 453/02; Y10S 514/826

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,714,357	A	1/1973	Gueremy et al.	
4,224,332	A	9/1980	Gueremy et al.	424/267
4,338,931	A	7/1982	Cavazza	
4,579,854	A	4/1986	Iwakuma et al.	
4,644,033	A	2/1987	Gnanou et al.	524/590

(Continued)

FOREIGN PATENT DOCUMENTS

CA	2062854	9/1992
EP	0003445	8/1979

(Continued)

OTHER PUBLICATIONS

Alabaster, V., "Discovery and Development of Selective M3 Antagonists for Clinical Use," Life Sciences, 1997, 60 (13-14), 1053-1060.

(Continued)

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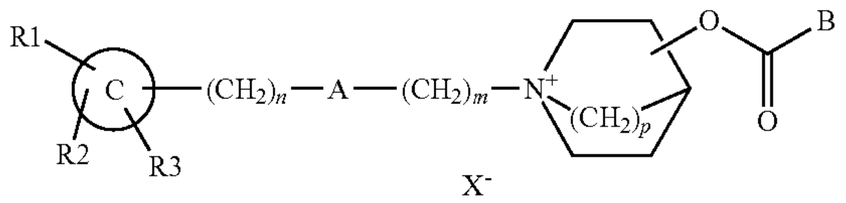
(57) **ABSTRACT**

A compound according to formula (I)



wherein:

© is a phenyl ring, a C_4 to C_9 heteroaromatic compound containing one or more heteroatoms, or a naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl or biphenyl group;

which shows high affinity for muscarinic M_3 receptors (Hm3).

27 Claims, No Drawings

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,675,326	A *	6/1987	Amitai et al.	514/304
4,843,074	A	6/1989	Rzeszotarski et al.	514/228.2
4,855,290	A	8/1989	Fisher et al.	
5,201,308	A	4/1993	Newhouse	
5,254,330	A	10/1993	Ganderton et al.	
5,263,475	A	11/1993	Altermatt et al.	
5,290,539	A	3/1994	Marecki	
5,290,815	A	3/1994	Johnson et al.	
5,435,301	A	7/1995	Herold et al.	
5,507,281	A	4/1996	Kuhnel et al.	
5,569,447	A	10/1996	Lee et al.	
5,575,280	A	11/1996	Gupte et al.	
5,610,163	A	3/1997	Banholzer et al.	
5,617,845	A	4/1997	Pass et al.	
5,654,314	A	8/1997	Banholzer et al.	514/291
5,676,930	A	10/1997	Jager et al.	
5,685,294	A	11/1997	Gupte et al.	
5,885,834	A	3/1999	Epstein	
5,962,505	A	10/1999	Bobrove et al.	
5,964,416	A	10/1999	Jaeger et al.	
6,150,415	A	11/2000	Hammock et al.	
6,299,861	B1	10/2001	Banholzer et al.	
6,299,863	B1	10/2001	Aberg et al.	
6,402,055	B1	6/2002	Jaeger et al.	
6,423,298	B2	7/2002	McNamara et al.	
6,497,373	B2	12/2002	Jaeger et al.	
6,521,260	B1	2/2003	Staniforth	
6,521,261	B2	2/2003	Sherwood et al.	
6,686,346	B2	2/2004	Nilsson et al.	
6,726,124	B2	4/2004	Jaeger et al.	
6,918,547	B2	7/2005	Jaeger et al.	
6,986,346	B2	1/2006	Hochrainer et al.	
7,040,311	B2	5/2006	Hochrainer et al.	
7,078,412	B2 *	7/2006	Fernandez Forner	A61K 31/4745 514/305
7,104,470	B2	9/2006	Jaeger et al.	
7,109,210	B2 *	9/2006	Fernandez Forner	A61K 31/4745 514/305
7,196,098	B2 *	3/2007	Fernandez Forner	A61K 31/4745 514/171
7,214,687	B2 *	5/2007	Fernandez Forner	A61K 31/4745 514/305
RE39,820	E	9/2007	Banholzer et al.	
7,358,260	B2 *	4/2008	Fernandez Forner	A61K 31/4745 514/305
7,750,023	B2 *	7/2010	Fernandez Forner	A61K 31/4745 514/305
7,897,617	B2 *	3/2011	Fernandez Forner	A61K 31/4745 514/305
8,129,405	B2 *	3/2012	Fernandez Forner	A61K 31/4745 514/305
8,513,279	B2 *	8/2013	Fernandez Forner	A61K 31/4745 514/305
8,802,699	B2 *	8/2014	Fernandez Forner	A61K 31/4745 514/305
9,056,100	B2 *	6/2015	Fernandez Forner	A61K 31/4745
9,333,195	B2 *	5/2016	Fernandez Forner	A61K 31/4745
2003/0085480	A1	5/2003	Yang	

FOREIGN PATENT DOCUMENTS

EP	0069715	1/1983
EP	0166294	1/1986
EP	2165159	4/1986
EP	0205247	12/1986
EP	0302699	2/1989
EP	0 418 716	3/1991
EP	0 424 021	4/1991
EP	0424790 A2	5/1991
EP	2242134	9/1991
EP	0505321	9/1992
EP	0424790 B1	8/1993
EP	0424021	3/1994
EP	0418716 B1	4/1994
EP	0 747 355	12/1996
EP	0 801 067	10/1997
EP	0603229	6/1998
FR	2012964	3/1970
GB	1219606	1/1971
GB	2041763	9/1980
HU	178679	6/1982
WO	WO 87/07502	12/1987
WO	WO 91/02558	3/1991
WO	WO 91/04252	4/1991
WO	WO 91/14468	10/1991
WO	WO 92/00771	1/1992
WO	WO 92/04928	2/1992
WO	WO 92/03175	3/1992
WO	WO 92/04068	3/1992
WO	WO 92/04345	3/1992
WO	WO 92/04346	3/1992
WO	WO 92/09322	6/1992
WO	WO 94/14492	7/1994
WO	WO 95/24889	9/1995
WO	WO 96/04346	2/1996
WO	WO 96/19968	7/1996
WO	WO 96/32150	10/1996
WO	WO 97/00703	1/1997
WO	WO 97/01337	1/1997
WO	WO 97/12687	4/1997
WO	WO 97/28801	8/1997
WO	WO 97/34871	9/1997
WO	WO 98/15280	4/1998
WO	WO 99/51205	10/1999
WO	WO 01/50080 A2	7/2001
WO	WO 01/50080 A3	7/2001
WO	WO 2013/175013 A1 *	11/2013

OTHER PUBLICATIONS

Atrovent® (ipratropium bromide) Inhalation Solution Prescribing Information, Boehringer Ingelheim International GmbH 830885-R, Revised Oct. 1998.

Auerbach, D. et al., "Routine Nebuilzed Ipratropium and Albuterol Together are Better Than Either Alone in COPD*," The Combivent Inhalation Solution Study Group, Chest, 1997 112,1514-1521.

Ayres, JG et al. Thorax 52(Supp 1): S1-S21 (1997).

Banner, K. et al., "The Effect of Selective Phosphodiesterase 3 and 4 Isoenzyme Inhibitors and Established Anti-Asthma Drugs on Inflammatory Cell Activation," British Journal of Pharmacology, 1996, 119, 1255-1261.

Barnes, P. et al., "The Effect of Platelet Activating Factor on Pulmonary-Adrenoceptors," British Journal of Pharmacology, 1987, 90, 709-715.

Barnes, P. et al., Eds., Asthma, vol. 2, Lippincott-Raven, Philadelphia, 1997, ISBN 0-397-51682-7, Chapter 142: Compliance by H. Mawhinney et al., pp. 2099-2113.

Beasley, R. et al., "Withdrawal of Fenoterol and the End of the New Zealand Asthma Mortality Epidemic," International Archives of Allergy and Immunology, 1995, 107, 325-327.

Berenbaum, M., "Synergy, Additivism and Antagonism in Immunosuppression, A Critical Review," Clinical and Experimental Immunology, 1977, 28, 1-18.

Berenbaum, M., "What is Synergy?," Pharmacological Reviews, 1989, 41, 93-141 and Errata, p. 422.

(56) **References Cited**

OTHER PUBLICATIONS

Berkow, R. et al., Eds., The Merck Manual of Diagnosis and Therapy, Sixteenth Edition, 1992, Foreword and Chapter 34, "Airways Obstruction Asthma," pp. 646-657.
Bone, R. et al., "In Chronic Obstructive Pulmonary Disease, A Combination oflpratropium and Albuterol is More Effective that Either Agent Alone: An 85-Day Multicenter Trial," Combivent Inhalation Aerosol Study Group, Chest, 1994, 105, 1411-1419.
British Thoracic Society, "BTS Guidelines for the Management of Chronic Obstructive Pulmonary Disease," The COPD Guidelines Group of the Standards of Care Committee of the BTS, Thorax, 1997, 52, Supplement 5, SI-S28.
Brodde, 0-E., "1- and 2-Adrenoceptors in the Human Heart: Properties, Function, and Alterations in Chronic Heart Failure," Pharmacological Reviews, 1991, 43 (2), 203-242.
Bryant, D., "Nebulized Ipratropium Bromide in the Treatment of Acute Asthma," Chest Journal, 88(1), 24-29.
Calverley, P.M.A., Ed., Chronic Obstructive Pulmonary Disease, Chapman and Hall, London, 1995, ISBN 0 412 46450, Chapter 16: Bronchodilators: Basic Pharmacology by P.J. Barnes, pp. 391 and 398-401.
Christensen et al., "1,4-Cyclohexanecarboxylates: Potent and Selective Inhibitors of Phosphodiesterase 4 for the Treatment of Asthma," J. Med. Chem. 41:821-835 (1998).
Clarkson, E. et al., "Binding and Active Transport of Large Analogues of Acetylcholine by Cholinergic Synaptic Vesicles In Vitro," Journal of Neurochemistry, 1992, 59, 695-700.
Costain, D. et al., "Guidelines for Management of Asthma in Adults: I-Chronic Persistent Asthma," Br. Med. J. 301: 651-653 (1990).
Dent, et al., "Effectis of a Selective PDE4 Inhibitor, D-22888, on Human Airways and Eosinophils in vitro and Late Phase Allergic Pulmonary Eosinophilia in Guinea Pigs," Pulmonary Pharma & Thera. 11:13-21 (1998).
Disse, B. et al., "BA 679 BR, A Novel Long-Acting Anticholinergic Bronchodilator," Life Sciences, 1993, 52, 537-544.
Dompeling, E. et al., "Slowing the Deterioration of Asthma and Chronic Obstructive Pulmonary Disease Observed During Bronchodilator Therapy by Adding Inhaled Corticosteroids," Annals of Internal Medicine, 1993, 118, 770-778.
Easton, P. et al., "A Comparison of the Bronchodilating Effects of a Beta-2 Andrenergic Agent (Albuterol) and an Anticholinergic Agent (Ipratropium Bromide), Given by Aerosol Alone or in a Sequence,"New England Journal of Medicine, 1986,315 (12), 735-730.
Eglen, R. et al, "Muscarinic Receptor Subtypes and Smooth Muscle Function," Pharmacological Reviews, 1996, 48 (4), 531-565.
Eglen, RM et al., "Muscarinic Receptor Subtypes: Pharmacology and Therapeutic Potential," *DN & P,* 10(8): 462-469 (Oct. 1997).
Emea, "Note for Guidance on Dose Response Information to Support Drug Registration," ICH Topic E 4. 1994. CPMP/ICH/378/95.
Foye, et al., Principles of Medicinal Chemistry, 4th Edition, pp. 338-340 (1995).
Frith, P. et al., "Oxitropium Bromide, Dose-Response and Time-Response Study of a New Anticholinergic Bronchodilator Drug," Chest, 1986, 89 (2), 249-253.
Gao, SH et al., Stereochemistry of the heterocyclic alcohols containing piperidine unit, Gaodeng Xuexiao Huaxue Xuebao, vol. 20: p. 232-236 (1999).
Global Initiative for Asthma, Global Strategy for Asthma Management and Prevention, NIH Publication No. 02-3659, Issued Jan. 1995, revised 2002.
Godoviko et al., "Synthesis and Muscarinolytic Activity of Quinuclidinyl Benzylate Iodoalkylates," Pharmceutical Chemistry Journal, vol. 19, No. 9, 602-604 (1985).
Gross, N. et al., "Dose Response to Ipratropium as a Nebulized Solution in Patients with Chronic Obstructive Pulmonary Disease, A Three-Center Study," American Review of Respiratory Disease, 1989, 139, 1188-1191.
Gross, N. et al., "Inhalation by Nebulization of Albuterol-Ipratropium Combination (Dey Combination) is Superior to Either Agent Alone in the Treatment of Chronic Obstructive Pulmonary Disease," Respiration, 1998, 65, 354-362.
Gross, N. et al., "Role of the Parasympathetic System in Airway Obstruction Due to Emphysema," New England Journal of Medicine, 1984, 16 311 (7), 421-425.
Hancox, RJ et al., "Randomised trial of an inhaled B2 agonist, inhaled corticosteroids and their combination in the treatment of asthma," Thorax, 54: 482-487 (1999).
Hardman, J. et al., Eds., Goodman and Gilman's: The Pharmacological Basis of Therapeutics, Ninth Edition, McGraw-Hill, New York, 1996, Chapter 28: Drugs Used in the Treatment of Asthma by W. Serafin, pp. 659-682.
Instructions for Medicine, The Merck Manual, M., "MIR", vol. 2, p. 693.
English Translation of Instructions for Medicine, The Merck Manual, M., "MIR", 1997, vol. 2, p. 693.
Johnson, M., "Salmeterol," Medicinal Research Reviews, 1995, 15 (3), 225-257.
Lopez-Vidiero, M. et al., "Effect of Atropine on Sputum Production," Thorax, 1975, 30, 543-547.
Lund, H. et al., "Quaternization Reactions," Acta Chemica Scandinavica, 1973, 27, 383-390.
Lygo, B. et al., "Asymmetric Approaches to 2-Hydroxymethylquinuclidine Derivatives," Tetrahedron, 1999, 55, 2795-2810.
Maesen, F.P.V. et al., "Ba 679 Br, A New Long-Acting Antimuscarinic Bronchodilator: A Pilot Dose-Escalation Study in COPD," European Respiratory Journal, 1993, 6, 1031-1036.
Martin, L. "Drugs for Asthma/COPD—A Medical Primer for Physicians," http://www/lakesidepress.com/pulmonary/Asthma-Rx.html (updated Feb. 1999).
Merck Manual of Diagnosis and Therapy, Robert Berkow ed., 16th Edition, p. 646-657 (1992).
Mery, P-F. et al., "Muscarinic Regulation of the L-Type Calcium Current in Isolated Cardiac Myocytes," Life Sciences, 1997, 60, (13-14), 1113-1120.
Nishikawa, M. et al., "Effect of Short and Long-Acting 2-Adrenoceptor Agonists on Pulmonary 2-Adrenoceptor Expression in Human Lung," European Journal of Pharmacology, 1996,318, 123-129.
Nishimura, et al., "Additive effect of oxitropium bromide in combination with inhaled corticosteroids in the treatment of elderly patients with chronic asthma," Allergology International 48: 85-88 (1999).
Noronha-Blob, L et al., Stereoselective antimuscarininc effects of 3-quinuclidinyl atrolactate and 3-quinuclidinyl xanthene-9-carboxylate, European Journal of Pharmacology 211:97-103 (1992).
Parfitt, K., Ed., Martindale: The Complete Drug Reference, Thirty-Second Edition, 1999, 745-747.
Rang, H et al., Eds., Pharmacology, Third Edition, 1995, Chapter 17, "The Respiratory System," pp. 351-366.
Rang, HP et al., "Pharmacology," Churchill Livingston Inc., pp. 358-361 (1995).
Rees, PJ "Bronchodilators in the therapy of chronic obstructive pulmonary disease," Eur. Respir. Mon. 7:135-149 (1998).
Rennard, SI, (1998) "Anticholinergics and beta2-agonists: Efficacy, Safety and Combination Therapy in Chronic Obstructive Pulmonary Disease," Chapter 9, Barnes and Bulst (Ed.) The Role of Anticholinergics in Chronic Obstructive Pulmonary Disease and Chronic Asthma, pp. 137-144, Gardiner-Caldwell Communications Limited.
Rzeszotarski, W. et al., "Affinity and Selectivity of the Opitcal Isomers of 3-Quinuclidinyl Benzilate and Related Muscarinic Antagonists," Journal of Medicinal Chemistry, 1988, 31, 1463-1466.
Schmidt, R. "Dose-Finding Studies in Clinical Drug Development," Eur J Clin Pharmacol, 1988. 34:15-19.
Serafin, W. "Drugs Used in the Treatment of Asthma," Goodman Gilman's The Pharmacological Basis of Therapeutics, Chapter 28 , Joel G. Hardman et al eds, 9th Edition, pp. 659-682 (1996).

(56) **References Cited**

OTHER PUBLICATIONS

Sharma, V. et al. "Does Mammalian Heart Contain Only the M2-Muscarinic Receptor Subtype?," Life Sciences, 1997, 60 (13-14), 1023-1029.
Spitzer, W. et al., "The Use of P-Agonists and the Risk of Death and Near Death from Asthma," New England Journal of Medicine, 1992, 326, 501-506.
Suissa, S. et al., "Patterns of Increasing P-Agonist Use and the Risk of Fatal or Near-Fatal Asthma," European Respiratory Journal, 1994, 7, 1602-1609.
Tavakkoli et al., "Drug Treatment of Asthma in the 1990s, Achievements and New Strategies," Drugs, 57(1): 1-8 (1999).
Teixera et al., "Phosphodiesterase (PDE) 4 inhibitors: anti-inflammatory drugs of the future," TiPS, 18:164 (May 1997).
The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, 1999, Foreword and Chapter 68, "Chronic Obstructive Airway Disorders," pp. 555-583.
Theolair™ Prescribing Information, 3M Phamaceuticals, 601000, May 1998, 12 pages.
Torphy, T. "Phosphodiesterase Isozymes, Molecular Targets for Novel Antiasthma Agents," Am. J. Respit. Crit. Care Med., 157:351-370 (1998).
Traunecker, W. et al., "Pharmacological Effects of a Combination of Fenoterol Hydrobromide and Ipratropium Bromide," Respiration, 1986, 50 (4), 244-251.
Walsh, D. et al., "Synthesis and Antiallergy Activity of 4-(Diarylhydroxymethyl)-1[3-(aryloxy)propyl]piperidines and Structurally Related Compounds," Journal of Medicinal Chemistry, 1989,32, 105-118.
Zaagsma, J. et al. "Muscarinic Control of Airway Function," Life Sciences, 1997, 60 (13-14), 1061-1068.
Etzler, F M. et al., "Particle size analysis; a comparative study of various methods", Part. Part. Syst. Charact., vol. 12, Oct. 1995; pp. 217-224.
Le Souef, P, "The meaning of lung dose", Allergy, vol. 54, Mar. 1999, pp. 93-96.
6001 Chemical Abstracts, Columbus, Ohio, US. vol. 104(19). XP-002128290, p. 659. (1 page total).
Burtner, R. and Cusic, J. W. (1943). "Antispasmodics, II. Basic Esters of Some Polynuclear Carboxylic Acids," *J. Am. Chem. Soc.* 65:1582-1585.
Cohen, V. I. et al. (1992). "Synthesis and Receptor Affinities of New 3-Quinuclidinyl α-Heteroaryl-α-aryl-α-Hydroxyacetates," *J. Pharm Sciences* 81:326-329.
Davis, M. A. et al. (1963). "New Psychotropic Agents. VI. Basic Esters of 5-Hydroxydibenzo[a,d] cycloheptadiene-5-carboxylic Acid," *J. Med. Chem* 6:513-516.
Davis. M. A. et al (1964). "Anticonvulsants. I. Dibenzo[a,d]cycloheptadiene-5-carboxamide and Related Compounds," *J. Med. Chem.* 7:88-94.
Grob, C. A. and Brenneisen, P. (1958). "Die Synthese von 4-Brom- und 4-Hydroxy-Chinuclidin," *Helv. Chim. Acta* 41:1184-1191.
Heacock, R.A. et al. (1958). "Materials and Methods," *The Annals of Applied Biology,* Marsh R. W. and Thomas, I, eds, Cambridge at the University Press, vol. 46, pp. 356-365.
Konzett, H. and Rössler, R. (1940). "Versuchsanordnung zu Untersuchungnen an der Bronchialmuskulatur," *Arch. Exp. Path. Pharmacol.* 195:71-74.
Kumazawa, T. et al. (1994). "Inhibitors of Acyl-CoA:Cholesterol Acyltransferase. 1. Synthesis and Hypocholesterolemic Activity of Dibenz[b,e]oxepin-11carboxanilides," *J. Med. Chem.* 37(6): 804-810.
Larsson, L. et al. (1974). "The Hydrogen Bond Condition in Some Anticholinergic Esters of Glycolic Acids. I" *Acta Pharm. Suec.* 11(3):304-308.
May, E. L and Mossettig, E. (1948). "Studies in the Anthracene Series. V. A Novel Rearrangement in the Reaction of Halomethyl Ketones with Secondary Amines," *J. Am. Chem. Soc.* 70: 1077-1079.
Meyers, A. I. et al. (1980). "Resolution of α-Substituted Mandelic Acids via Chiral Oxazolines Using Pressurized Chromatography," *J. Org. Chem.* 45(14): 2912-2914.
Nyberg, K. et al. (1970). "Investigations of Dithienylglycolic Esters," *Acta Chem. Scand.* 24:1590-1596.
Rigaudy, J. et al. (1959). "Cétones Derivées du Dibenzo[a,d] cycloheptadiène. La Dibenzo-2-,3-6,7 Cycloheptadiènedione-4,5," *Bull. Soc. Chim. France.* 638-643.
Ringdahl, R. et al. (1979). "Facile Preparation of the Enantiomers of 3-Acetoxyquinuclidinol," *Acta Pharm Suec.* 16:281-283.
Sestanj, K. (1971). "A Facile Formation of Dibenzo[a,b] cycloheptenylium Ion by Decarbonylation. Color Reactions of the Cyhemptaminde Metabolites," *Can. J. Chem.* 49:664-665.
Ueda, I. (1975). "The Rearrangement of 10-Bromo-10, 11-Dihydrodibenzo[b,f]thiepin-11-one and Related Compounds in an Alkaline Solution," *Bulletin of the Chemical Society of Japan* 48(8):2306-2309.
Waelbroek, M. et al. (1990). "Binding of Selective Antagonists to Four Muscarinic Receptors (M1 to M4) in Rat Forebrain," *Mol. Pharmacol.* 38:267-273.

* cited by examiner

QUINUCLIDINE DERIVATIVES AND THEIR USE AS MUSCARINIC M3 RECEPTOR LIGANDS

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue; a claim printed with strikethrough indicates that the claim was canceled, disclaimed, or held invalid by a prior post-patent action or proceeding.

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority from Spain application No. 9901580 filed Jul. 14, 1999 and PCT application No. PCT/EP00/06469 filed Jul. 7, 2000, the contents of each are incorporated herein by reference.

This invention relates to new therapeutically useful quinuclidine derivatives, to some processes for their preparation and to pharmaceutical compositions containing them.

The novel structures according to the invention are anti-muscarinic agents with a potent and long lasting effect. In particular, these compounds show high affinity for muscarinic M_3 receptors(Hm3).

In accordance with their nature as M_3 antagonists, the new compounds are suitable for treating the following diseases: respiratory disorders such as chronic obstructive pulmonary disease (COPD), chronic bronchitis, bronchial hyperreactivity, asthma and rhinitis; urological disorders such as urinary incontinence, pollakinuria in neuripenia pollakinuria, neurogenic or unstable bladder, cystospasm and chronic cystitis; and gastrointestinal disorders such as irritable bowel syndrome, spastic colitis, diverticulitis and peptic ulceration.

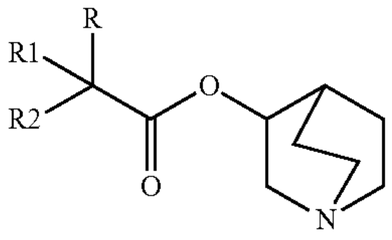
The compounds claimed are also useful for the treatment of the respiratory diseases detailed above in association with β_2 agonists, steroids, antiallergic drugs or phosphodiesterase IV inhibitors.

Compounds of the present invention may also be expected to have anti-tussive properties.

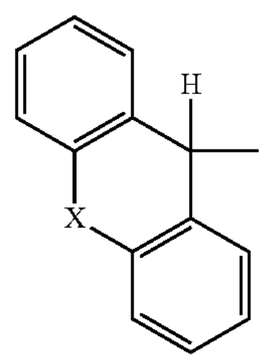
Depending on their nature the new compounds may be suitable for treating vagally induced sinus bradycardia.

Compounds with related structures have been described as anti-spasmodics and anti-cholinergic agents in several patents.

For example, in patent FR 2012964 are described quinuclidinol derivatives of the formula:

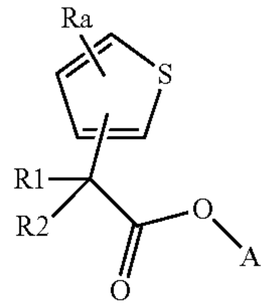


in which R is H, OH or an alkyl group having 1 to 4 carbon atoms; R_1 is a phenyl or thienyl group; and R_2 is a cyclohexyl, cyclopentyl or thienyl group, or, when R is H, R_1 and R_2 together with the carbon atom to which they are attached, form a tricyclic group of the formula:

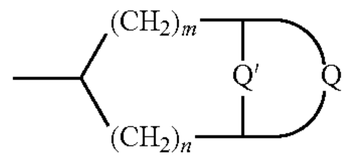


in which X is —O—, —S— or —CH_2—, or an acid addition or quaternary ammonium salt thereof.

EP-418716 describes thienyl carboxylate esters of formula

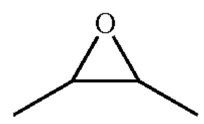


wherein A is a group



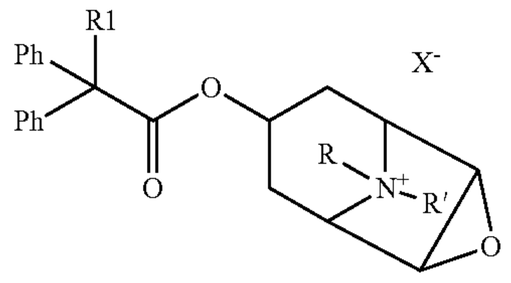
m and n=1 or 2

Q is a —CH_2—CH_2—, —CH_2—CH_2—CH_2—, —CH═CH—, group



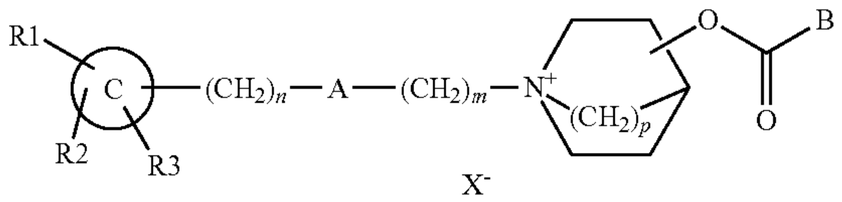
Q' is a ═NR or NRR═ group; R_1 is a thienyl, phenyl, furyl, cyclopentyl or cyclohexyl group, optionally substituted; R_2 is H, OH, C_1-C_4 alkoxy or C_1-C_4 alkyl and R_a is H, F, Cl, CH_3— or —NR.

U.S. Pat. No. 5,654,314 describes compounds of formula:



wherein R is an optionally halo- or hydroxy-substituted C_{1-4} alkyl group; R is a C_{1-4} alkyl group; or R and R═ together form a C_{4-6} alkylene group; X^- is an anion; and R_1 is H, OH, —CH_2OH, C_{1-4} alkyl or C_{1-4} alkoxy.

The present invention provides new quinuclidine derivatives with potent antagonist activity at muscarinic M_3 receptors which have the chemical structure described in formula (I):



wherein:

© is a phenyl ring, a C_4 to C_9 heteroaromatic group containing one or more heteroatoms (preferably selected from nitrogen, oxygen and sulphur atoms), or a naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl or biphenyl group;

R^1, R^2 and R^3 each independently represent a hydrogen or halogen atom, or a hydroxy group, or a phenyl, —OR^4, —SR^4, —NR^4R^5, —$NHCOR^4$, —$CONR^4R^5$, —CN, —NO_2, —$COOR^4$ or —CF_3 group, or a straight or branched lower alkyl group which may optionally be substituted, for example, with a hydroxy or alkoxy group, wherein R^4 and R^5 each independently represent a hydrogen atom, straight or branched lower alkyl group, or together form an alicyclic ring; or R^1 and R^2 together form an aromatic, alicyclic or heterocyclic ring;

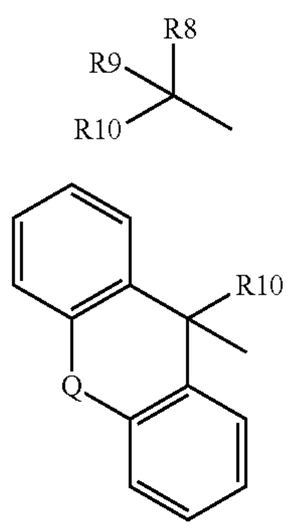
n is an integer from 0 to 4;

A represents a —CH_2—, —CH═CR^6—, —CR^6═CH—, —CR^6R^7—, —CO—, —O—, —S—, —S—(O)—, SO_2 or —NR^6— group, wherein R^6 and R^7 each independently represent a hydrogen atom, straight or branched lower alkyl group, or R^6 and R^7 together form an alicyclic ring;

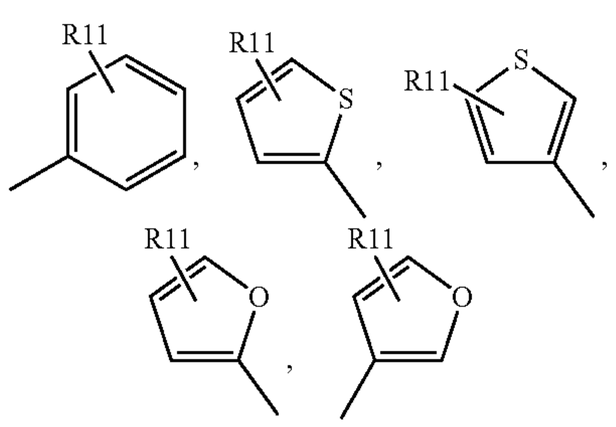
m is an integer from 0 to 8; provided that when m=0, A is not —CH_2—;

p is an integer from 1 to 2 and the substitution in the azoniabicyclic ring may be in the 2, 3 or 4 position including all possible configurations of the asymmetric carbons;

B represents a group of formula i) or ii):



wherein R^{10} represents a hydrogen atom, a hydroxy or methyl group; and R^8 and R^9 each independently represents



wherein R^{11} represents a hydrogen or halogen atom, or a straight or branched lower alkyl group and Q represents a single bond, —CH_2—, —CH_2—CH_2—, —O—, —O—CH_2—, —S—, —S—CH_2— or —CH═CH—, and when i) or ii) contain a chiral centre they may represent either configuration; X represents a pharmaceutically acceptable anion of a mono or polyvalent acid.

In the quaternary ammonium compounds of the present invention represented by formula (I) an equivalent of an anion (X^-)is associated with the positive charge of the N atom. X^- may be an anion of various mineral acids such as, for example, chloride, bromide, iodide, sulfate, nitrate, phosphate, and organic acids such as, for example, acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulfonate and p-toluenesulfonate. X^- is preferably an anion selected from chloride, bromide, iodide, sulphate, nitrate, acetate, maleate, oxalate or succinate. More preferably X^- is chloride, bromide or trifluoroacetate.

The compounds of the present invention represented by the formula (I) described above, which may have one or more assymetric carbons, include all the possible stereoisomers. The single isomers and mixtures of the isomers fall within the scope of the present invention.

If any of R^1 to R^7 or R^{11} represents an alkyl group, it is preferred that said alkyl group contains 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms. In particular it is preferred that any alkyl group is represented by a methyl, ethyl, propyl, including i-propyl, butyl including a n-butyl, sec-butyl and tert-butyl.

The alicyclic and heterocyclic rings mentioned in relation to formula (I) preferably comprise from 3 to 10, preferably from 5 to 7 members. The aromatic rings mentioned in relation to formula (I) above preferably contain from 6 to 14, preferably 6 or 10 members.

Preferred compounds of formula (I) are those wherein © represents a phenyl, pyrrolyl, thienyl, furyl, biphenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl, imidazolyl or benzothiazolyl group, in particular a phenyl, pyrrolyl, or thienyl group; R^1, R^2 and R^3 each independently represent a hydrogen or halogen atom, or a hydroxyl, methyl, tert-butyl, —CH_2OH, 3-hydroxypropyl, —OMe, —NMe_2, —NHCOMe, —$CONH_2$, —CN, —NO_2, —COOMe or —CF_3 group, in particular a hydrogen atom, a hydroxy group or a halogen atom, wherein the halogen atom is preferably fluorine; n=0 or 1; m is an integer from 1 to 6, particularly 1, 2 or 3; A represents a —CH_2—, —CH═CH—, —CO—, —NH—, —NMe—, —O— or —S— group, in particular a —CH_2—, —CH═CH— or —O— group.

It is also preferred that p=2 and the substituent group —OC(O)B attached to the azoniabicyclo[2.2.2]octane is at the 3 position, preferably having the (R) configuration.

Further preferred compounds of formula I are those wherein B is a group of formula i) or ii) as defined above wherein, if B is a group of formula (i), R^8 and R^9 each independently represent a phenyl, 2-thienyl, 3-thienyl, 2-furyl or 3-furyl group, wherein R^{11} is hydrogen atom; and, if B is a group of formula (Ii), Q represents a single bond, —CH_2—, —CH_2—CH_2—, —O— or —S— group, in particular a single bond, —CH_2—, —CH_2—CH_2— or —O— group, most preferably a single bond or —O— group; and in any case R^{10} is a hydrogen atom or a hydroxy or methyl group; and when i) or ii) contain a chiral centre they may represent either the (R) or the (S) configuration.

Most preferably the —OC(O)B group in formula (I) is diphenylacetoxy, 2-hydroxy-2,2-diphenyl-acetoxy, 2,2-di-

phenylpropionyloxy, -hydroxy-2-phenyl-2-thien-2-yl-acetoxy, 2-furan-2-yl-2-hydroxy-2-phenylacetoxy, 2,2-dithien-2-ylacetoxy, 2-hydroxy-2,2-di-thien-2-ylacetoxy, 2-hydroxy-2,2-di-thien-3-ylacetoxy, 9-hydroxy-9[H]-fluorene-9-carbonyloxy, 9-methyl-9[H]-fluorene-9-carbonyloxy, 9[H]-xanthene-9-carbonyloxy, 9-hydroxy-9[H]-xanthene-9-carbonyloxy, 9-methyl-9[H]-xanthene-9-carbonyloxy, 2,2-bis(4-fluorophenyl)-2-hydroxyacetoxy, 2-hydroxy-2,2-di-p-tolylacetoxy, 2,2-difuran-2-yl-2-hydroxy acetoxy, 2,2-dithien-2-ylpropionyloxy, 9,10-dihydroanthracene-9-carbonyloxy, 9 [H]-thioxanthene-9-carbonyloxy, or 5[H]-dibenzo[a,d]cycloheptene-5-carbonyloxy. Especially preferred compounds are those wherein the —OC(O)B group in formula (I) is diphenylacetoxy, 2-hydroxy-2,2-diphenyl-acetoxy, 2,2-diphenylpropionyloxy, 2-hydroxy-2-phenyl-2-thien-2-yl-acetoxy, 2-furan-2-yl-2-hydroxy-2-phenylacetoxy, 2,2-dithien-2-ylacetoxy, 2-hydroxy-2,2-di-thien-2-ylacetoxy, 2-hydroxy-2,2-di-thien-3-ylacetoxy, 9-hydroxy-9[H]-fluorene-9-carbonyloxy, 9-methyl-9[H]-fluorene-9-carbonyloxy, 9[H]-xanthene-9-carbonyloxy, 9-hydroxy-9[H]-xanthene-9-carbonyloxy or 9-methyl-9[H]-xanthene-9-carbonyloxy.

The most preferred compounds of formula (I) are those wherein the azoniabicyclo group is substituted on the nitrogen atom with a 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 4-phenylbutyl, 3-phenylpropyl, 3-[2-hydroxyphenoxy]propyl, 3-[4-fluorophenoxy]propyl, 2-benzyloxyethyl, 3-pyrrol-1-ylpropyl, 2-thien-2-ylethyl, 3-thien-2-ylpropyl, 3-phenylaminopropyl, 3(methylphenylamino)propyl, 3-phenylsulfanylpropyl, 3-o-tolyloxypropyl, 3-(2,4,6-trimethylphenoxy)propyl, 3-(2-tert-butyl-6-methylphenoxy)propyl, 3-(biphenyl-4-yloxy)propyl, 3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)-propyl, 3-(naphthalen-2-yloxy) propyl, 3-(naphthalen-1-yloxy) propyl, 3-(2-chlorophenoxy)propyl, 3-(2,4-difluorophenoxy)propyl, 3-(3-trifluoromethyl phenoxy)propyl, 3-(3-cyanophenoxy) propyl, 3-(4-cyanophenoxy)propyl, 3-(3-methoxyphenoxy) propyl, 3-(4-methoxyphenoxy)propyl, 3-(benzo[1,3]dioxol-5-yloxy) propyl, 3-(2-carbamoylphenoxy)propyl, 3-(3-dimethylaminophenoxy)propyl, 3-(4-nitrophenoxy)propyl, 3-(3-nitrophenoxy)propyl, 3-(4-acetylaminophenoxy) propyl, 3-(3-methoxycarbonylphenoxy)propyl, 3-[4-(3-hydroxypropyl) phenoxy]propyl, 3-(2-hydroxymethylphenoxy)propyl, 3-(3-hydroxymethylphenoxy)propyl, 3-(4-hydroxymethylphenoxy)propyl, 3-(2-hydroxyphenoxy) propyl, 3-(4-hydroxyphenoxy)propyl, 3-(3-hydroxyphenoxy)propyl, 4-oxo-4-thien-2-ylbutyl, 3-(1-methyl-[1H]-imidazol-2-ylsulfanyl)propyl, 3-(benzothiazol-2-yloxy)propyl, 3-benzyloxypropyl, 6-(4-phenylbutoxy) hexyl, 4-phenoxybutyl, or 2-benzyloxyethyl group. Especially preferred compounds are those wherein the azoniabicyclo group is substituted on the nitrogen atom with a 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 4-phenylbutyl, 3-phenylpropyl, 3-[2-hydroxyphenoxy]propyl, 3-[4-fluorophenoxy]propyl, 2-benzyloxyethyl, 3-pyrrol-1-ylpropyl, 2-thien-2-ylethyl or 3-thien-2-ylpropyl group.

The following compounds are intended to illustrate but not to limit the scope of the present invention.

3(R)-Diphenylacetoxy-1-(3-phenoxy-propyl)-1-azoniabicyclo[2.2.2]octane; bromide

3(R)-(2-Hydroxy-2,2-diphenyl-acetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide

3(R)-(2,2-Diphenylpropionyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide

3(R)-(2-Hydroxy-2-phenyl-2-thien-2-yl-acetoxy)-1-(3-phenoxypropyl)-1-azonia-bicyclo[2.2.2]octane; bromide

3(R)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane; bromide

3(R)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide

3(R)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide

3(R)-(2,2-Dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azonia-bicyclo[2.2.2]octane; bromide

3(R)-(2-Hydroxy-2,2-di-thien-2-ylacetoxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; bromide

3(R)-(2-Hydroxy-2,2-di-thien-2-ylacetoxy)-1-(4-phenylbutyl)-1-azoniabicyclo[2.2.2]octane; bromide

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxy-propyl)-1-azonia-bicyclo[2.2.2]octane; bromide

1-[3-(4-Fluorophenoxy)propyl]-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo[2.2.2]octane; chloride

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(2-hydroxyphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(2-thien-2-yl-ethyl)-1-azoniabicyclo[2.2.2]octane; bromide

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-thien-2-yl-propyl)-1-azoniabicyclo[2.2.2]octane; bromide

1-(2-Benzyloxyethyl)-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

3(R)-(2-Hydroxy-2,2-dithien-3-ylacetoxy)-1-(3-phenoxy-propyl)-1-azoniabicyclo[2.2.2]octane; bromide

1-(3-phenylallyl)-3(R)-(9-Hydroxy-9[H]-fluorene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; bromide

3(R)-(9-Hydroxy-9[H]-fluorene-9-carbonyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide

3(R)-(9-Hydroxy-9[H]-fluorene-9-carbonyloxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; bromide

3(R)-(9-Hydroxy-9H-fluorene-9-carbonyloxy)-1-(3-thien-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide

3(R)-(9-Methyl-9[H]-fluorene-9-carbonyloxy)-1-(3-phenyl-allyl)-1-azoniabicyclo[2.2.2]octane; bromide

3(R)-(9-Methyl-9[H]-fluorene-9-carbonyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide

1-(4-Phenylbutyl)-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; bromide

1-(2-Phenoxyethyl)-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; bromide

1-(3-Phenoxypropyl)-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; bromide

1-Phenethyl-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; bromide

3(R)-(9-Hydroxy-9[H]-xanthene-9-carbonyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide

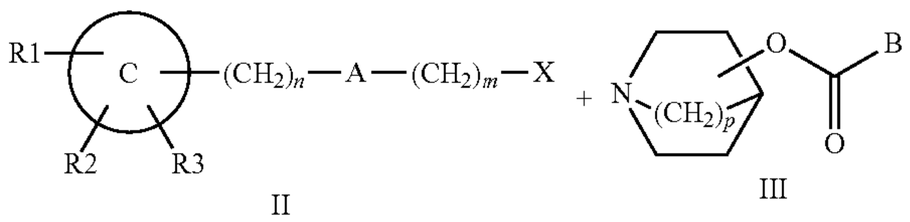
3(R)-(9-Hydroxy-9[H]-xanthene-9-carbonyloxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; bromide

3(R)-(9-Hydroxy-9H-xanthene-9-carbonyloxy)-1-(3-thien-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide

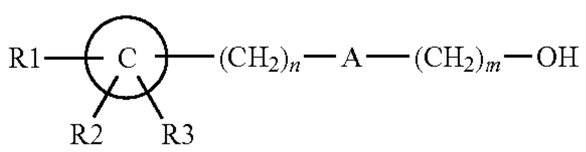
3(R)-(9-Methyl-9[H]-xanthene-9-carbonyloxy)-1-(3-phenoxy-propyl)-1-azonia-bicyclo[2.2.2]octane; bromide

The present invention also provides processes for preparing compounds of formula (I).

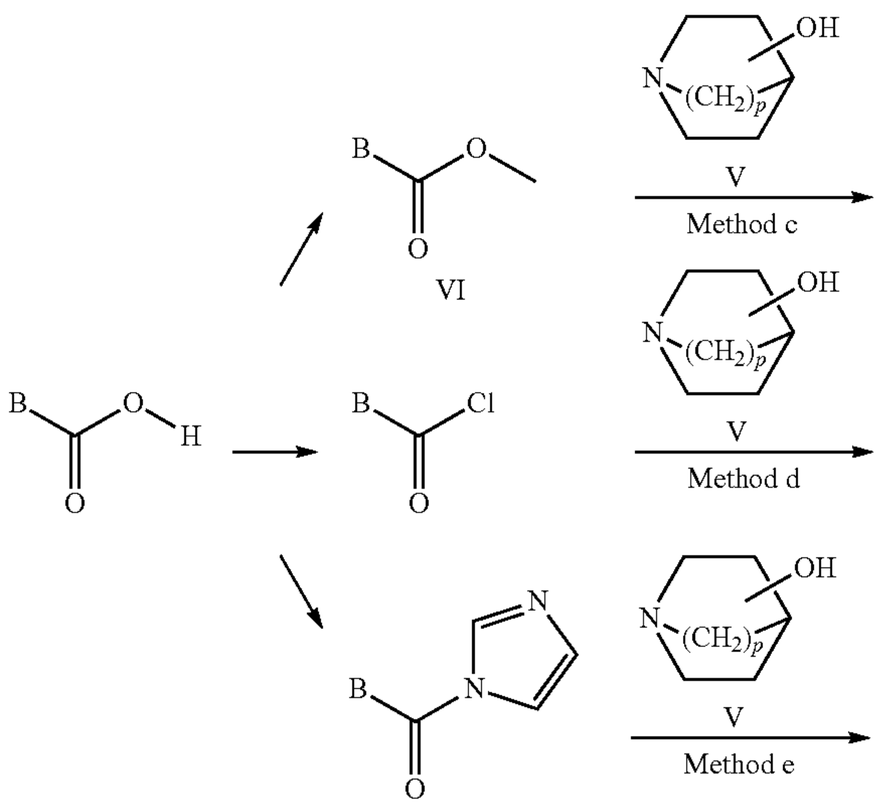
The quaternary ammonium derivatives of general Formula I, may be prepared by reaction of an alkylating agent of general Formula II with compounds of general Formula III. In Formulas I, II and III, R^1, R^2, R^3, ©, A, X, B, n, m and p are as defined above.



This alkylation reaction may be carried out by two different experimental procedures, a) and b) which are described below. In particular method b) provides a new experimental process, using solid phase extraction methodologies, that allows the parallel preparation of several compounds. Methods a) and b) are described in the experimental section. Compounds of general Formula II which are not commercially available have been prepared by synthesis according to standard methods. For example, compounds wherein n=0 and A=—O—, —S— or —$NR^6{}_1$ wherein R^6 is as defined above, were obtained by reaction of the corresponding aromatic derivative or its potassium salt with an alkylating agent of general formula Y—(CH_2)m-X, wherein X may be a halogen and Y may be a halogen or a sulphonate ester. In other examples, compounds of general Formula II, where n>=1 were synthesised from the corresponding alcohol derivative of general Formula IV by known methods.



Compounds of general Formula III may be prepared by three different methods c, d and e illustrated in the following scheme and detailed in the experimental section.



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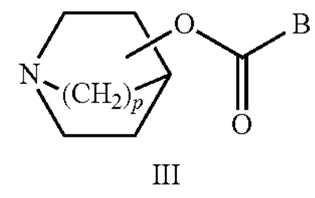
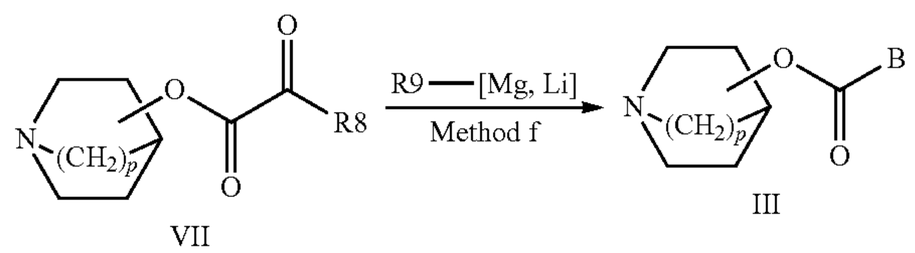


Some compounds of general formula III where B is a group of formula i), R^8 and R^9 are as described above and R^{10} is a hydroxy group, may also be prepared from the glyoxalate esters of general formula VII by reaction with the corresponding organometallic derivative.



Compounds of general formula VII may be prepared from the corresponding glyoxylic acids following the standard methods c, d and e described above and detailed in the experimental section. The glyoxalate derivatives of formula VII where R^8 is a 2-thienyl or 2-furyl group have not been described before.

The following compounds are examples of compounds of general formula III and VII which have not been described before:

9-Methyl-9[H]-fluorene-9-carboxylic acid 1-azabicyclo [2.2.2]oct-3(R)-yl ester (intermediate I-1c);

9-Methyl-9[H]-xanthene-9-carboxylic acid 1-azabicyclo [2.2.2]oct-3(R)-yl ester (intermediate I-1d);

2-Hydroxydithien-2-yl-acetic acid 1-azabicyclo[2.2.2]oct-4-yl ester (intermediate I-4a).

Oxothien-2-yl-acetic acid 1-azabicyclo[2.2.2]oct-4-yl ester (intermediate I-4b).

Oxothien-2-yl-acetic acid 1-azabicyclo[2.2.2]oct-3(R)-yl ester (intermediate I-4 g).

Oxofuran-2-yl-acetic acid 1-azabicyclo[2.2.2]oct-3(R)-yl ester (intermediate I-4e).

2-Hydroxy-2,2-difuran-2-yl-acetic acid 1-azabicyclo[2.2.2]oct-3(R)-yl ester (intermediate I-4d).

Compounds of Formula V could be:

4-hydroxy-1-azabicyclo[2.2.1]heptane, described in WO150080

4-hydroxy-1-azabicyclo[2.2.2]octane, described in Grob, C. A. et. al. Helv. Chim. Acta (1958), 41, 1184-1190

3(R)-hydroxy-1-azabicyclo[2.2.2]octane or 3(S)-hydroxy-1-azabicyclo[2.2.2]octane, described in Ringdahl, R. Acta Pharm Suec. (1979), 16, 281-283 and commercially available from CU Chemie Uetikon GmbH.

The following examples are intended to illustrate, but not to limit, the experimental procedures that have been described above.

The structures of the prepared compounds were confirmed by ^{1}H-NMR and MS. The NMR were recorded using a Varian 300 MHz instrument and chemical shifts are expressed as parts per million (δ) from the internal reference tetramethyl silane. Their purity was determined by HPLC, using reverse phase chromatrography on a Waters instrument, with values greater than 95% being obtained. Molecular ions were obtained by electrospray ionization mass spectometry on a Hewlett Packard instrument.

Method-a

EXAMPLE 20

Preparation of 3(R)-(2-Furan-2-yl-2-hydroxy-2-phenyl acetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane, Bromide

200 mg of (Furan-2-yl)-hydroxy-phenylacetic acid 1-azabicyclo[2.2.2]oct-3(R)-yl ester (0.6 mmol) were suspended in 4 ml of CH3CN and 6 ml of CHCl3. To this suspension were added 0.48 ml (3 mmol) of 3-phenoxypropyl bromide. After stirring for 72 h at room temperature in inert atmosphere, solvents were evaporated. Ether was added and the mixture stirred. The solid obtained was filtered and washed several times with ether. The yield was 0.27 g (83%) of title compound as a mixture of diastereomers.

^{1}H-NMR (DMSO-d6): δ 1.50-2.20 (m, 6H), 2.25 (m, 1H), 3.10 (m, 1H), 3.20-3.60 (m, 6H), 3.95 (m, 1H), 4.05 (m, 2H), 5.20 (m, 1H), 6.25-6.35 (double dd, 1H), 6.45 (m, 1H), 6.95 (m, 4H), 7.30-7.50 (m, 7H), 7.70 (m, 1H); MS [M-Br]$^+$: 462; mp 166° C.

Method-b

EXAMPLE 51

Preparation of 3(R)-(2-Hydroxy-2,2-di-thien-2-yl acetoxy)-1-[3-(naphthalen-1-yloxy)propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

60 mg (0.17 mmols) of hydroxy-dithien-2-yl-acetic acid 1-aza-bicyclo[2.2.2]oct-3(R)-yl ester were dissolved in 1 ml of dmso. To this solution 188 mg (0.85 mmol) of 3-(naphthalen-1-yloxy)-propyl chloride were added. After stirring overnight at room temperature, the mixture was purified by solid phase extraction with a cation exchange Mega Bond Elut cartridge, previously conditioned at pH=7.5 with 0.1 M NaH2PO4 buffer. The reaction mixture was applied to the cartridge and washed first with 2 ml of DMSO and then three times with 5 ml of CH3CN, rinsing away all starting materials. The ammonium derivative was eluted with 5 ml of 0.03 M TFA solution in CH3CN:CHCl3 (2:1). This solution was neutralized with 300 mg of poly(4-vinylpyridine), filtered and evaporated to dryness.

The yield was 17 mg (15%) of title compound. ^{1}H-NMR (DMSO-d6): δ 1.7-2.1 (m, 4H), 2.2-2.4 (m, 3H), 3.2-3.6 (m, 7H), 4.0 (m, 1H), 4.2 (t, 2H), 5.25 (m, 1H), 7.0 (m 3H), 7.2 (m, 2H), 7.4-7.6 (m, 7H), 7.85 (d, 1H), 8.2 (d, 1H); MS [M-CF_3COO]$^+$: 534.

Method-c

Methyl ester derivatives of general Formula VI were prepared by standard methods of esterification from the corresponding carboxylic acid or following the procedures described in examples I-1e, I-1f and I-1g or according to procedures described in literature: FR 2012964; Larsson. L et al. Acta Pharm. Suec. (1974), 11(3), 304-308; Nyberg, K. et. al. Acta Chem. Scand. (1970), 24, 1590-1596; and Cohen, V. I. et. al. J. Pharm. Sciences (1992), 81, 326-329.

EXAMPLE I-1a

Preparation of (Furan-2-yl)hydroxyphenylacetic acid 1-azabicyclo[2.2.2]oct-3(R)-yl Ester

3.24 g (0.014 mols) of (Furan-2-yl)-hydroxy-phenylacetic acid methyl ester were dissolved in 85 ml of toluene. To this solution were added 2.08 g (0.016 mols) of 3-(R)-hydroxy-1-azabicyclo[2.2.2]octane and 0.224 g (5.6 mmols) of HNa (60% dispersion in mineral oil). The mixture was refluxed with continuous removal of distillate and when necessary replacement with fresh toluene for 1.5 hours. The cooled mixture was extracted with 2N HCl acid, the aqueous layer washed with ethyl acetate, basified with K2CO3 and extracted with CHCl3. The organic layer was dried over Na2SO4 and evaporated. The oil obtained (3.47 g) crystallised after cooling at room temperature. This solid was suspended in hexane and filtered. The yield was 2.5 g (54%) of a mixture of diasteroisomers, mp: 140-142° C.; GC/MS [M]$^+$: 327; ^{1}H-NMR (CDCl3): δ 1.20-1.70 (m, 4H), 1.90-2.10 (m, 1H), 2.45-2.80 (m, 5H), 3.10-3.30 (m, 1H), 4.8 (bs, OH), 4.90-5.0 (m, 1H), 6.20 (m, 1H), 6.35 (m, 1H), 7.30-7.50 (m, 4H), 7.60-7.70 (m, 2H).

After four crystallizations of 0.5 g of this mixture from boiling acetonitrile, 0.110 g of a pure diastereomer(I) were obtained. From the mother liquors of crystallization was obtained the other diastereomer (2). (*:configuration not assigned). Diastereomer 1 was hydrolysed to yield (+)-2-hydroxy-2-phenyl-2-furan-2-ylacetic acid as a pure enantiomer, $[\alpha]^{25}_D$=+5.6 (c=2, EtOH). Diastereomer 2 was hydrolysed to yield (−)-2-hydroxy-2-phenyl-2-furan-2-ylacetic acid as a pure enantiomer, $[\gamma]^{25}_D$=−5.7 (c=2, EtOH).

Diastereomer 1: 2(*)—(Furan-2-yl)hydroxyphenylacetic Acid 1-azabicyclo[2.2.2]oct-3(R)-yl Ester.

^{1}H-NMR (CDCl3): δ 1.20-1.70 (m, 4H), 1.90 (m, 1H), 2.45-2.50 (m, 1H), 2.50-2.80 (m, 4H), 3.10-3.20 (m, 1H), 4.8 (bs, OH), 4.90-5.0 (m, 1H), 6.20 (m, 1H), 6.35 (m, 1H), 7.30-7.50 (m, 4H), 7.60-7.70 (m, 2H).

Diastereomer 2: 2(*)—(Furan-2-yl)hydroxyphenylacetic Acid 1-azabicyclo[2.2.2]oct-3(R)-yl Ester.

^{1}H-NMR (CDCl3): δ 1.20-1.70 (m, 4H), 2.10 (m, 1H), 2.50-2.80 (m, 5H), 3.20-3.30 (m, 1H), 4.8 (bs, OH), 4.90-5.0 (m, 1H), 6.20 (m, 1H), 6.35 (m, 1H), 7.30-7.50 (m, 4H), 7.60-7.70 (m, 2H).

EXAMPLE I-1b

Preparation of Furan-2-ylhydroxythien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)-yl Ester

Prepared as in example I-1a. The yield was 3.06 g (64.3%) of a mixture of diastereoisomers, mp: 1721C; GC/MS [M]$^+$: 333; ^{1}H-NMR (DMSO-d6): δ 1.21-1.27 (m, 1H), 1.41-1.60 (m, 3H), 1.87 (m, 1H), 2.36-2.69 (m, 5H), 3.02-3.14 (m, 1H), 4.75-4.82 (m, 1H), 6.24-6.25 (m, 1H), 6.42-6.45 (m, 1H), 7.01-7.06 (m, 1H), 7.11-7.14 (m, 2H), 7.51-7.54 (m, 1H), 7.66-7.69 (m, 1H).

EXAMPLE I-1c

Preparation of 9-Methyl-9[H]-fluorene-9-carboxylic Acid 1-azabicyclo[2.2.2]oct-3(R)-yl Ester

Prepared as in example I-1a. The yield was 3.34 g of an oil (80%). This product was solidified by formation of the oxalate salt (1:1), mp: 1861C. MS [M free base+1]$^+$: 334.

Oxalate salt, ^{1}H-NMR (DMSO-d6): δ 1.43-1.55 (m, 2H), 1.68-1.78 (m, 2H), 1.75 (s, 3H), 2.02 (m, 1H), 2.70-2.90 (m,

1H), 2.92-3.15 (m, 4H), 3.50-3.57 (m, 1H), 4.88 (m, 1H), 7.35-7.47 (m, 4H), 7.62-7.70 (m, 2H), 7.89-7.91 (m, 2H).

EXAMPLE I-1d

Preparation of 9-Methyl-9[H]-xanthene-9-carboxylic Acid 1-azabicyclo[2.2.2]oct-3(R)-yl Ester

Prepared as in example I-1a. The yield was 1.91 g of an oil (53%). This product was solidified by formation of the oxalate salt (1:1), mp: 1521C. MS [M free base+1]$^+$: 350.

Oxalate salt, ^{1}H-NMR (DMSO-d6): δ 1.20-1.30 (m, 1H), 1.40-1.52 (m, 1H), 1.64-1.81 (m, 2H), 1.90 (s, 3H), 2.0 (m, 1H), 2.53-2.66 (m, 1H), 2.71-2.76 (m, 1H), 2.97-3.10 (m, 3H), 3.44-3.52 (m, 1H), 4.90-4.92 (m, 1H), 7.12-7.18 (m, 4H), 7.32-7.38 (m, 2H), 7.43-7.48 (m, 2H), 8.0-9.8 (bs, 1H, H+).

EXAMPLE I-1e

Preparation of 9-Methyl-9[H]-fluorene-9-carboxylic Acid Methyl Ester

Lithium diisopropylamide (26.7 ml of a 2M solution in heptane/tetrahydrofurane/ethylbenzene, 0.053 mol) was added to a stirred solution of 9[H]-fluorene-9-carboxylic acid (5 g, 0.0237 mol) in THF (70 ml) at between 0 and 51C in N_2 atmosphere. The mixture was warmed to room temperature and refluxed 1.5 hours. The reaction mixture was cooled to room temperature and a solution of CH3I (1.85 ml, 0.03 mol) in THF (1.85 ml) was added. The mixture was stirred overnight at room temperature and evaporated. To the residue in MeOH (70 ml) was added concentrated sulfuric acid (3.9 ml) in MeOH (25 ml), the mixture was refluxed for 2 hours and evaporated. The residue was partitioned between chloroform and saturated K2CO3 solution. The aqueous layer was extracted again with chloroform and the organic layers were combined, washed with water, dried over sodium sulphate and evaporated to dryness to obtain 5.73 g of a brown oil. This product was purified by column chromatography (silica gel, hexane/ethyl acetate 95:5) to yield 4.43 g (78.5%) of a pure product, structure confirmed by ^{1}H-NMR.

^{1}H-NMR (CDCl3): δ 1.80 (s, 3H), 3.60 (s, 3H), 7.50-7.65 (m, 4H), 7.75 (m, 2H), 8.0 (m, 2H).

EXAMPLE I-1f

Preparation of 9-Methyl-9[H]-xanthene-9-carboxylic Acid Methyl Ester

Prepared as in example I-1e. The yield was 2.65 g (47.2%). ^{1}H-NMR (CDCl3): δ 1.90 (s, 3H), 3.6 (s, 3H), 7.05-7.35 (m, 8H).

EXAMPLE I-1g

Preparation of 9-Hydroxy-9[H]-xanthene-9-carboxylic Acid Methyl Ester

Lithium diisopropylamide (20.3 ml of a 2M solution in heptane/tetrahydrofurane/ethylbenzene, 0.041 mol) was added to a stirred solution of 7 g (0.029 mol) of 9[H]-xantene-9-carboxylic acid methyl ester (prepared by a standard method) in THF (70 ml) at between 0 and 51C in N_2 atmosphere. The mixture was stirred 1 h at this temperature and then was added by N2 pressure to a dry solution of oxygen in ether at 01C. After 30 min, an equal volum of NaHSO3, 40% aqueous solution, was added, and the reaction mixture was warmed to room temperature and stirred for 30 min. The two layers were separated and the aqueous phase was extracted twice with ethyl acetate. The organic phases were combined, treated with NaHSO3 (40% aqueous solution), washed with water, dried over sodium sulphate and evaporated to dryness to obtain 8.89 g of a brown solid.

This procedure was repeated with 5 g of starting material yielding 6.049 of the same brown solid. The products were combined and purified by column chromatography (silica gel, hexane/ethyl acetate 90:10) to yield 7.60 g (global Rt: 59.4%) of a pure product, structure confirmed by ^{1}H-NMR.

^{1}H-NMR (DMSO-d6): δ 3.5 (s, 3H), 7.0 (s, 1H, OH), 7.2 (m, 4H), 7.4 (m, 2H), 7.55 (m, 2H).

Method-d

EXAMPLE I-2a

Preparation of 10,11-Dihydro-5[H]-dibenzo[a,d] cycloheptane-5-carboxylic Acid 1-azabicyclo[2.2.2] oct-3-(R)-yl Ester

2.15 g of 10,11-Dihydro-5[H]-dibenzo[a,d]cycloheptane-5-carboxylic acid (9.0 mmol) were dissolved in 40 ml of CHCl3 (ethanol free). The solution was cooled at 0° C. and 0.86 ml of oxalyl chloride (9.9 mmols) and a drop of DMF were added. The mixture was stirred and allowed warm to room temperature. After an hour at this temperature the solvents were evaporated and the residue was dissolved in CHCl3 and evaporated again. This procedure was repeated two times. The obtained oil was dissolved in 20 ml of toluene and added to a solution of 1.26 g (9.9 mmol) of 3-(R)-hydroxy-1-azabicyclo[2.2.2]octane in 40 ml of hot toluene. The reaction mixture was refluxed for 2 hours. After cooling the mixture was extracted with 2N HCl acid. The aqueous layer was basified with K2CO3 and extracted with CHCl3. The organic layer was dried over Na2SO4 and evaporated to dryness. The residue was purified by column chromatography (silica gel, CHCl3:MeOH:NH40H, 95:5:0.5). The yield was 1.5 g (48%); mp: 112-113° C.; CG/MS [M]$^+$: 347; ^{1}H-NMR (CDCl3): δ 1.10-1.35 (m, 2H), 1.40-1.52 (m, 1H), 1.52-1.68 (m, 1H), 1.90 (m, 1H), 2.40-2.60 (m, 2H), 2.60-2.77 (m, 3H), 2.83-2.96 (m, 2H), 3.07-3.19 (m, 1H), 3.25-3.40 (m, 2H), 4.80 (m, 2H), 7.10-7.30 (m, 8H). 10,11-Dihydro-5[H]-dibenzo[a,d]cycloheptane-5-carboxylic acid was prepared as described in Kumazawa T. et al., J. Med. Chem., (1994), 37, 804-810.

EXAMPLE I-2b

Preparation of 5[H]-Dibenzo[a,d]cycloheptene-5-carboxylic Acid 1-azabicyclo[2.2.2]oct-3-(R)-yl Ester

Prepared as in example I-2a. The yield was 3.12 g (71%); mp 1291C; MS [M+1]$^+$: 346; ^{1}H-NMR (DMSO-d6): δ 0.90-1.10 (m, 2H), 1.30-1.50 (m, 2H), 1.58 (m, 1H), 2.21-2.26 (m, 2H), 2.47-2.50 (m, 3H), 2.86-2.94 (m, 1H), 4.48-4.51 (m, 1H), 5.33 (s, 1H), 7.0 (m, 2H), 7.29-7.43 (m, 6H), 7.49-7.51 (m, 2H).

5[H]-Dibenzo[a,d]cycloheptene-5-carboxylic acid was prepared as described in M. A. Davis et al; J. Med. Chem., (1964), Vol 7, 88-94.

EXAMPLE I-2c

Preparation of 9,10-Dihydroanthracene-9-carboxylic Acid 1-azabicyclo[2.2.2]oct-3-(R)-yl Ester

Prepared as in example I-2a. The yield was 0.77 g (62.6%); mp 1391C; MS $[M+1]^+$: 334; ^{1}H-NMR (DMSO-d6): δ 1.1-1.2 (m, 1H), 1.25-1.40 (m, 2H), 1.40-1.55 (m, 1H), 1.73 (m, 1H), 2.20 (m, 1H), 2.35-2.65 (m, 4H), 2.90-2.98 (m, 1H), 3.93-4.14 (dd, 2H, J=1.8 Hz, J=4.3 Hz), 4.56 (m, 1H), 5.14 (s, 1H), 7.25-7.35 (m, 4H), 7.35-7.50 (m, 4H).

9,10-Dihydro-anthracene-9-carboxylic acid was prepared as described in E. L. May and E. Mossettig; J. Am. Chem. Soc., (1948), Vol 70, 1077-9.

Method-e

EXAMPLE I-3

Preparation of 2,2-Diphenylpropionic Acid 1-azabicyclo[2.2.2]oct-3(R)-yl Ester

1.1 g (4.8 mmol) of 2,2-diphenylpropionic acid were dissolved in 20 ml of THF. To this solution were added 0.87 g (5.3 mmol) of 1,1=-carbonyldiimidazole and the mixture was refluxed for an hour. The reaction was monitored by TLC following the formation of the imidazolide. When the reaction was completed part of the solvent was evaporated and 0.67 g (5.3 mmol) of 3-(R)-hydroxy-1-azabicyclo[2.2.2] octane were added. The reaction mixture was refluxed for 16 h, cooled, diluted with ether and washed with water. The organic layer was extracted with HCl 2N, the acid solution basified with K2CO3 and extracted with CHCl3. The organic solution was dried over Na2SO4 and evaporated to dryness to yield 1.21 g (75.2%) of an oil that was identified as the title ester.

0.64 g (1.9 mmol) of 2,2-Diphenylpropionic acid 1-azabicyclo[2.2.2]oct-3(R)-yl ester were dissolved in 6 ml of ketone and 0.085 g(0.95 mmol) of oxalic acid were added. After slow addition of ether a white solid was formed. The yield was 0.33 g (45.6%) of oxalate of 2,2-Diphenylpropionic acid 1-azabicyclo[2.2.2]oct-3(R)-yl ester; mp: 1461C; MS [M free base+1]$^+$: 336.

Oxalate salt, ^{1}H-NMR (CDCl3): δ 1.40-1.64 (m, 2H), 1.90 (s, 3H), 1.80-2.0 (m, 2H), 2.31 (m, 1H), 2.73-2.85 (m, 1H), 3.0-3.10 (m, 1H), 3.10-3.32 (m, 3H), 3.53-3.70 (m, 1H), 5.13 (m, 1H), 7.14-7.40 (m, 10H), 9.25 (broad band, 2H, H+).

Method-f

EXAMPLE I-4a

Preparation of 2-Hydroxy-2,2-dithien-2-ylacetic Acid 1-azabicyclo[2.2.2]oct-4-yl Ester

A solution of 2-thienylmagnesium bromide was prepared from 220 mg (9 mmols)of Magnesium and 0.86 ml (9 mmols) of 2-bromothiophene in 15 ml of THF. This solution was added to 1.95 g (7 mmols) of oxothien-2-yl -acetic acid 1-azabicyclo[2.2.2]oct-4-yl ester (intermediate I-4b) dissolved in 20 ml of THF. The mixture was stirred at room temperature for 1 hour, refluxed for 1 hour, cooled, treated with a saturated solution of ammonium chloride and extracted with ether. After removal of the solvent the solid obtained was recrystallised from acetonitrile to yield 1.45 g, of a white solid (56%). ^{1}H-NMR (DMSO-d6): δ 1.80-2.0 (m, 6H), 2.80-3.0 (m, 6H), 7.0 (m, 2H), 7.13 (m, 2H), 7.18 (s, 1H), 7.51 (m, 2H); MS [M+1]: 350; mp 174° C.

EXAMPLE I-4b

Preparation of Oxothien-2-yl-acetic Acid 1-azabicyclo[2.2.2]oct-4-yl Ester

Oxalyl chloride (1.5 ml, 0.017 mol) was added to a solution of oxothien-2-yl-acetic acid (2.24 g, 0,014 mol) and dimethylformamide (one drop) in 30 ml of chloroform (etanol free) at 01C. The mixture was stirred and allowed to warm at room temperature. After one hour the solvent was evaporated. The residue was dissolved in chloroform and evaporated again. This procedure was repeated two times. The product obtained was disolved in CHCl3 (30 ml) and added to a suspension of 1.1 g (0.009 mols) of 4-hydroxy-1-azabicyclo[2.2.2]octane, 1.8 ml of triethylamine (0,013 mols), 0.6 g (0.9 mmols) of N-(methylpolystyrene)-4-(methylamino) pyridine at 70° C. The mixture was refluxed for 1 hour, cooled, filtered and washed with water. The title product was extracted with a solution of diluted HCl, washed with CHCl3, basified with K2CO3 and extracted again with CHCl3. After removal of the solvent 1.47 g (45%) of a solid was obtained. ^{1}H-NMR (dmso): δ 2.0 (m, 6H), 2.9 (m, 6H), 7.35 (m, 1H), 8.05 (m, 1H), 8.3 (m, 1H).

EXAMPLE I-4c

Preparation of (Furan-2-yl)hydroxyphenylacetic Acid 1-azabicyclo[2.2.2]oct-3(R)-yl Ester

Phenylmagnesium bromide, 0.0057 mol (5.7 ml of a solution 1M in THF), was added to a solution of 1.3 g (0.0052 mol) of oxofuran-2-ylacetic acid 1-azabicyclo [2.2.2]oct-3(R)-yl ester (intermediate I-4e-) dissolved in 15 ml of THF, at −701C in N2 atmosphere. The mixture was stirred at this temperature for 10 minuts, and then warmed to room temperature. After 1 hour, the reaction mixture was treated with a saturated solution of ammonium chloride and extracted three times with ethyl acetate The organic phases were combined, washed with water and dried over Na2SO4. After removal of the solvent, the solid obtained was treated with ether and filtered to yield 0.67 g (40%) of a product whose structure was confirmed by ^{1}H-NMR. This compound was also prepared as is described in Example I-1a (Method c). The diastereomers were separated by crystallization from acetonitrile and distinguished by ^{1}H-NMR.

EXAMPLE I-4d

Preparation of 2-Hydroxy-2,2-difur-2-yl-acetic Acid 1-azabicyclo[2.2.2]oct-3(R)-yl Ester

The title compound was synthesised as in example I-4c from intermediate I-4e—and 2-furanyl lithium which was prepared with furane and butyl lithium following a standard method. The yield was 380 mg (8%). ^{1}H-NMR (CDCl3): δ 1.2-1.4 (m, 1H), 1.4-1.8 (m, 3H), 2.0 (m, 1H), 2.6-2.85 (m, 5H), 3.2 (m, 1H), 5.0 (m, 1H), 6.4 (m, 3H), 7.3 (m, 1H), 7.5 (m, 2H). MS $[M+1]^+$: 318.

EXAMPLE I-4e

Preparation of Oxofuran-2-yl-acetic Acid 1-azabicyclo[2.2.2]oct-3(R)-yl Ester

Oxalyl chloride (9.75 ml, 0.112 mol) was added to a solution of oxofuran-2-ylacetic acid (10 g, 0.071 mol) and

dimethylformamide (one drop) in 150 ml of chloroform (etanol free) at 01C. The mixture was stirred and allowed to warm at room temperature. After five hours the solvent was evaporated. The residue was dissolved in chloroform and evaporated again. This procedure was repeated two times. The product obtained was disolved in CHCl3 (150 ml) and a solution of 3(R)-quinuclidinol (10.90 g, 0.086 mol) in CHCl3 (150 ml) was added to this at 01C. The mixture was stirred and allowed to warm at room temperature. After 15 h at r.t., the mixture was washed with 10% aqueous potassium carbonate, then with water, dried over Na2SO4 and evaporated to give 9.34 g (52.5%) of the title compound as a dark oil. Estructure confirmed by NMR.

^{1}H-NMR (CDCl3): δ 1.40-1.60 (m, 1H), 1.60-1.80 (m, 2H), 1.80-2.05 (m, 1H), 2.20 (m, 1H), 2.70-3.10 (m, 5H), 3.30-3.45 (m, 1H), 5.10 (m, 1H), 6.7 (m, 1H), 7.7 (m, 1H), 7.8 (m, 1H).

EXAMPLE I-4f

Preparation of 2-Hydroxy-2-phenyl-2-thien-2-ylacetic Acid 1-azabicyclo[2.2.2]oct-3(R)-yl Ester

The title compound was prepared as described in example I-4c from intermediate I-4 g. The yield was 3 g (33%) as a mixture of diastereomers. After five crystallizations of 1.5 g of this mixture from boiling isopropanol, 0.200 g of a pure diastereomer(1) were obtained. The mother liquors from first crystallization were enriched with the other diastereomer (2). Diastereomer 1 was hidrolysed to yield (+)-2-Hydroxy-2-phenyl-2-thien-2-ylacetic acid as a pure enantiomer, $[\alpha]^{25}_{D}$=+25.4 (c=2, EtOH). This value was assigned to the R configuration provided that in literature (A. I. Meyers et. al. J. Org. Chem.(1980), 45(14), 2913) the 2(S) enantiomer has been described whith $[\alpha]^{25D}$=−20 (c=2, EtOH).

Diastereomer 1: 2(R)-2-Hydroxy-2-phenyl-2-thien-2-ylacetic Acid 1-azabicyclo[2.2.2]oct-3(R)-yl Ester.

^{1}H-NMR (DMSO-d6): δ 1.1-1.25 (m, 1H), 1.3-1.6 (m, 3H), 1.83 (m, 1H), 2.4-2.7 (m, 5H), 3.1 (m, 1H), 4.8 (m, 1H), 7.0 (m, 2H), 7.05 (m, 1H), 7.3-7.4 (m, 3H), 7.4-7.45 (m, 2H), 7.5 (m, 1H).

Diastereomer 2: 2(S)-2-Hydroxy-2-phenyl-2-thien-2-ylacetic Acid 1-aza Bicyclo[2.2.2]oct-3(R)-yl Ester.

^{1}H-NMR (DMSO-d6): δ 1.1-1.25 (m, 1H), 1.4-1.6 (m, 3H), 1.9 (m, 1H), 2.3-2.7 (m, 5H), 3.05 (m, 1H), 4.8 (m, 1H), 7.0 (m, 2H), 7.05 (m, 1H), 7.3-7.4 (m, 3H), 7.4-7.45 (m, 2H), 7.5 (m, 1H).

EXAMPLE I-4g

Preparation of Oxothien-2-yl-acetic Acid 1-azabicyclo [2.2.2]oct-3(R)-yl Ester

Oxalyl chloride (1.34 ml, 0.0154 mol) was added to a solution of oxothien-2-yl-acetic acid (2 g, 0,0128 mol) and dimethylformamide (one drop) in 30 ml of chloroform (etanol free) at 01C. The mixture was stirred and allowed to warm at room temperature. After one hour the solvent was evaporated. The residue was dissolved in chloroform and evaporated again. This procedure was repeated two times. The product obtained was disolved in CHCl3 (30 ml) and a solution of 3(R)-quinuclidinol (1.95 g, 0.0154 mol) in CHCl3 (30 ml) was added to this at 01C. The mixture was stirred and allowed to warm at room temperature. After 1.5 h at r.t., the mixture was washed with 10% aqueous potassium carbonate, then with water, dried over Na2SO4 and evaporated to give 3.14 g (92.6%) of the title compound as a yellow oil. ^{1}H-NMR (CDCl3): δ 1.40-1.50 (m, 1H), 1.50-1.70 (m, 1H), 1.70-1.80 (m, 1H), 1.90-2.0 (m, 1H), 2.15 (m, 1H), 2.70-3.05 (m, 5H), 3.30-3.40 (m, 1H), 5.05 (m, 1H), 7.20 (m, 1H), 7.85 (m, 1H), 8.10 (m, 1H).

Other carboxylic acids of Formula B—C(O)OH, whose preparation (or the syntheses of their derivatives methyl ester, chloride or imidazolide) have not been described in methods c, d, e or in the Examples I-1e, 1-1f and I-1g, and that are not commercially available, could be prepared as is described in the following references:

FR 2012964

M. A. Davis et al; J. Med. Chem. (1963), 6, 513-516.

T. Kumazawa et al; J. Med. Chem, (1994), 37(6), 804-810.

M. A. Davis et al; J. Med. Chem., (1964), Vol (7), 88-94.

Sestanj, K; Can. J. Chem., (1971), 49, 664-665.

Burtner, R.; J. Am. Chem. Soc., (1943), 65, 1582-1585

Heacock R. A. et al.; Ann. Appl. Biol., (1958), 46(3), 352-365.

Rigaudy J. et. al.; Bull. Soc. Chim. France, (1959), 638-43.

Ueda I. et al.; Bull. Chem. Soc. Jpn; (1975), 48 (8), 2306-2309.

E. L. May et. al.; J. Am. Chem. Soc., (1948), 70, 1077-9.

Also included within the scope of the present invention are pharmaceutical composition which comprise, as the active ingredient, at least one quinuclidine derivative of general formula (I) in association with a pharmaceutically acceptable carrier or diluent. Preferably the composition is made up in a form suitable for oral administration.

The pharmaceutically acceptable carrier or diluents which are mixed with the active compound or compounds, to form the composition of this invention are well-known per se and the actual excipients used depend inter alia on the intended method of administration of the composition.

Compositions of this invention are preferably adapted for oral administration. In this case, the composition for oral administration may take the form of tablets, film-coated tablets, liquid inhalant, powder inhalant and inhalation aerosol; all containing one or more compounds of the invention; such preparations may be made by methods well-known in the art.

The diluents which may be used in the preparations of the compositions include those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents, if desired. Tablets or film-coated tablets may conveniently contain between 500 and 1 mg, preferably from 5 to 300 mg of active ingredient. The inhalant compositions may contain between 1Φg and 1,000 Φg, preferably from 10 to 800 Φg of active ingredient. In human therapy, the dose of the compound of general formula (I) depend on the desired effect and duration of treatment; adult doses are generally between 3 mg and 300 mg per day as tablets and 10 Φg and 800 Φg per day as inhalant composition.

Pharmacological Action

The following examples demonstrate the excellent pharmacological activities of the compounds of the present invention. The results on human muscarinic receptors binding and in the test on bronchospasm in guinea pig, were obtained as described below.

Human Muscarinic Receptor Studies.

The binding of [^{3}H]-NMS to human muscarinic receptors was performed according to Waelbroek et al (1990) (1). Assays were carried out at 25° C. Membrane preparations from stably transfected chinese hamster ovary-K1 cells (CHO) expressing the genes for the human muscarinic receptors Hm3 were used.

For determination of IC_{50}, membrane preparations were suspended in DPBS to a final concentration of 89 μg/ml for the Hm3 subtype. The membrane suspension was incubated

with the tritiated compound for 60 min. After incubation the membrane fraction was separated by filtration and the bound radioactivity determined. Non specific binding was determined by addition of 10^{-4} M atropine. At least six concentrations were assayed in duplicate to generate individual displacement curves.

COMPOUNDS No	BINDING TO RECEPTOR M_3 (IC_{50} nM)
ATROPINE	3.2
IPRATROPIUM	3.0
1	31
2	15
7	22
8	4.8
17	14
18	6.6
20	6.8
35	13
36	2.7
39	3.8
44	4.4
53	5.6
71	8.2
74	16
77	3.1
78	5
84	9.9
89	5.4
99	31
100	14
101	7.6
109	31
114	14
116	23
126	13
127	16
128	8.8
129	6.3
136	11
137	6.9
138	19
146	13

(1) M. Waelbroek, M. Tastenoy, J. Camus, J Christophe. Binding of selective antagonists to four muscarinic receptors (M1 to M4) in rat forebrain. Mol. Pharmacol. (1990) 38: 267-273.

Our results show that the compounds of the present invention have affinities for the M_3 receptors which are very similar to the reference compounds.

The compounds of the invention preferably have high affinities for muscarinic M_3 receptors (HM3), preferably human muscarinic receptors. Affinity levels can typically be measured by in vitro assays, for example, as described above.

Preferred compounds of the invention have an IC_{50} (nM) value for M_3 receptors of less than 35, preferably less than 25,20 or 15, more preferably less than 10, 8 or 5.

Test on Bronchospasm in Guinea Pig

The studies were performed according to Konzett and Rössler (2). Aqueous solutions of the agents to be tested were nebulized and inhaled by anaesthetized ventilated male guinea pigs (Dunkin-Hartley). The bronchial response to intravenous acetylcholine challenge was determined before and after drug administration and the percent change in pulmonary resistance at several time-points.

2. Konzett H., Roössler F. Versuchsanordnung zu Untersuchungen ander bronchialmuskulatur. Arch. Exp. Path. Pharmacol. 195: 71-74 (1940)

The compounds of the present invention inhibited the bronchospasm response to acetylcholine with high potency and a long duration of action.

From the above described results one of ordinary skill in the art can readily understand that the compounds of the present invention have excellent antimuscarinic activity (M_3) and thus are useful for the treatment of diseases in which the muscarinic M_3 receptor is implicated, including respiratory diseases such as chronic obstructive pulmonary disease, chronic bronchitis, asthma and rhinitis, urinary diseases such as urinary incontinence and pollakinuria in neuripenia pollakinuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystitis and gastrointestinal diseases such as irritable bowel syndrome, spastic colitis and diverticulitis.

The present invention further provides a compound of formula (I) or a pharmaceutically acceptable composition comprising a compound of formula(I) for use in a method of treatment of the human or animal body by therapy, in particular for the treatment of respiratory, urinary or gastrointestinal disease.

The present invention further provides the use of a compound of formula (I) or a pharmaceutically acceptable composition comprising a compound of formula (I) for the manufacture of a medicament for the treatment of respiratory, urinary or gastrointestinal disease.

Further, the compounds of formula (I) and pharmaceutical compositions comprising a compound of formula (I) can be used in a method of treating respiratory, urinary or gastrointestinal disease, which method comprises administering to a human or animal patient in need of such treatment an effective amount of a compound of formula (I) or a pharmaceutical composition comprising a compound of formula (I).

The present invention will be further illustrated by the following examples. The examples are given by way of illustration only and are not to be construed as limiting.

EXAMPLE 1

3(R)-Diphenylacetoxy-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods d and a. The yield of final step was 500 mg, 81%. ^{1}H-NMR (CDCl3): δ 1.72-2.18 (m, 6H), 2.35 (m, 1H), 3.0 (m, 1H), 3.23 (m, 1H), 3.59-3.88 (m, 5H), 4.0 (m, 2H), 4.30 (m, 1H), 5.1 (s, 1H), 5.25 (m, 1H), 6.8-6.9 (m, 2H), 6.9-7.0 (m, 1H), 7.2-7.4 (m, 12H); MS $[M-Br]^+$: 456; mp 129° C.

EXAMPLE 2

3(R)-(2-Hydroxy-2,2-diphenylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 280 mg,42%. ^{1}H-NMR (DMSO-d6): δ 1.5-1.7 (m, 2H), 1.9-2.1 (m, 4H), 2.3 (m, 1H), 3.1 (m, 1H), 3.2-3.5 (m, 6H), 3.9-4.1 (m, 3H), 5.25 (m, 1H), 6.8 (bs, OH), 6.95 (m, 3H), 7.2-7.5 (m, 12H); MS $[M-Br]^+$: 472; mp 199° C.

EXAMPLE 3

3(R)-[2,2-Bis(4-fluorophenyl)-2-hydroxyacetoxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 400 mg,85%. ^{1}H-NMR (DMSO-d6): δ 1.5-1.65 (m, 1H), 1.7-1.8 (m, 1H), 1.85-2.0 (m, 2H), 2.05-2.2 (m, 2H), 2.3 (m, 1H), 3.1-3.2 (m, 1H),

3.3-3.5 (m,6H), 3.95 (m, 1H), 4.05 (m, 2H), 5.25 (m, 1H), 6.9-7.0 (m, 4H), 7.1-7.5 (m, 10H); MS $[M-Br]^+$: 508; mp 253° C.

EXAMPLE 4

3(R)-[2,2-Bis(4-fluorophenyl)-2-hydroxyacetoxy]-1-phenethyl-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 300 mg,67%. ^{1}H-NMR (DMSO-d6): δ 1.5-1.65 (m, 1H), 1.7-1.85 (m, 1H), 1.85-2.1 (m, 2H), 2.3 (m, 1H), 2.9-3.1 (m, 2H), 3.15-3.25 (m, 1H), 3.3-3.6 (m, 6H), 3.95-4.05 (m, 1H), 5.25 (m, 1H), 6.95 (s, OH), 7.1-7.5 (m, 13H); MS $[M-Br]^+$: 478; mp 182° C.

EXAMPLE 5

3(R)-(2-Hydroxy-2,2-di-p-tolylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 500 mg, 54%. ^{1}H-NMR (DMSO-d6): δ 1.55-1.8 (m, 2H), 1.85-2.0 (m, 2H), 2.05-1.15 (m, 2H), 2.3 (s, 7H), 3.05-3.15 (m, 1H), 3.25-3.5 (m, 6H), 3.95 (m, 1H), 4.05 (t, 2H), 5.2 (m, 1H), 6.8 (s, OH), 6.95 (m, 3H), 7.1-7.2 (m, 4H), 7.2-7.35 (m, 6H); MS $[M-Br]^+$: 500; mp 183° C.

EXAMPLE 6

3(R)-(2-Hydroxy-2,2-di-p-tolylacetoxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 650 mg, 74%. ^{1}H-NMR (DMSO-d6): δ 1.55-1.8 (m, 2H), 1.85-2.05 (m, 2H), 2.25 (s, 7H), 2.9-3.05 (m, 2H), 3.1-3.25 (m, 1H), 3.3-3.55 (m, 6H), 3.95 (m, 1H), 5.25 (m, 1H), 6.8 (s, OH), 7.1-7.2 (m, 4H), 7.2-7.35 (m, 9H); MS $[M-Br]^+$: 470; mp 144° C.

EXAMPLE 7

3(R)-(2,2-Diphenylpropionyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods e and a. The yield of final step was 250 mg, 61%. ^{1}H-NMR (CDCl3): δ 1.47-1.60 (m, 1H), 1.8-2.0 (m, 1H), 2.0 (s, 3H), 2.0-2.15 (m, 4H), 2.39 (s, 1H), 2.6 (m, 1H), 2.92 (d, 1H), 3.6 (m, 1H), 3.7-3.9 (m, 4H), 4.0 (m, 2H), 4.3 (m, 1H), 5.25 (m, 1H), 6.85 (m, 2H), 7.0 (m, 1H), 7.3 (m, 12H); MS $[M-Br]^+$: 470; mp 186° C.

EXAMPLE 8

3(R)-(2-Hydroxy-2-phenyl-2-thien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised as a mixture of diastereomers according to methods c and a. The yield of final step was 520 mg, 62%.^{1}H-NMR (DMSO-d6): δ 1.5-1.95 (m, 4H), 2.1 (m, 2H), 2.3 (m, 1H), 3.1 (m, 1H), 3.3-3.5 (m, 6H), 3.9 (m, 1H), 4.05 (t, 2H), 5.2 (m, 1H), 7.0 (m, 4H), 7.15 (m, 2H), 7.35 (m, 5H), 7.5 (m, 3H); MS $[M-Br]^+$: 478; mp 220° C.

EXAMPLE 9

3(R)-[2(R)-(2-Hydroxy-2-phenyl-2-thien-2-ylacetoxy)]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods f and b from intermediate I-4f, diastereomer 1. The yield of final step was 10 mg, 23%. ^{1}H-NMR (DMSO-d6): δ 1.5-1.6 (m, 1H), 1.65-1.75 (m, 1H), 1.8-2.0 (m, 2H), 2.05-2.1 (m, 2H), 2.3 (m, 1H), 3.05-3.2 (m, 1H), 3.25-3.55 (m, 6H), 3.85-3.95 (m, 1H), 4.0 (t, 2H), 5.2 (m, 1H), 6.95 (m, 3H), 7.03 (m, 1H), 7.15 (dd, 1H), 7.2 (s, OH), 7.3-7.5 (m, 5H), 7.45-7.55 (m, 3H); MS $[M-CF3COO]^+$: 478.

EXAMPLE 10

3(R)-[2(S)-(2-Hydroxy-2-phenyl-2-thien-2-ylacetoxy)]-1-(3-phenoxy propyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods f and b from intermediate I-4f, diastereomer 2. The yield of final step was 3 mg, 11%. ^{1}H-NMR (DMSO-d6): δ 1.6-1.75 (m, 2H), 1.8-2.0 (m, 4H), 2.25 (m, 1H), 2.8 (t, 2H), 2.95-3.1 (m, 1H), 3.15-3.5 (m, 6H), 3.8-3.95 (m, 1H), 5.2 (m, 1H), 6.92 (m, 1H), 6.96-7.03 (m, 2H), 7.1 (dd, 1H), 7.18 (s, OH), 7.3-7.4 (m, 4H), 7.43-7.5 (m, 2H), 7.51 (dd, 1H); MS $[M-CF3COO]^+$: 478.

EXAMPLE 11

3(R)-[2(R)-(2-Hydroxy-2-phenyl-2-thien-2-ylacetoxy)]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods f and b from intermediate I-4f, diastereomer 1. The yield of final step was 9 mg, 22%. ^{1}H-NMR (DMSO-d6): δ 1.45-1.55 (m, 1H), 1.65-1.75 (m, 1H), 1.85-2.05 (m, 2H), 2.3 (m, 1H), 2.9-3.1 (m, 2H), 3.1-3.25 (m, 1H), 3.25-3.55 (m, 6H), 3.9-4.0 (m, 1H), 5.25 (m, 1H), 7.05 (m, 1H), 7.15 (m, 1H), 7.2 (m, 1H), 7.25-7.4 (m, 8H), 7.45 (m, 2H, 7.55 (m, 1H); MS $[M-CF3COO]^+$: 448.

EXAMPLE 12

3(R)-[2(R)-(2-Hydroxy-2-phenyl-2-thien-2-ylacetoxy)]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods f and b from intermediate I-4f, diastereomer 1. The yield of final step was 11 mg, 26%. ^{1}H-NMR (DMSO-d6): δ 1.45-1.55 (m, 1H), 1.6-1.75 (m, 1H), 1.8-2.0 (m, 4H), 2.25 (m, 1H), 2.55 (t, 2H), 3.0-3.1 (m, 1H), 3.15-3.55 (m, 6H), 3.8-3.9 (m, 1H), 5.2 (m, 1H), 7.0 (m, 1H), 7.1 (m, 1H), 7.15-7.4 (m, 9H), 7.45 (m, 2H), 7.5 (m, 1H); MS $[M-CF3COO]^+$: 462.

EXAMPLE 13

3(R)-[2(R)-(2-Hydroxy-2-phenyl-2-thien-2-ylacetoxy)]-1-(2-thien-2-ylethyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods f and b from intermediate I-4f, diastereomer 1. The yield of final step was 10 mg, 24%. ^{1}H-NMR (DMSO-d6): δ 1.45-1.55 (m, 1H), 1.65-1.75 (m, 1H), 1.8-2.0 (m, 2H), 2.3 (m, 1H), 3.1-3.6 (m, 9H), 3.9-4.0 (m, 1H), 5.25 (m, 1H), 7.0 (m, 3H), 7.15 (dd, 1H), 7.2 (s, OH), 7.3-7.4 (m, 3H), 7.45-7.55 (m, 4H); MS $[M-CF3COO]^+$: 454.

EXAMPLE 14

3(R)-[2(R)-(2-Hydroxy-2-phenyl-2-thien-2-ylacetoxy)]-1-(3-thien-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods f and b from intermediate I-4f, diastereomer 1. The yield of final step was 8 mg, 19%. ^{1}H-NMR (DMSO-d6): δ 1.45-1.6 (m, 1H), 1.65-1.75 (m, 1H), 1.8-2.05 (m, 4H), 2.25 (m, 1H), 2.8 (t, 2H), 3.0-3.15 (m, 1H), 3.2-3.5 (m, 6H), 3.8-3.95 (m, 1H), 5.2 (m, 1H), 6.92 (m, 1H), 6.96-7.03 (m, 2H), 7.13 (dd, 1H), 7.2 (s, OH), 7.3-7.4 (m, 4H), 7.45-7.5 (m, 2H), 7.52 (dd, 1H); MS [M-CF3COO]$^+$: 468.

EXAMPLE 15

3(R)-[2(S)-(2-Hydroxy-2-phenyl-2-thien-2-ylacetoxy)]-1-(3-thien-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods f and b from intermediate I-4f, diastereomer 2. The yield of final step was 7 mg, 26%. ^{1}H-NMR (DMSO-d6): δ 1.6-1.75 (m, 2H), 1.8-2.0 (m, 4H), 2.25 (m, 1H), 2.8 (t, 2H), 2.95-3.1 (m, 1H), 3.15-3.5 (m, 6H), 3.8-3.95 (m, 1H), 5.2 (m, 1H), 6.92 (m, 1H), 6.96-7.03 (m, 2H), 7.1 (dd, 1H), 7.18 (s, OH), 7.3-7.4 (m, 4H), 7.43-7.5 (m, 2H), 7.51 (dd, 1H); MS [M-CF3COO]$^+$: 468.

EXAMPLE 16

3(R)-[2(R)-(2-Hydroxy-2-phenyl-2-thien-2-ylacetoxy)]-1-(2-phenoxy ethyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods f and b from intermediate I-4f, diastereomer 1. The yield of final step was 11 mg, 26%. ^{1}H-NMR (DMSO-d6): δ 1.5-1.6 (m, 1H), 1.65-1.75 (m, 1H), 1.8-2.0 (m, 2H), 2.25 (m, 1H), 3.15-3.6 (m, 5H), 3.7 (m, 2H), 4.0 (m, 2H), 4.4 (m, 2H), 5.25 (m, 1H), 6.95-7.03 (m, 4H), 7.12 (dd, 1H), 7.2 (s, OH), 7.3-7.4 (m, 5H), 7.4-7.5 (m, 3H); MS [M-CF3COO]$^+$: 464.

EXAMPLE 17

3(R)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised as a mixture of diastereomers according to methods c and a. The yield of final step was 240 mg, 77%. ^{1}H-NMR (DMSO-d6): δ 1.55-2.0 (m, 4H), 2.27 (m, 1H), 3.05-3.55 (m, 5H), 3.88-3.98 (m, 1H), 4.0-4.10 (m, 2H), 5.21 (m, 1H), 6.23-6.31 (doble dd, 1H), 6.36-6.48 (m, 2H), 6.83-6.90 (dd, 1H), 6.95 (d, OH), 7.26-7.66 (m, 11H); MS [M-Br]$^+$: 444; mp 99° C.

EXAMPLE 18

3(R)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised as a mixture of diastereomers according to methods c and a. The yield of final step was 210 mg, 66%. ^{1}H-NMR (DMSO-d6): δ 1.50-2.05 (m, 4H), 2.27 (m, 1H), 3.20 (m, 1H), 3.37-3.65 (m, 4H), 3.65-3.75 (m, 2H), 4.04 (m, 1H), 4.40 (m, 2H), 5.21 (m, 1H), 6.23-6.32 (doble dd, 1H), 6.44 (m, 1H), 6.94-7.04 (m, 4H), 7.33-7.50 (m, 7H), 7.64 (m, 1H); MS [M-Br]$^+$: 448; mp 163° C.

EXAMPLE 19

3(R)-[2(*)—(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)]-1-(2-phenoxy ethyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b from intermediate I-la, diastereomer 1. The yield of final step was 11 mg, 23%. ^{1}H-NMR (DMSO-d6): δ 1.65-1.80 (m, 2H), 1.80-2.10 (m, 2H), 2.27 (m, 1H), 3.15-3.65 (m, 5H), 3.68 (m, 2H), 4.0 (m, 1H), 4.40 (t, 2H), 5.20 (m, 1H), 6.23 (d, 1H), 6.42 (m, 1H), 6.92-7.04 (m, 4H), 7.30-7.38 (m, 5H), 7.44-7.50 (m, 2H), 7.64 (m, 1H); MS [M-CF3COO]$^+$: 448.

EXAMPLE 20

3(R)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)-1-(3phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound has been described in method-a-.

EXAMPLE 21

3(R)-[2(*)—(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)]-1-(3-phenoxy propyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a from intermediate I-1a, diastereomer 1. The yield of final step was 1.15 g 99%. ^{1}H-NMR (DMSO-d6): δ 1.60-2.20 (m, 6H), 2.25 (m, 1H), 3.10 (m, 1H), 3.20-3.60 (m, 6H), 3.95 (m, 1H), 4.05 (m, 2H), 5.20 (m, 1H), 6.25 (dd, 1H), 6.45 (m, 1H), 6.95 (m, 4H), 7.30-7.50 (m, 7H), 7.70 (m, 1H); MS [M-Br]$^+$: 462; mp 156° C.

EXAMPLE 22

3(R)-[2(*)—(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)]-1-(3-phenoxy propyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b from intermediate I-la, diastereomer 2. The yield of final step was 10 mg, 20%. ^{1}H-NMR (DMSO-d6): δ 1.50-2.20 (m, 6H), 2.25 (m, 1H), 3.10 (m, 1H), 3.20-3.60 (m, 6H), 3.95 (m, 1H), 4.05 (m, 2H), 5.20 (m, 1H), 6.35 (dd, 1H), 6.45 (m, 1H), 6.95 (m, 4H), 7.30-7.50 (m, 7H), 7.70 (m, 1H); MS [M-CF3COO]$^+$: 462.

EXAMPLE 23

3(R)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised as a mixture of diastereomers according to methods c and b. The yield of final step was 12 mg, 13%. ^{1}H-NMR (DMSO-d6): δ 1.5 (m, 1H), 1.7 (m, 1H), 1.9-2.05 (m, 2H), 2.3 (m, 1H), 2.95 (m, 2H), 3.15 (m, 1H), 3.25-3.55 (m, 6H), 3.95 (m, 1H), 5.25 (m, 1H), 6.3 (d, 1H), 6.45 (m, 1H), 6.95 (d, 1H), 7.25-7.45 (m, 8H), 7.5 (m, 2H), 7.7 (m, 1H); MS [M-CF_3COO]$^+$: 432.

EXAMPLE 24

3(R)-[2(*)—(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)]-1-phenethyl-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b from intermediate I-1a, diastereomer 1. The yield of final step was 16 mg, 40%. ^{1}H-NMR (DMSO-d6): δ 1.65-1.80 (m, 2H), 1.90-2.05 (m, 2H), 2.3 (m, 1H), 2.95 (m, 2H), 3.15 (m, 1H), 3.25-3.55 (m, 6H), 3.95 (m, 1H), 5.25 (m, 1H), 6.26 (dd, 1H), 6.46 (m, 1H), 6.95 (s, 1H, OH), 7.25-7.45 (m, 8H), 7.5 (m, 2H), 7.7 (m, 1H); MS [M-CF3COO]$^+$: 432.

EXAMPLE 25

3(R)-[2(*)—(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)]-1-phenethyl-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b from intermediate I-la, diastereomer 2. The yield of final step was 14 mg, 35% ^{1}H-NMR (DMSO-d6): δ 1.50-1.80 (m, 2H), 1.90-2.05 (m, 2H), 2.3 (m, 1H), 2.95 (m, 2H), 3.15 (m, 1H), 3.25-3.55 (m, 6H), 3.95 (m, 1H), 5.25 (m, 1H), 6.32 (dd, 1H), 6.46 (m, 1H), 6.95 (s, 1H, OH), 7.25-7.45 (m, 8H), 7.5 (m, 2H), 7.7 (m, 1H) MS [M-CF3COO]$^+$: 432.

EXAMPLE 26

3(R)-[2(*)—(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b from intermediate I-la, diastereomer 1. The yield of final step was 10 mg, 21%. ^{1}H-NMR (DMSO-d6): δ 1.60-1.75 (m, 2H), 1.80-2.0 (m, 4H), 2.25 (m, 1H), 2.50-2.60 (m, 2H), 3.0 (m, 1H), 3.10-3.50 (m, 6H), 3.83 (m, 1H), 5.17 (m, 1H), 6.25 (d, 1H), 6.45 (m, 1H), 6.95 (s, 1H), 7.20-7.40 (m, 8H), 7.46-7.48 (m, 2H), 7.66 (m, 1H); MS [M-CF3COO]$^+$: 446.

EXAMPLE 27

3(R)-[2(*)—(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)]-1-(2-thien-2-ylethyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b from intermediate I-la, diastereomer 1. The yield of final step was 9 mg, 19%. ^{1}H-NMR (DMSO-d6): δ 1.65-1.80 (m, 2H), 1.85-2.05 (m, 2H), 2.30 (m, 1H), 3.10-3.40 (m, 3H), 3.40-3.60 (m, 6H), 3.95 (m, 1H), 5.24 (m, 1H), 6.27 (d, 1H), 6.47 (m, 1H), 6.96 (s, 1H), 7.0-7.04 (m 2H), 7.36-7.48 (m, 4H), 7.49-7.54 (m, 2H), 7.70 (m, 1H).; MS [M-CF3COO]$^+$: 438.

EXAMPLE 28

3(R)-[2(*)—(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)]-1-(3-thien-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesized according to methods c and b from intermediate I-1a, diastereomer 1. The yield of final step was 9 mg, 19%. ^{1}H-NMR (DMSO-d6): δ 1.60-1.75 (m, 2H), 1.80-2.05 (m, 4H), 2.26 (m, 1H), 2.81 (t, 2H), 3.02 (m, 1H), 3.10-3.45 (m, 6H), 3.85 (m, 1H), 5.18 (m, 1H), 6.25 (d, 1H), 6.45 (m, 1H), 6.90-7.0 (m, 3H), 7.32-7.42 (m, 4H), 7.45-7.51 (m, 2H), 7.66 (m, 1H); MS [M-CF3COO]$^+$: 452.

EXAMPLE 29

3(R)-(2-Furan-2-yl-2-hydroxy-2-thien-2-ylacetoxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised as a mixture of diastereomers according to methods c and b. The yield of final step was 18 mg, 20%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.05 (m, 4H), 2.3 (m, 1H), 3.0 (m, 2H), 3.15-3.6 (m, 7H), 3.95 (m, 1H), 5.25 (m, 1H), 6.35 (dd, 1H), 6.45 (m, 1H), 7.05 (m, 1H), 7.2 (dd, 1H), 7.25-7.5 (m, 6H), 7.55 (m, 1H), 7.65 (m, 1H); MS [M-CF_3COO]$^+$: 438.

EXAMPLE 30

3(R)-(2-Furan-2-yl-2-hydroxy-2-thien-2-ylacetoxy)-1 -(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised as a mixture of diastereomers according to methods c and b. The yield of final step was 22 mg, 23%. ^{1}H-NMR (DMSO-d6): δ 2.65-2.05 (m, 4H), 2.3 (m, 1H), 3.15-3.65 (m, 7H), 4.05 (m, 1H), 4.4 (m, 2H), 5.15 (m, 1H), 6.35 (dd, 1H), 6.45 (m, 1H), 6.95-7.05 (m, 4H), 7.15 (d, 1H), 7.3-7.4 (m, 3H), 7.5 (dd, 1H), 7.65 (d, 1H); MS [M-CF_3COO]$^+$: 454.

EXAMPLE 31

3(R)-(2-Furan-2-yl-2-hydroxy-2-thien-2-ylacetoxy)-1-(4-oxo-4-phenylbutyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised as a mixture of diastereomers according to methods c and b. The yield of final step was 15.4 mg, 15%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.1 (m, 6H), 7.05-7.55 (m, 9H), 3.95 (m, 1H), 5.1 (m, 1H), 6.35 (dd, 1H), 6.5 (m, 1H), 7.05 (m, 1H), 7.15 (m, 1H), 7.3 (d, 1H), 7.55 (m, 3H), 7.7 (dd, 2H), 8.0 (d, 2H); MS [M-CF_3COO]$^+$: 480.

EXAMPLE 32

1-(3-phenoxypropyl)-3(R)-(2-Furan-2-yl-2-hydroxy-2-thien-2-yl-acetoxy)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised as a mixture of diastereomers according to methods c and a. The yield of final step was 100 mg, 41%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.05 (m, 4H), 2.1-2.0 (m, 2H), 2.3 (m, 1H), 3.15 (m, 1H), 3.25-3.6 (6H), 3.9-4.1 (m, 3H), 5.1 (m, 1H), 6.35 (d, 1H), 6.45 (s, 1H), 6.95 (m, 3H), 7.05 (m, 1H), 7.2 (d, 1H), 7.3 (m, 3H), 7.55 (d, 1H), 7.7 (s, 1H); MS [M-Br]$^+$: 520; mp 173° C.

EXAMPLE 33

1-(3-phenoxypropyl)-3(R)-(2,2-difuran-2-yl-2-hydroxy acetoxy)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods f and a. The yield of final step was 200 mg, 60%. ^{1}H-NMR (DMSO-d6): δ 1.6-2.20 (m, 6H), 2.3 (m, 1H), 2.95-3.65 (m, 7H), 3.80-4.10 (m, 3H), 5.2 (m, 1H), 6.3-6.6 (m, 4H), 6.8-7.0 (m, 3H), 7.1 (s, OH), 7.3 (m, 2H), 7.7 (m, 2H); MS [M-Br]$^+$: 452.

EXAMPLE 34

3(R)-(2,2-Dithien-2-ylacetoxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 240 mg, 60%. ^{1}H-NMR (DMSO-d6): δ 1.85-2.10 (m, 4H), 2.30 (s, 1H), 3.40 (m, 1H), 3.44-3.80 (m, 6H), 4.10 (m, 1H), 4.45 (m, 2H), 5.20 (m, 1H), 5.90 (s, 1H), 6.95-7.05 (m, 5H), 7.05-7.15 (m, 2H), 7.30-7.40 (m, 2H), 7.45 (m, 2H); MS [M-Br]$^+$: 454; mp 98° C.

EXAMPLE 35

3(R)-(2,2-Dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 280 mg, 83%. ^{1}H-NMR (DMSO-d6): δ 1.80-2.06 (m, 4H), 2.06-2.20 (m, 2H), 2.20-2.30 (m, 1H), 3.20-3.65 (m, 7H), 3.90-4.10 (m, 3H), 5.20

(m, 1H), 5.90 (s, 1H), 6.95-7.05 (m, 5H), 7.05-7.20 (m, 2H), 7.30-7.35 (m, 2H), 7.50 (m, 2H); MS $[M-Br]^+$: 468; mp 148° C.

EXAMPLE 36

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 180 mg, 59%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.0 (4H, m), 2.35 (m, 1H), 3.0 (m, 2H), 3.2-3.6 (m, 7H), 3.95 (m, 1H), 5.25 (m, 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.35 (m, 5H), 7.55 (m, 3H); MS $[M-Br]^+$: 454; mp 216° C.

EXAMPLE 37

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 450 mg, 58%. ^{1}H-NMR (CDCl3): δ 1.8-2.1 (m, 6H), 2.4 (m, 1H), 2.6 (m, 2H), 3.4-3.8 (m, 7H), 4.2 (m, 1H), 5.25 (m, 1H), 6.1 (bs, OH), 6.9 (m, 2H), 7.1-7.3 (m, 9H); MS $[M-Br]^+$: 468; mp 64° C.

EXAMPLE 38

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 260 mg, 34%. ^{1}H-NMR (CDCl3): δ 1.8-2.05 (m, 4H), 2.4 (m, 1H), 3.55-3.95 (m, 5H), 4.15-4.5 (m, 3H), 5.25 (m, 1H), 5.9 (s, OH), 6.15 (m, 1H), 6.85 (t, 1H), 6.9-7.05 (m, 3H), 7.15 (m, 1H), 7.2-7.45 (m, 7H); MS $[M-Br]^+$: 466; mp 124° C.

EXAMPLE 39

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(4-phenylbutyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 320 mg, 40%. ^{1}H-NMR (CDCl3): δ 1.6-2.0 (m, 8H), 2.4 (m, 1H), 2.6 (m, 2H), 3.4-3.8 (m, 7H), 4.2 (m, 1H), 5.25 (m, 1H), 6.05 (bs, OH), 6.95 (m, 2H), 7.1-7.3 (m, 9H); MS $[M-Br]^+$: 482; mp 64° C.

EXAMPLE 40

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(4-oxo-4-phenylbutyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 16 mg, 15%. ^{1}H-NMR (DMSO-d6): δ 1.7-2.0 (m, 6H), 2.15 (m, 1H), 3.1 (t, 2H), 3.15-3.55 (m, 7H), 3.95 (m, 1H), 5.25 (m, 1H), 7.0 (d, 2H), 7.15 (d, 2H), 7.55 (m, 5H), 7.65 (t, 1H), 8.0 (d, 2H); MS$[M-CF_3COO]^+$: 496.

EXAMPLE 41

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenylaminopropyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 14 mg, 14%. ^{1}H-NMR (DMSO-d6): δ 1.7-2.0 (m, 5H), 2.3 (m, 1H), 3.0-3.5 (m, 9H), 3.9 (m, 1H), 5.25 (m, 1H), 5.65 (t, 1H), 6.55 (m, 3H), 7.0 (d, 2H), 7.1 (t, 2H), 7.15 (m, 2H), 7.5 (m, 3H); MS$[M-CF_3COO]^+$: 483.

EXAMPLE 42

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(methylphenylamino)propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 20 mg, 19%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.0 (m, 6H), 2.9 (s, 3H), 3.1 (m, 1H), 3.2-3.45 (m, 8H), 3.95 (m, 1H), 5.2 (m, 1H), 6.65 (t, 1H), 6.75 (d, 2H), 7.0 (m, 2H), 7, 2 (m, 4H), 7.5 (m, 3H); MS $[M-CF_3COO]^+$: 497.

EXAMPLE 43

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenylsulfanylpropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 800 mg, 83%. ^{1}H-NMR (DMSO-d6): δ 1.6-1.9 (m, 6H), 2.3 (m, 1H), 2.95 (t, 2H), 3.05 (m, 1H), 3.2-3.5 (m, 6H), 3.9 (m, 1H), 5.2 (m, 1H), 7.0 (m, 2H), 7.15 (m, 2H), 7.2 (m, 1H), 7.35 (m, 4H), 7.5 (m, 2H); MS $[M-Br]^+$: 500.

EXAMPLE 44

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 490 mg, 90%. ^{1}H-NMR (DMSO-d6): δ 1.7 (m, 2H), 1.95 (m, 2H), 2.1 (m, 2H), 2.3 (m, 1H), 3.2 (m, 1H), 3.45 (m, 6H), 4.0 (m, 3H), 5.15 (m, 1H), 6.9 (m, 3H), 7.0 (m, 2H), 7.2 (m, 2H), 7.3 (t, 2H), 7.5 (m, 3H); MS $[M-Br]^+$: 484; mp 227° C.

EXAMPLE 45

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-otolyloxypropyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b The yield of final step was 19 mg, 18%. ^{1}H-NMR (DMSO-d6): δ 1.7-2.0 (m, 4H), 2.1-2.2 (m, 5H), 2.3 (m, 1H), 3.15-3.5 (m, 7H), 3.9-4.05 (m, 3H), 5.05 (m, 1H), 6.85 (t, 1H), 6.9 (d, 1H), 7.0 (m, 2H), 7.15 (m, 4H), 7.5 (m, 3H); MS $[M-CF_3COO]^+$: 498.

EXAMPLE 46

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(2,4,6-trimethylphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 22 mg, 20%. ^{1}H-NMR (DMSO-d6): δ 1.7 (m, 2H), 1.95 (m, 2H), 2.1 (m, 2H), 2.2 (s, 9H), 2.35 (m, 1H), 3.2-3.5 (m, 7H), 3.7 (t, 2H), 3.95 (m, 1H), 5.25 (m, 1H), 6.8 (s, 2H), 7.0 (m, 2H), 7.2 (m, 2H), 7.5 (m, 3H); MS $[M-CF_3COO]^+$: 526.

EXAMPLE 47

1-[3-(2-tert-Butyl-6-methylphenoxy)propyl]-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 18 mg, 16%. ^{1}H-NMR (DMSO-d6): δ 1.3 (s, 9H), 2.7 (m, 2H), 2.9 (m, 2H), 2.1 (m,

2H), 2.2 (s, 3H), 2.3 (m, 1H), 3.2-3.5 (m, 7H), 3.8 (t, 2H), 5 3.95 (m, 1H), 5.2 (m, 1H), 6.9-7.15 (m, 7H), 7.5 (m, 3H); MS $[M\text{-}CF_3COO]^+$: 554.

EXAMPLE 48

1-[3-(Biphenyl-4-yloxy)propyl]-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo[2.2.2]-octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 22 mg, 19%. ^{1}H-NMR (DMSO-d6): δ 1.7 (m, 2H), 1.9 (m, 2H), 2.15 (m, 2H), 2.3 (m, 1H), 3.2-3.5 (m, 7H), 3.95 (m, 1H), 4.1 (t, 2H), 5.25 (m, 1H), 7.0 (m, 4H), 7.2 (m, 2H), 7.3 (t, 1H), 7.45 (t, 2H), 7.5 (m, 3H), 7.6 (m, 4H); MS $[M\text{-}CF_3COO]^+$: 560.

EXAMPLE 49

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)-propyl]-1-azoniabicyclo [2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 23 mg, 21%. ^{1}H-NMR (DMSO-d6): δ 1.7 (m, 6H), 1.9-2.1 (m, 4H), 2.3 (m, 1H), 2.65 (m, 4H), 3.15-3.5 (m, 7H), 3.95 (m, 2H), 5.25 (m, 1H), 6.65 (m, 2H), 6.95 (d, 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.5 (m, 3H); MS $[M\text{-}CF_3COO]^+$: 538.

EXAMPLE 50 3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3(naphthalen-2-yloxy) propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 17 mg, 15%. ^{1}H-NMR (DMSO-d6): δ 1.7-2.0 (m, 4H), 2.1 (m, 1H), 2.35 (m, 1H), 3.15-3.35 (m, 7H), 3.95 (m, 1H), 4.17 (t, 2H), 5.25 (m, 1H), 7.0 (m, 2H), 7.15 (m, 3H), 7.35 (m, 2H), 7.5 (m, 4H), 7.85 (m, 3H); MS $[M\text{-}CF_3COO]^+$: 534.

EXAMPLE 51

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(naphthalen-1-yloxy)propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound has been described in method-b-.

EXAMPLE 52

1-[3-(2-Chlorophenoxy)propyl]-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 20 mg, 18%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.0 (m, 6H), 2.35 (m, 1H), 3.2 (m, 1H), 3.3-3.55 (m, 6H), 3.95 (m, 1H), 4.15 (t, 2H), 5.25 (m, 2H), 7.0 (m, 3H), 7.2 (m, 3H), 7.35 (t, 1H), 7.45 (d, 1H), 7.55 (m, 3H); MS $[M\text{-}CF_3COO]^+$: 519.

EXAMPLE 53

1-[3-(4-Fluorophenoxy)propyl]-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo[2.2.2]octane; Chloride

The title compound was synthesised according to methods c and a. The yield of final step was 180 mg, 59%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.15 (m, 6H), 2.25 (m, 1H), 3.2 (m, 1H), 3.25-3.55 (m, 6H), 3.95 (m, 2H), 4.0 (t, 2H), 5.25 (m, 1H), 7.0 (m, 4H), 7.15 (m, 4H), 7.55 (m, 3H); MS $[M\text{-}Cl]^+$: 502; mp 160° C.

EXAMPLE 54

1-[3-(2,4-Difluorophenoxy)propyl]-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 14 mg, 13%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.0 (m, 4H), 2.15 (m, 2H), 2.35 (m, 1H), 3.2 (m, 1H), 3.25-3.35 (m, 6H), 3.95 (m, 1H), 4.1 (t, 2H), 5.15 (m, 1H),! 7.05 (m, 3H), 7.2 (d, 2H), 7.25-7.35 (m, 2H), 7.55 (m, 3H); MS $[M\text{-}CF_3COO]^+$: 520.

EXAMPLE 55

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(3-trifluoromethyl phenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 17%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.1 (m, 6H), 2.35 (m, 1H), 3.2 (m, 1H), 3.3-3.55 (m, 6H), 3.95 (m, 1H), 4.15 (t, 2H), 5.25 (m, 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.25-7.35 (m, 3H), 7.5-7.6 (m, 4H); MS $[M\text{-}CF_3COO]^+$: 552.

EXAMPLE 56

1-[3-(3-Cyanophenoxy)propyl]-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 18 mg, 17%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.1 (m, 6H), 2.35 (m, 1H), 3.2 (m, 1H), 3.3-3.55 (m, 6H), 3.95 (m, 1H), 4.15 (t, 2H), 5.25 (m, 1H), 7.0 (m, 2H), 7, 18 (m, 2H), 7.3 (d, 1H), 7.45 (m, 2H), 7.55 (m, 4H); MS $[M\text{-}CF_3COO]^+$: 509.

EXAMPLE 57

1-[3-(4-Cyanophenoxy)propyl]-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 180 mg, 53%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.2 (m, 6H), 2.3 (m, 1H), 3.2 (m, 1H), 3.3-3.55 (m, 6H), 3.95 (m, 1H), 4.15 (t, 2H), 5.25 (m, 1H), 7.0 (m, 2H), 7.1 (d, 2H), 7.15 (m, 2H), 7.5 (m, 2H), 7.8 (d, 2H); MS $[M\text{-}Br]^+$: 509; mp 158° C.

EXAMPLE 58

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(3-methoxyphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 18%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.15 (m, 6H), 2.15 (m, 1H), 3.2 (m, 1H), 3.3-3.5 (m, 6H), 3.75 (s, 3H), 3.95 (m, 1H), 4.0 (t, 2H), 5.25 (m, 1H), 6.55 (m, 3H), 7.0 (m, 2H), 7.2 (m, 3H), 7.55 (m, 3H); MS $[M\text{-}CF_3COO]^+$: 514.

EXAMPLE 59

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(4-methoxyphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 14 mg, 13%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.15 (m, 6H), 2.35 (m, 1H), 3.2 (m, 1H), 3.3-3.55 (m, 6H), 3.7 (s, 3H), 3.9-4.0 (m, 3H), 5.25 (m, 1H), 6.9 (s, 4H), 7.0 (m, 2H), 7.15 (m, 2H), 7.5 (m, 3H); MS [M-CF_3COO]$^+$: 514.

EXAMPLE 60

1-[3-(Benzo[1,3]dioxol-5-yloxy)propyl]-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo [2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 17%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.15 (m, 7H), 2.3 (m, 1H), 3.15 (m, 1H), 3.25-3.5 (m, 6H), 3.9-4.0 (m, 3H), 5.25 (m, 1H), 5.95 (s, 2H), 6.4 (d, 1H), 6.65 (s, 1H), 6.85 (d, 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.5 (m, 3H); MS [M-CF_3COO]$^+$: 528.

EXAMPLE 61

1-[3-(2-Carbamoylphenoxy)propyl]-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 18 mg, 16%.^{1}H-NMR (DMSO-d6): δ 1.65-2.0 (m, 4H), 2.2 (m, 2H), 2.3 (m, 1H), 3.15 (m, 1H), 3.25-3.55 (m, 6H), 3.95 (m, 1H), 4.15 (t, 2H), 5.25 (m, 1H), 7.0-7.2 (m, 6H), 7.4-7.6 (m, 6H), 7.7 (d, 1H); MS [M-CF_3COO]$^+$: 527.

EXAMPLE 62

1-[3-(3-Dimethylaminophenoxy)propyl]-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 17%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.15 (m, 6H), 2.3 (m, 1H), 2.85 (s, 6H), 3.1-3.5 (m, 7H), 3.85-4.0 (m, 3H), 5.25 (m, 1H), 6.2 (m, 1H), 6.25 (d, 1H), 6.35 (d, 1H), 7.0 (m, 2H), 7.1 (t, 1H), 7.2 (m, 2H), 7.5 (m, 3H); MS [M-CF_3COO]$^+$: 527.

EXAMPLE 63

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(4-nitrophenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 22 mg, 20%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.0 (m, 4H), 2.2 (m, 2H), 2.3 (m, 1H), 3.2 (m, 1H), 3.3 3.5 (m, 6H), 3.95 (m, 1H), 4.2 (t, 2H), 5.25 (m, 1H), 7.0 (m, 2H), 7.15 (m, 4H), 7.5 (m, 3H), 8.15 (d, 2H); MS [M-CF_3COO]$^+$: 529.

EXAMPLE 64

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(3-nitrophenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 18 mg, 16%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.2 (m, 6H), 2.3 (m, 1H), 3.15-3.55 (m, 7H), 3.95 (m, 1H), 4.2 (t, 2H), 5.25 (m, 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.45 (dd, 1H), 7.55 (m, 3H), 7.6 (t, 1H), 7.75 (s, 1H), 7.85 (d, 1H); MS [M-CF_3COO]$^+$: 529.

EXAMPLE 65

1-[3-(4-Acetylaminophenoxy)propyl]-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 17%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.15 (m, 6H), 2.0 (s, 3H), 2.3 (m, 1H), 3.2 (m, 1H), 3.3-3.55 (m, 6H), 3.9-4.0 (m, 3H), 5.25 (m, 1H), 6.85 (d, 2H), 7.0 (m, 2H), 7.2 (m, 2H), 7.5 (m, 5H), 9.8 (s, 1H); MS [M-CF_3COO]$^+$: 541.

EXAMPLE 66

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(3-methoxycarbonylphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 18 mg, 16%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.2 (m, 6H), 2.3 (m, 1H), 3.2 (m, 1H), 3.3-3.5 (m, 6H), 3.85 (s, 3H), 3.95 (m, 1H), 4.1 (t, 2H), 5.25 (m, 1H), 7.0 (m, 2H), 7.15 (m, 2H), 7.25 (dd, 1H), 7.45-7.6 (m, 6H); MS [M-CF_3COO]$^+$: 542.

EXAMPLE 67

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-{3-[4-(3-hydroxypropyl)phenoxy]propyl}-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 14 mg, 13%. ^{1}H-NMR (DMSO-d6): δ 1.6-2.15 (m, 8H), 2.3 (m, 1H), 2.55 (t, 2H), 3.2 (m, 1H), 3.25-3.55 (m, 9H), 3.85-4.0 (m, 3H), 4.45 (t, OH), 5.25 (m, 1H), 7.85 (d, 2H), 7.0 (m, 2H), 7.1 (d, 2H), 7.15 (m, 2H), 7.5 (m, 2H); MS [M-CF_3COO]$^+$: 542.

EXAMPLE 68

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(2-hydroxymethylphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 16 mg, 15%. ^{1}H-NMR (DMSO-d6): δ 1.7-2.2 (m, 6H), 2.35 (m, 1H), 3.1-3.5 (m, 7H), 3.9-4.05 (m, 3H), 4.5 (m, 2H), 5.0 (t, OH), 5.15 (m, 1H), 6.9-7.05 (m, 4H), 7.2 (m, 2H), 7.4 (d, 1H), 7.5 (m, 3H); MS [M-CF_3COO]$^+$: 514.

EXAMPLE 69

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(3-hydroxymethylphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 16 mg, 15%. ^{1}H-NMR (DMSO-d6): δ 1.7-2.2 (m, 6H), 2.35 (m, 1H), 3.15-3.5 (m, 7H), 3.9 (m, 1H), 4.05 (t, 2H), 4.45 (d, 2H), 5, 25 (m, 2H), 6.8 (d, 1H), 6.9 (m, 2H), 7.2 (m, 2H), 7.25 (t, 1H), 7.5 (m, 3H); MS [M-CF_3COO]$^+$: 514.

EXAMPLE 70

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(4-hydroxymethylphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 17 mg, 16%. ^{1}H-NMR

(DMSO-d6): δ 1.65-2.2 (m, 6H), 2.3 (m, 1H), 3.15-3.55 (m, 7H), 3.9-4.05 (m, 3H), 4.4 (d, 2H), 5.1 (t, OH), 5.25 (t, 1H), 6.9 (d, 2H), 7.0 (m, 2H), 7.2 (m, 2H), 7.25 (d, 2H), 7.5 (m, 3H); MS $[M\text{-}CF_3COO]^+$: 514.

EXAMPLE 71

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(2-hydroxyphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 24 mg, 19%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.15 (m, 6H), 2.35 (m, 1H), 3.2 (m, 1H), 3.25-3.55 (m, 6H), 3.95 (m, 1H), 4.0 (t, 2H), 5.25 (m, 1H), 6.7-6.85 (m, 3H), 6.95 (d, 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.5 (m, 3H), 8.85 (s, OH); MS $[M\text{-}CF_3COO]^+$: 500.

EXAMPLE 72

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(4-hydroxyphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 16 mg, 15%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.1 (m, 6H), 2.3 (m, 1H), 3.2 (m, 1H), 3.25-3.5 (m, 6H), 3.95 (m, 3H), 5.25 (m, 1H), 6.7 (d, 2H), 6.75 (d, 2H), 7.0 (m, 2H), 7.2 (m, 2H), 7.5 (t, 3H), 9.0 (s, OH); MS $[M\text{-}CF_3COO]^+$: 500.

EXAMPLE 73

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(3-hydroxyphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 16 mg, 15%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.15 (m, 6H), 2.3 (m, 1H), 3.2 (m, 1H), 3.3-3.55 (m, 6H), 3.9-4.0 (m, 3H), 5.25 (m, 1H), 6.9-6.0 (m, 3H), 7.0-7.1 (m, 3H), 7.2 (m, 2H), 7.5 (m, 3H), 9.45 (s, OH); MS $[M\text{-}CF_3COO]^+$: 500.

EXAMPLE 74

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-pyrrol-1-ylpropyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 21 mg, 22%. ^{1}H-NMR (DMSO-d6): δ 1.65-1.8 (m, 2H), 1.8-2.0 (m, 2H), 2.0-2.15 (m, 2H), 2.3 (m, 1H), 3.05-3.2 (m, 3H), 3.2-3.5 (m, 4H), 3.8-3.95 (m, 3H), 5.2 (m, 1H), 6.05 (t, 2H), 6.75 (t, 2H), 7.0 (t, 2H), 7.15 (d, 2H), 7.55 (m, 3H);MS $[M\text{-}CF_3COO]^+$: 457.

EXAMPLE 75

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(4-oxo-4-thien-2-ylbutyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 18 mg, 17%. ^{1}H-NMR (DMSO-d6): δ 1.7-1.85 (m, 2H), 1.9-2.1 (m, 4H), 2.3 (m, 1H), 3.1 (t, 2H), 3.15-3.55 (m, 7H), 3.95 (m, 1H), 5.25 (m, 1H), 7.0 (t, 2H), 7.4 (d, 2H), 7.25 (t, 1H), 7.55 (m, 3H), 7.95 (d, 1H), 8.05 (d, 1H); MS $[M\text{-}CF_3COO]^+$: 502.

EXAMPLE 76

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(1-methyl[1H]-imidazol-2-ylsulfanyl)propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 26 mg, 25%. ^{1}H-NMR (DMSO-d6): δ 1.7 (m, 2H), 1.85-2.05 (m, 4H), 2.3 (m, 1H), 3.25-3.5 (m, 7H), 3.6 (s, 3H), 3.9 (m, 1H), 4.2 (t, 2H), 5.2 (m, 1H), 7.0 (m, 3H), 7.15 (m, 2H), 7.3 (m, 1H), 7.5 (m, 3H); MS $[M\text{-}CF_3COO]^+$: 504.

EXAMPLE 77

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(2-thien-2-ylethyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 430 mg, 54%. ^{1}H-NMR (DMSO-d6): δ 1.6-1.8 (m, 2H), 2.3 (m, 1H), 3.15-3.3 (m, 4H), 3.35-3.55 (m, 5H), 3.95 (m, 1H), 5.25 (m, 1H), 7,0 (m, 4H), 7,15 (m, 2H), 7.4-7.5 (m, 4H); MS $[M\text{-}Br]^+$: 460; mp 206° C.

EXAMPLE 78

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-thien-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 600 mg, 77%. ^{1}H-NMR (DMSO-d6): δ 1.6-1.8 (m, 2H), 1.85-2.1 (m, 4H), 2.3 (m, 1H), 2.8 (t, 2H), 3.1-3.5 (m, 7H), 3.9 (m, 1H), 5.2 (m, 1H), 6.9-7.05 (m, 4H), 7.15 (m, 2H), 7.4 (d, 1H), 7.5 (m, 3H); MS $[M\text{-}Br]^+$: 474; $_{mp}$ 138° C.

EXAMPLE 79

1-[3-(Benzothiazol-2-yloxy)propyl]-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesized according to methods c and b. The yield of final step was 23 mg, 21%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.1 (m, 6H), 2.3 (m, 1H), 3.15 (m, 1H), 3.25-3.5 (m, 6H), 3.85 (m, 1H), 4.0 (t, 2H), 5.2 (m, 1H), 7.0 (t, 2H), 7.15 (m, 2H), 7.25 (m, 1H), 7.45 (m, 5H), 7.7 (d, 1H); MS $[M\text{-}CF_3COO]^+$: 541.

EXAMPLE 80

1-(3-Benzyloxypropyl)-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 16 mg, 15%. ^{1}H-NMR (DMSO-d6): δ 1.65 (m, 2H), 1.9 (m, 4H), 2.3 (m, 1H), 3.1-3.4 (m, 7H), 3.5 (t, 2H), 3.9 (m, 1H), 3.9 (s, 2H), 5.2 (m, 1H), 7.0 (m, 2H), 7.15 (m, 2H), 7.35 (m, 5H), 7.5 (m, 3H); MS $[M\text{-}CF_3COO]^+$: 498.

EXAMPLE 81

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[6-(4-phenylbutoxy)hexyl]-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 560 mg, 60%. ^{1}H-NMR (CDCl3): δ 1.2-1.75 (m, 16H), 1.8-2.1 (m, 4H), 2.4 (m, 1H), 2.6 (t, 2H), 3.3-3.75 (m, 11H), 4.2 (m, 1H), 5.3 (m, 1H), 6.0 (bs, OH), 6.95 (m, 2H), 7.15-7.3 (m, 9H); MS $[M\text{-}Br]^+$: 582.

EXAMPLE 82

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(4-phenoxybutyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 240 mg, 30%. ^{1}H-NMR (DMSO-d6/CDCl3): δ 1.8-1.95 (m, 6H), 2.1 (m, 2H), 2.45 (m, 1H), 3.18 (m, 1H), 3.5-3.8 (m, 6H), 4.0 (t, 2H), 4.15 (m, 1H) 5.15 (m, 1H), 6.7 (s, OH), 6.9 (m, 5H), 7.15 (d, 1H), 7.25 (m, 5H); MS [M-Br]$^+$: 498; mp 161° C.

EXAMPLE 83

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 380 mg, 50%. ^{1}H-NMR (DMSO-d6): δ 1-85 (m, 2H), 2.05 (m, 2H), 2.4 (m, 1H), 3.6-4.1 (m, 7H), 4.35 (m, 3H), 5.25 (m, 1H), 6.0 (bs, OH), 6.9 (m, 4H), 7.0 (t, 1H), 7.1 (dd, 2H), 7.2 (dd, 2H), 7.3 (t, 2H); MS [M-Br]$^+$: 470; mp 48° C.

EXAMPLE 84

1-(2-Benzyloxyethyl)-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 17 mg, 17%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.0 (m, 4H), 2.3 (m, 1H), 3.2-3.55 (m, 7H), 3.85 (m, 2H), 4.5 (s, 2H), 5.25 (m, 1H), 7.0 (t, 2H), 7.15 (t, 2H), 7.3-7.4 (m, 4H), 7.5 (m, 3H); MS [M-CF_3COO]$^+$: 484.

EXAMPLE 85

3(S)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 600 mg, 54%. ^{1}H-NMR (DMSO-d6/CDCl3): δ 1.85-2.3 (m, 6H), 2.5 (m, 1H), 3.3 (m, 1H), 3.4 (d, 1H), 3.5-3.7 (m, 5H), 4.05 (t, 2H), 4.2 (m, 1H), 5.25 (m, 1H), 6.85 (d, 2H), 7.0 (m, 3H), 7.15 (m, 2H), 7.2 (d, 1H), 7.3 (m, 4H); MS [M-Br]$^+$: 484; mp 230° C.

EXAMPLE 86

4-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods f and a. The yield of final step was 290 mg, 60%. ^{1}H-NMR (DMSO-d6): δ 2.15 (m, 2H), 2.35 (m, 6H), 3.35 (m, 2H), 3.65 (m, 6H), 4.05 (t, 2H), 6.9-7.05 (m, 5H), 7.1 (m, 2H), 7.3 (m, 3H), 7.55 (m, 2H); MS [M-Br]$^+$: 484; mp 1681C.

EXAMPLE 87

4-(2-Hydroxy-2,2-dithien-2-yl-acetoxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods f and a. The yield of final step was 260 mg, 57%. ^{1}H-NMR (DMSO-d6): δ 2.35 (m, 6H), 3.0 (m, 2H), 3.4 (m, 2H), 3.75 (m, 6H), 7.0 (m, 2H), 7.3-7.5 (m, 6H), 7.55 (m, 2H); MS [M-Br]$^+$: 454; mp 1951C.

EXAMPLE 88

1-(3-phenoxypropyl)-3(R)-(2,2-dithien-2-ylpropionyloxy)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 390 mg, 92%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.20 (m, 6H), 2.10 (s, 3H), 2.30 (bs, 1H), 3.10 (m, 1H), 3.30-3.60 (m, 6H), 3.95-4.10 (m, 3H), 5.20 (m, 1H), 6.90-7.05 (m, 5H), 7.05-7.10 (m, 2H), 7.25-7.35 (m, 2H), 7.50 (m, 2H); MS [M-Br]$^+$: 482; mp 170° C.

EXAMPLE 89

3(R)-(2-Hydroxy-2,2-dithien-3-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 300 mg, 76%. ^{1}H-NMR (DMSO-d6): δ 1.6 (m, 1H), 1.75 (m, 1H), 1.8-2.0 (m, 2H), 2.0-2.2 (m, 2H), 2.3 (m, 1H), 3.15 (m, 1H), 3.3-3.6 (m, 6H), 3.9 (m, 1H), 4.05 (t, 2H), 5.2 (m, 1H), 6.75 (s, OH), 6.95 (m, 3H), 7.15 (m, 2H), 7.3 (t, 2H), 7.4-7.5 (m, 4H); MS [M-Br]$^+$: 484; mp 2191C.

EXAMPLE 90

3(R)-(2-Hydroxy-2,2-dithienyl-3-ylacetoxy)-1-(3-thien-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 300 mg, 77%. ^{1}H-NMR (DMSO-d6): δ 1.5-1.6 (m, 1H), 1.6-1.75 (m, 1H), 1.8-2.1 (m, 4H), 2.25 (m, 1H), 2.8 (t, 2H), 3.05-3.5 (m, 7H), 3.8-3.95 (m, 1H), 5,15 (m, 1H), 6.75 (s, OH), 6.9-7.0 (m, 2H), 7.1 (m, 2H), 7.35-7.55 (m, 5H); MS [M-Br]$^+$: 474; mp 1921C.

EXAMPLE 91

3(R)-(2-Hydroxy-2,2-dithien-3-yl-acetoxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 63 mg, 48%. ^{1}H-NMR (DMSO-d6): δ 1.5-1.7 (m, 1H), 1.7-1.85 (m, 1H), 1.9-2.1 (m, 2H), 2.3 (m, 1H), 2.9-3.1 (m, 2H), 3.15-3.6 (m, 7H), 3.9-4.0 (m, 1H), 5.2 (m, 1H), 6.8 (s, OH), 7.1 (m, 2H), 7.25-7,35 (m, 5H), 7.4 (m, 2H), 7.5 (m, 2H); MS [M-CF3COO]$^+$: 454.

EXAMPLE 92

3(R)-(2-Hydroxy-2,2-dithien-3-yl-acetoxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 75 mg, 55%. ^{1}H-NMR (DMSO-d6): δ 1.5-2.0 (m, 6H), 2.25 (m, 1H), 2.5-2.6 (m, 2H), 3.05-3.6 (m, 8H), 3.8-3.9 (m,1H), 5.15 (m,1H), 6.75 (s, OH), 7.1 (d, 2H), 7.2-7,35 (m, 5H), 7.4 (m, 2H), 7.5 (m, 2H); MS [M-CF3COO]$^+$: 468.

EXAMPLE 93

3(R)-(2-Hydroxy-2,2-dithien-3-ylacetoxy)-1-(4-phenylbutyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 68 mg, 48%. ^{1}H-NMR (DMSO-d6): δ 1.5-1.8 (m, 6H), 1.8-2.0 (m, 2H), 2.25 (m, 1H), 2.6 (m, 2H), 3.05 (m,1H), 3.15-3.45 (m, 6H), 3.85 (m, 1H), 5.15 (m, 1H), 6.75 (s, OH), 7.1 (d, 2H), 7.2 (m, 2H), 7,3 (m, 3H), 7.4 (m, 2H), 7.5 (m, 2H); MS [M-CF3COO]$^+$: 482.

EXAMPLE 94

3(R)-(2-Hydroxy-2,2-dithien-3-ylacetoxy)-1-(2-thien-2-ylethyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 65 mg, 49%. ^{1}H-NMR (DMSO-d6): δ 1.5-1.65 (m, 1H), 1.65-1.78 (m, 1H), 1.85-2.05 (m, 2H), 2.3 (m, 1H), 3.1-3.6 (m, 9H), 3.95 (m, 1H), 5,2 (m, 1H), 6.75 (s, OH), 7.0 (m, 2H), 7.15 (m, 2H), 7.45 (m, 3H), 7,5 (m, 2H); MS [M-CF3COO]$^+$: 460.

EXAMPLE 95

3(R)-(2-Hydroxy-2,2-dithien-3-ylacetoxy)-1-(4-phenoxy-butyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 63 mg, 43%. ^{1}H-NMR (DMSO-d6): δ 1.5-2.0 (m, 8H), 2.3 (m, 1H), 3.1 (m, 1H), 3.2-3.5 (m, 6H), 3.85 (m, 1H), 4.0 (m, 2H), 5.2 (m, 1H), 6.75 (s, OH), 6.95 (m, 3H), 7.1 (d, 2H), 7.2 (m, 2H), 7,3 (t, 2H), 7.45 (m, 2H), 7.5 (m, 2H); MS [M-CF3COO]$^+$: 498.

EXAMPLE 96

3(R)-(2-Hydroxy-2,2-dithien-3-ylacetoxy)-1-(2-phenoxy-ethyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 72 mg, 52%. ^{1}H-NMR (DMSO-d6): δ 1.55-1.65 (m, 1H), 1.7-1.8 (m, 1H), 1.85-2.05 (m, 2H), 2.3 (m, 1H), 3.2-3.6 (m, 5H), 3.7 (m, 2H), 4.05 (m, 1H), 4.4 (m, 2H), 5.2 (m, 1H), 6.75 (s, OH), 6.95-7.05 (m, 3H), 7.1 (d, 2H), 7.3-7.5 (m, 6H); MS [M-CF3COO]$^+$: 470.

EXAMPLE 97

1-[3-(4-Fluorophenoxy)propyl]-3(R)-(2-hydroxy-2,2-dithien-3-ylacetoxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 79 mg, 54%. ^{1}H-NMR (DMSO-d6): δ 1.55-1.65 (m, 1H), 1.7-1.8 (m, 1H), 1.85-2.0 (m, 2H), 2.05-2.2 (m, 2H), 2.3 (m, 1H), 3.1-3.2 (m, 1H), 3.25-3.55 (m, 6H), 3.85-3.95 (m, 1H), 4.0 (t, 2H), 5.2 (m, 1H), 6.75 (s, OH), 6.95 (m, 2H), 7.15 (m, 4H), 7.4 (m, 2H), 7.5 (m, 2H); MS [M-CF3COO]$^+$: 502.

EXAMPLE 98

3(R)-(2-Hydroxy-2,2-dithien-3-ylacetoxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 24 mg, 17%. ^{1}H-NMR (DMSO-d6): δ 1.8-2.05 (m, 4H), 2.3 (m, 1H), 3.15 (m, 1H), 3.3-3.5 (m, 4H), 3.9 (m, 1H), 4.05 (m 2H), 5.25 (m, 1H), 6.35 (m,1H), 6.75 (s, OH), 6.85 (t, 1H), 7.1 (m, 2H), 7.3-7.5 (m, 5H), 7.55 (m, 4H); MS [M-CF3COO]$^+$: 502.

EXAMPLE 99

1-(3-phenylallyl)-3(R)-(9-Hydroxy-9[H]-fluorene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 400 mg, 93%. ^{1}H-NMR (DMSO-d6): δ 1.35-1.50 (m, 1H), 1.60-1.75 (m, 1H), 10 1.75-1.95 (m, 2H), 2.10 (m, 1H), 2.85 (m, 1H), 3.10 (d, 1H), 3.20-3.50 (m, 3H), 3.85 (m,1H), 4.0 (dd, 2H), 5.05 (m,1H), 6.40 (dd, 1H), 6.80-6.90 (d, 1H), 6.85 (s, OH), 7.20-7.50 (m, 7H), 7.60 (m, 4H), 7.80 (m, 2H); MS [M-Br]$^+$: 452; mp 146° C.

EXAMPLE 100

3(R)-(9-Hydroxy-9[H]-fluorene-9-carbonyloxy)-1-(3-phenoxy-propyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 690 mg, 83%. ^{1}H-NMR (DMSO-d6): δ 1.47 (m, 1H), 1.68 (m, 1H), 1.87 (m, 2H), 2.1 (m, 3H), 2.89 (m, 1H), 3.15 (d, 1H), 3.4 (m, 5H), 3.9 (m, 1H), 4.0 (m, 2H), 5.04 (m,1H), 6.85 (s, OH), 6.97 (m, 3H), 7.35 (m, 4H), 7.45 (m, 2H), 7.65 (m, 2H), 7.85 (m, 2H); MS [M-Br]$^+$: 470; mp 108° C.

EXAMPLE 101

3(R)-(9-Hydroxy-9[H]-fluorene-9-carbonyloxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 170 mg, 74%. ^{1}H-NMR (DMSO-d6): δ 1.45 (m, 1H), 1.65 (m, 1H), 1.85 (m, 2H), 2.1 (m, 1H), 2.9 (m, 3H), 3.15 (m, 1H), 3.3-3.5 (m, 5H), 3.85 (m,1H), 5.05 (m,1H), 6.85 (s, OH), 7.2-7.4 (m, 7H), 7.45 (t, 2H), 7.55 (d, 1H), 7.65 (d, 1H), 7.85 (d, 2H); MS [M-Br]$^+$: 440; mp 118° C.

EXAMPLE 102

3(R)-(9-Hydroxy-9[H]-fluorene-9-carbonyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 460 mg, 96%. ^{1}H-NMR (DMSO-d6): δ 1.42 (m, 1H), 1.66 (m, 1H), 1.80-1.88 (m, 2H), 2.08 (m, 1H), 2.93 (m, 1H), 3.25-3.60 (m, 4H), 3.65 (m, 2H), 3.95 (m, 1H), 4.35 (m 2H), 5.02 (m,1H), 6.85 (s, 1H, OH), 6.97 (d, 2H), 7.04 (t, 1H), 7.20-7.45 (m, 6H), 7.55-7.60 (t, 2H), 7.80 (d, 2H); MS [M-Br]$^+$: 456; mp 140° C.

EXAMPLE 103

3(R)-(9-Hydroxy-9[H]-fluorene-9-carbonyloxy)-1-(4-oxo-4-phenylbutyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 15 mg, 15%. ^{1}H-NMR (DMSO-d6): δ 1.45 (m, 1H), 1.65 (m, 1H), 1.7-2.0 (m, 4H), 2.1 (m, 1H), 2.75 (m, 1H), 3.0-3.2 (m 4H), 3.25-3.4 (m, 4H), 3.85 (m,1H), 5.05 (m, 1H), 6.85 (s, OH), 7.35 (t, 2H), 7.45 (t, 2H), 7.55-7.7 (m, 5H), 7.85 (d, 2H), 8.0 (d, 2H); MS [M-CF_3COO]$^+$: 482.

EXAMPLE 104

1-[3-(4-Fluorophenoxy)propyl]-3(R)-(9-hydroxy-9[H]-fluorene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Chloride

The title compound was synthesised according to methods c and a. The yield of final step was 440 mg, 94%. ^{1}H-NMR (DMSO-d6): δ 1.4 (m, 1H), 1.65 (m, 2H), 1.7-1.95 (m, 2H), 2.0-2.1 (m, 3H), 2.8 (m, 1H), 3.1 (d, 1H), 3.2-3.4 (m, 5H), 3.8 (m, 1H), 4.0 (t, 2H), 5.0 (m, 1H), 6.85 (s, OH), 6.95 (m, 2H), 7.15 (t, 2H), 7.35 (t, 2H), 7.45 (t, 2H), 7.55 (d, 1H), 7.65 (d, 1H), 7.85 (d, 2H); MS [M-Br]$^+$: 488; mp 142° C.

EXAMPLE 105

1-[3-(2,4-Difluorophenoxy)propyl]-3(R)-(9-hydroxy-9[H]-fluorene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 14 mg, 13%. ^{1}H-NMR (DMSO-d6): δ 1.4 (m, 1H), 1.6-1.9 (m, 3H), 2.1 (m, 3H), 2.8 (m, 1H), 3.1 (d, 1H), 3.2-3.4 (m, 5H), 3.85 (m, 1H), 4.05 (t, 2H), 5.0 (m, 1H), 6.85 (s, OH), 7.05 (t, 1H), 7.15-7.4 (m, 4H), 7.45 (t, 2H), 7.55 (d, 1H), 7.65 (d, 1H), 7.85 (d, 2H); MS [M-CF_3COO]$^+$: 506.

EXAMPLE 106

3(R)-(9-Hydroxy-9[H]-fluorene-9-carbonyloxy)-1-(3-phenylaminopropyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 14 mg, 15%. ^{1}H-NMR (DMSO-d6): δ 1.4 (m, 1H), 1.6 (m, 1H), 1.8 (m, 4H), 2.05 (m, 1H), 2.7 (m, 1H), 3, 0 (m, 3H), 3.2-3.4 (m, 6H), 3.8 (m, 1H), 5.0 (m, 1H), 5.6 (t, NH), 6.55 (m, 3H), 6.85 (s, OH), 7.1 (t, 2H), 7.35 (dd, 2H), 7.45 (dd, 2H), 7.55 (dd, 2H), 7.8 (d, 2H); MS [M-CF_3COO]$^+$: 469.

EXAMPLE 107

3(R)-(9-Hydroxy-9[H]-fluorene-9-carbonyloxy)-1-[3-(4-hydroxyphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 15 mg, 15%. ^{1}H-NMR (DMSO-d6): δ 1.4 (m, 1H), 1.6 (m, 1H), 1.7-1.9 (m, 2H), 1.95-2.05 (m, 2H), 2.1 (m, 1H), 2.8 (m, 1H), 3.1 (d, 1H) 3.25-3.4 (m, 5H), 3.8-3.9 (m, 3H), 5.0 (m, 1H), 6.7 (d, 2H), 6.75 (d, 2H), 6.85 (s, OH), 7.35 (t, 2H), 7.45 (t, 2H), 7.55 (d, 1H), 7.65 (d, 1H), 7.85 (d, 2H), 9.0 (s, OH); MS [M-CF_3COO]$^+$: 486.

EXAMPLE 108

1-(2-Benzyloxyethyl)-3(R)-(9-hydroxy-9[H]-fluorene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 470 mg, 96%. ^{1}H-NMR (DMSO-d6): δ 1.4 (m, 1H), 1.65 (m, 1H), 1.7-1.9 (m, 2H), 2.1 (m, 1H), 2.9 (m, 1H), 3.15-3.5 (m, 6H), 3.75 (m, 2H), 3.85 (m, 1H), 4.5 (s, 2H), 5.0 (m, 1H), 6.85 (s, OH), 7.3-7.5 (m, 9H), 7.55 (m, 2H), 7.8 (d, 2H); MS [M-Br]$^+$: 470; mp 86° C.

EXAMPLE 109

3(R)-(9-Hydroxy-9H-fluorene-9-carbonyloxy)-1-(3-thienyl-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 180 mg, 70%. ^{1}H-NMR (DMSO-d6): δ 1.37 (m, 1H), 1.62 (m, 1H), 1.75-1.95 (m, 4H), 2.06 (m, 1H), 2.72 (m, 1H), 2.80 (m, 2H), 3.02-3.06 (m, 1H), 3.15-3.20 (m, 2H), 3.25-3.40 (m, 3H), 3.80 (m, 1H), 5.0 (m, 1H), 6.85 (s, 1H, OH), 6.95-7.0 (m, 2H), 7.25-7.50 (m, 5H), 7.55-7.65 (m, 2H), 7.85 (d, 2H); MS [M-Br]$^+$: 460; mp 140° C.

EXAMPLE 110

3(R)— (9-Hydroxy-9H-fluorene-9-carbonyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 80 mg, 40%. ^{1}H-NMR (DMSO-d6): δ 1.35 (m, 1H), 1.6 (m, 1H), 1.7-1.90 (m, 2H), 2.05 (m, 1H), 2.5 (m, 2H), 2.7 (m, 1H), 3.0 (m, 1H), 3.15 (m, 2H), 3.2-3.4 (m, 3H), 3.75 (m, 1H), 5.0 (m, 1H), 6.85 (s, OH), 7.20-7.50 (m, 9H), 7.55 (dd, 2H), 7.85 (d, 2H); MS [M-CF3COO]$^+$: 454.

EXAMPLE 111

3(R)-(9-Hydroxy-9H-fluorene-9-carbonyloxy)-1-(4-phenylbutyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 74 mg, 35%. ^{1}H-NMR (DMSO-d6): δ 1.35 (m, 1H), 1.45-1.65 (m, 5H), 1.7-1.90 (m, 2H), 2.05 (m, 1H), 2.55-2.75 (m, 3H), 3.0 (m, 1H), 3.15-3.45 (m, 5H), 3.75 (m, 1H), 5.0 (m, 1H), 6.85 (s, OH), 7.20 (m, 3H), 7.25-7.35 (m, 4H), 7.45-7.5 (m, 2H), 7.55-7.6 (dd, 2H), 7.85 (d, 2H); MS [M-CF3COO]$^+$: 468.

EXAMPLE 112

3(R)-(9-Hydroxy-9H-fluorene-9-carbonyloxy-1-(2-thienyl-2-ylethyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 79 mg, 39%. ^{1}H-NMR (DMSO-d6): δ 1.4 (m, 1H), 1.65 (m, 1H), 1.8-1.95 (m, 2H), 2.1 (m, 1H), 2.9 (m, 1H), 3.1-3.25 (m, 4H), 3.15-3.45 (m, 5H), 3.85 (m, 1H), 5.05 (m, 1H), 6.85 (s, OH), 7.0 (m, 2H), 7.35 (t, 2H), 7.45-7.5 (m, 3H), 7.55 (d, 1H), 7.65 (d, 1H), 7.85 (d, 2H); MS[M-CF3COO]$^+$: 446.

EXAMPLE 113

3(R)-(9-Hydroxy-9H-fluorene-9-carbonyloxy)-1-(4-phenoxybutyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 72 mg, 33%. ^{1}H-NMR (DMSO-d6): δ 1.4 (m, 1H), 1.55-1.9 (m, 7H), 2.05 (m, 1H), 2.7 (m, 1H), 3.0 (m, 1H), 3.15-3.5 (m, 7H), 3.8 (m, 1H), 4.0 (m, 2H), 5.05 (m, 1H), 6.85 (s, OH), 6.95 (m, 3H), 7.25-7.35 (m, 4H), 7.4-7.45 (m, 2H), 7.6 (dd, 2H), 7.85 (d, 2H); MS [M-CF3COO]$^+$: 484.

EXAMPLE 114

3(R)-(9-Methyl-9[H]-fluorene-9-carbonyloxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 200 mg, 76%. ^{1}H-NMR (DMSO-d6): δ 1.54 (m, 1H), 1.70-1.86 (m, 3H), 1.76 (s, 3H), 2.13 (m, 1H), 3.06 (m, 1H), 3.20-3.50 (m, 4H), 3.86 (m, 1H), 4.05 (dd, 2H), 5.02 (m, 1H), 6.43 (dd, 1H), 6.86 (d, 1H), 7.26-7.46 (m, 7H), 7.58-7.65 (m, 3H), 7.70-7.72 (m, 1H), 7.87-7.90 (m, 2H); MS [M-Br]$^+$: 450; mp 234° C.

EXAMPLE 115

3(R)-(9-Methyl-9[H]-fluorene-9-carbonyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 210 mg, 66%. ^{1}H-NMR (DMSO-d6): δ 1.55 (m, 1H), 1.60-2.0 (m, 3H), 1.76 (s, 3H), 2.12 (m, 1H), 3.10-3.25 (m, 1H), 3.40-3.80 (m, 6H), 4.0 (m, 1H), 4.41 (m, 2H), 4.98 (m, 1H), 6.98-7.05 (m, 3H), 7.27-7.46 (m, 6H), 7.63-7.71 (m, 2H), 7.87-7.90 (m, 2H); MS [M-Br]$^+$: 454; mp 202° C.

EXAMPLE 116

3(R)-(9-Methyl-9[H]-fluorene-9-carbonyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 210 mg, 61%. ^{1}H-NMR (DMSO-d6): δ 1.55 (m, 1H), 1.60-2.0 (m, 3H), 1.78 (s, 3H), 2.0-2.20 (m, 3H), 3.0-3.10 (m, 1H), 3.25-3.53 (m, 6H), 3.86 (m, 1H), 4.03 (m, 2H), 4.98 (m, 1H), 6.95-7.0 (m, 3H), 7.30-7.48 (m, 6H), 7.65-7.92 m, 4H); MS [M-Br]$^+$: 468; mp 204° C.

EXAMPLE 117

3(R)-(9-Methyl-9[H]-fluorene-9-carbonyloxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 18 mg, 19%. ^{1}H-NMR (DMSO-d6): δ 1.55 (m, 1H), 1.65-1.95 (m, 3H), 1.75 (s, 3H), 2.15 (m, 1H), 2.9-3.1 (m, 4H), 3.25-3.55 (m, 5H), 3.85 (m, 1H), 5.05 (m, 1H), 7.25-7.55 (m, 9H), 7.65 (d, 1H), 7.75 (d, 1H), 7.95 (d, 2H); MS [M-CF_3COO]$^+$: 438.

EXAMPLE 118

3(R)-(9-Methyl-9[H]-fluorene-9-carbonyloxy)-1-(4-oxo-4-phenylbutyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 19%. ^{1}H-NMR (DMSO-d6): δ 1.55 (m, 1H), 1.65-2.05 (m, 5H), 1.75 (s, 3H), 2.1 (m, 1H) 3.0 (m, 1H), 3.1-3.5 (m, 8H), 3.85 (m, 1H), 7.35-7.5 (m, 4H), 7.55 (t, 2H), 7.65 (t, 2H), 7.7 (d, 1H), 7.9 (d, 2H), 8.0 (d, 2H); MS [M-CF_3COO]$^+$: 480.

EXAMPLE 119

1-[3-(4-Fluorophenoxy)propyl]-3(R)-(9-methyl-9[H]-fluorene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 23 mg, 23%. ^{1}H-NMR (DMSO-d6): δ 1.55 (m, 1H), 1.65-1.95 (m, 3H), 1.75 (s, 3H), 2.05-2.15 (m, 3H), 3.0 (m, 1H), 3.25-3.5 (m, 6H), 3.85 (m, 1H), 4.0 (t, 2H), 5.0 (m, 1H), 6.95 (m, 2H), 7.15 (t, 2H), 7.35-7.5 (m, 4H), 7.65 (d, 1H), 7.75 (d, 1H), 7.9 (d, 2H); MS [M-CF_3COO]$^+$: 486.

EXAMPLE 120

1-[3-(2,4-Difluorophenoxy)propyl]-3(R)-(9-methyl-9H-fluorene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 20 mg, 19%. ^{1}H-NMR (DMSO-d6): δ 1.55 (m, 1H), 1.65-1.95 (m, 3H), 1.75 (s, 3H), 2.05-2.2 (m, 3H), 3.0 (m, 1H), 3.25-3.55 (m, 6H), 3.85 (m, 1H), 4.1 (t, 2H), 5.0 (m, 1H), 7.05 (t, 1H), 7.2-7.5 (m, 6H), 7.65 (d, 1H), 7.75/d, 1H), 7.9 (d, 2H); MS [M-CF_3COO]$^+$: 504.

EXAMPLE 121

3(R)-(9-Methyl-9[H]-fluorene-9-carbonyloxy)-1-(3-phenylaminopropyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 19%. ^{1}H-NMR (DMSO-d6): δ 1.55 (m, 1H), 1.65-1.95 (m, 5H), 1.75 (s, 3H), 2.1 (m, 1H), 2.95 (m, 1H), 3.05 (m, 2H), 3.15-3.45 (m, 6H), 3.8 (m, 1H), 5.0 (m, 1H), 5.65 (t, NH), 6.6 (m, 3H), 7.1 (t, 2H), 7.35-7.55 (m, 4H), 7.65 (d, 1H), 7.75 (d, 1H), 7.9 (d, 2H); MS [M-CF_3COO]$^+$: 467.

EXAMPLE 122

1-[3-(4-Hydroxyphenoxy)propyl]-3(R)-(9-methyl-9[H]-fluorene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 22 mg, 22%. ^{1}H-NMR (DMSO-d6): δ 1.55 (m, 1H), 1.65-1.9 (m, 3H), 1.75 (s, 3H), 2.0-2.15 (m, 3H), 3.0 (m, 1H), 3.25-3.5 (m, 6H), 3.8-3.95 (m, 3H), 5.0 (m, 1H), 6.7 (d, 1H), 6.75 (d, 1H), 7.35-7.45 (m, 4H), 7.65 (d, 1H), 7.75 (d, 1H), 7.9 (d, 2H), 9.0 (s, OH); MS [M-CF_3COO]$^+$: 484.

EXAMPLE 123

1-(2-Benzyloxyethyl)-3(R)-(9-methyl-9[H]-fluorene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 17 mg, 17%. ^{1}H-NMR (DMSO-d6): δ 1.55 (m, 1H), 1.65-1.95 (m, 4H), 1.75 (s, 3H), 2.15 (m, 1H), 3.1 (m, 1H), 3.3-3.55 (m, 6H), 3.8-3.95 (m, 3H), 4.5 (s, 2H), 5.0 (m, 1H), 7.3-7.5 (m, 9H), 7.6-7.7 (m, 2H), 7.9 (d, 2H); MS [M-CF_3COO]$^+$: 468.

EXAMPLE 124

3(R)-(9,10-Dihydroanthracene-9-carbonyloxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods d and a. The yield of final step was 420 mg, 89%. ^{1}H-NMR (DMSO-d6): δ 1.55 (m, 1H), 1.65-1.95 (m, 3H), 2.15 (m, 1H), 2.95 (m, 2H), 3.15 (m, 1H), 3.25-3.60 (m, 6H), 3.85 (m, 1H), 3.95-4.15 (dd, 2H, J1=1.8 Hz, J2=4.2 Hz), 5.02 (m, 1H), 5.25 (s, 1H), 7.25-7.43 (m, 11H), 7.48-7.55 (m, 2H); MS [M-Br]$^+$: 438; mp 216° C.

EXAMPLE 125

3(R)-(9,10-Dihydroanthracene-9-carbonyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods d and a. The yield of final step was 450 mg, 82%. ^{1}H-NMR (DMSO-d6): δ 1.56 (m, 1H), 1.65-1.95 (m, 3H), 2.05-2.15 (m, 3H), 3.10 (m, 1H), 3.20-3.50 (m, 6H), 3.80 (m, 1H), 3.94-4.14 (m, 4H), 5.0 (m, 1H), 5.22 (s, 1H), 6.94-7.0 (m, 3H), 7.25-7.35 (m, 6H), 7.40 (m, 2H), 7.54-7.47 (m, 2H); MS [M-Br]$^+$: 468; mp 157° C.

EXAMPLE 126

1-(4-Phenylbutyl)-3(R)-(9[H]-xanthene-9-carbonyloxy)-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods d and a. The yield of final step was 83 mg, 21%. ^{1}H-NMR (DMSO-d6): δ 1.50-2.0 (m, 8H), 2.15 (m, 1H), 2.65 (m, 2H), 3.05-3.65 (m, 7H), 3.80 (m, 1H), 5.0 (m, 1H), 5.30 (s, 1H), 7.10-7.45 (m, 11H), 7.45-7.60 (m, 2H); MS [M-Br]$^+$: 468; mp 95° C.

EXAMPLE 127

1-(2-Phenoxyethyl)-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods d and a. The yield of final step was 300 mg, 73%. ^{1}H-NMR (DMSO-d6): δ 1.70-2.0 (m, 4H), 2.2 (m, 1H), 3.20-3.80 (m, 7H), 4.0 (m, 1H), 4.40 (m, 2H), 5.05 (m, 1H), 5.30 (s, 1H), 7.0-7.10 (m, 7H), 7.30-7.45 (m, 4H), 7.45-7.55 (m, 2H); MS [M-Br]$^+$: 456; mp 200° C.

EXAMPLE 128

1-(3-Phenoxypropyl)-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods d and a. The yield of final step was 350 mg, 83%. ^{1}H-NMR (DMSO-d6): δ 1.70-2.0 (m, 4H), 2.0-2.25 (m, 3H), 3.15-3.65 (m, 7H), 3.85-3.95 (m, 1H), 3.95-4.10 (m, 2H), 5.0 (m, 1H), 5.30 (s, 1H), 6.90-7.0 (m, 3H), 7.10-7.25 (m, 4H), 7.25-7.40 (m, 4H), 7.40-7.60 (m, 2H); MS [M-Br]$^+$: 470; mp 184° C.

EXAMPLE 129

1-Phenethyl-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo [2.2.2]octane; Bromide

The title compound was synthesised according to methods d and a. The yield of final step was 100 mg, 44%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.0 (m, 4H), 2.1 (m, 1H), 2.9-3.05 (m, 2H), 3.15-3.6 (m, 7H), 3.85 (m, 1H), 5.05 (m, 1H), 5.3 (s, 1H)), 7.15-7.55 (m, 13H); MS [M-Br]$^+$: 440.

EXAMPLE 130

1-(4-Oxo-4-phenylbutyl)-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods d and b. The yield of final step was 16 mg, 15%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.05 (m, 6H), 2.1 (m, 1H), 3.1-3.55 (m, 9H), 3.8 (m, 1H), 5.05 (m, 1H), 5.25 (s, 1H), 7.1-7.3 (m, 4H), 7.35 (t, 2H), 7.45-7.6 (m, 4H), 7.7 (d, 1H), 8.0 (d, 1H); MS [M-CF_3COO]$^+$: 482.

EXAMPLE 131

1-[3-(4-Fluorophenoxy)propyl]-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane, Trifluoroacetate

The title compound was synthesised according to methods d and b. The yield of final step was 18 mg, 18%. ^{1}H-NMR (DMSO-d6): δ 1.7-2.1 (m, 6H), 2.15 (m, 1H), 3.1-3.5 (m, 7H), 3.8 (m, 1H), 4.0 (t, 2H), 5.0 (m, 1H), 5.3 (s, 1H), 6.95 (m, 2H), 7.1-7.3 (m, 6H), 7.4 (t, 2H), 7.5 (dd, 2H); MS [M-CF_3COO]$^+$: 488.

EXAMPLE 132

1-[3-(2,4-Difluorophenoxy)propyl]-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods d and b. The yield of final step was 14 mg, 14%. ^{1}H-NMR (DMSO-d6): δ 1.65-1.95 (m, 4H), 2.05-2.2 (m, 3H), 3.1-3.55 (m, 7H), 3.8 (m, 1H), 4.05 (t, 2H), 5.0 (m, 1H), 5.3 (s, 1H), 7.05 (t, 1H), 7.1-7.55 (m, 10H); MS [M-CF_3COO]$^+$: 506.

EXAMPLE 133

1-(3-Phenylaminopropyl)-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods d and b. The yield of final step was 17 mg, 17%. ^{1}H-NMR (DMSO-d6): δ 1.65-2.0 (m, 6H), 2.15 (m, 1H), 3.0-3.5 (m, 9H), 1.75 (m, 1H), 5.0 (m, 1H), 5.3 (s, 1H), 6.65 (t, NH), 6.55 (m, 3H), 0.05-7.3 (m, 6H), 7.35-7.55 (m, 4H); MS [M-CF_3COO]$^+$: 469.

EXAMPLE 134

1-[3-(4-Hydroxyphenoxy)propyl]-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods d and b. The yield of final step was 21 mg, 20%. ^{1}H-NMR (DMSO-d6): δ 1.7-2.1 (m, 6H), 2.15 (m, 1H), 3.1-3.5 (m, 7H), 3.7-3.95 (m, 3H), 5.0 (m, 1H), 5.3 (s, 1H), 6.7 (d, 2H), 6.75 (d, 2H), 7.1-7.3 (m, 4H), 7.35-7.55 (m, 4H), 9.0 (s, OH); MS [M-CF_3COO]$^+$: 486.

EXAMPLE 135

1-(2-Benzyloxyethyl)-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods d and b. The yield of final step was 16 mg, 16%. ^{1}H-NMR (DMSO-d6): δ 1.65-1.95 (m, 4H), 2.1 (m, 1H), 3.1-3.9 (m, 10H), 4.5 (s, 2H), 5.0 (m, 1H), 5.3 (s, 1H), 7.15 (m, 4H), 7.3-7.5 (m, 7H), 7.55 (t, 2H); MS [M-CF_3COO]$^+$: 470.

EXAMPLE 136

3(R)-(9-Hydroxy-9[H]-xanthene-9-carbonyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 340 mg, 71%. ^{1}H-NMR (DMSO-d6): δ 1.30 (m, 1H), 1.65 (m, 1H), 1.70-1.95 (m, 2H), 1.95-2.10 (m, 3H), 2.70 (m, 1H), 2.90 (m, 1H), 3.2-3.5 (m, 5H), 3.80 (m, 1H), 4.0 (t, 2H), 5.05 (m, 1H), 6.90-7.0 (m, 3H), 7.20-7.35 (m, 7H), 7.40-7.46 (m, 2H), 7.65-7.70 (m, 2H); MS [M-Br]$^+$: 486; mp 219° C.

EXAMPLE 137

3(R)-(9-Hydroxy-9[H]-xanthene-9-carbonyloxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 290 mg, 64%. ^{1}H-NMR (DMSO-d6): δ 1.32 (m, 1H), 1.65 (m, 1H), 1.70-1.95 (m, 2H), 2.1 (m, 1H), 2.75-2.90 (m, 3H), 3.05 (m, 1H), 3.30-3.50 (m, 5H), 3.82 (m, 1H), 5.05 (m, 1H), 7.20-7.40 (m, 10H), 7.40-7.50 (m, 2H), 7.65-7.70 (m, 2H); MS [M-Br]$^+$: 456; mp 221° C.

EXAMPLE 138

3(R)-(9-Hydroxy-9H-xanthene-9-carbonyloxy)-1-(3-thien-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 310 mg, 97%. ^{1}H-NMR (DMSO-d6): δ 1.30 (m, 1H), 1.62 (m, 1H), 1.70-1.90 (m, 4H), 2.05 (m, 1H), 2.60 (m, 1H), 2.75-2.85 (m, 4H), 3.15 (m, 2H), 3.25-3.40 (m, 2H), 3.75 (m, 1H), 5.0 (m, 1H), 6.93 (m, 1H), 7.0 (m, 1H), 7.14-7.26 (m, 5H), 7.36-7.45 (m, 3H), 7.63-7.67 (m, 2H); MS [M-Br]$^+$: 476; mp 111° C.

EXAMPLE 139

3(R)-(9-Hydroxy-9H-xanthene-9-carbonyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 85 mg, 41%. ^{1}H-NMR (DMSO-d6): δ 1.30 (m, 1H), 1.65 (m, 1H), 1.70-1.95 (m, 2H), 2.05 (m, 1H), 2.5-2.6 (m, 2H), 2.80 (m, 1H), 3.05-3.75 (m, 7H), 5.05 (m, 1H), 7.1-7.45 (m, 12H), 7.65-7.70 (m, 2H); MS [M-CF3COO]$^+$: 470.

EXAMPLE 140

3(R)-(9-Hydroxy-9H-xanthene-9-carbonyloxy)-1-(4-phenylbutyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 84 mg, 38%. ^{1}H-NMR (DMSO-d6): δ 1.30 (m, 1H), 1.4-1.85 (m, 7H), 2.05 (m, 1H), 2.5-2.6 (m, 2H), 2.80 (m, 1H), 3.05-3.4 (m, 6H), 3.7 (m, 1H), 5.05 (m, 1H), 7.15-7.35 (m, 10H), 7.4 (m, 1H), 7.65 (m, 2H); MS [M-CF3COO]$^+$: 484.

EXAMPLE 141

3(R)-(9-Hydroxy-9H-xanthene-9-carbonyloxy)-1-(2-thien-2-ylethyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 81 mg, 39%. ^{1}H-NMR (DMSO-d6): δ 1.30 (m, 1H), 1.6 (m, 1H), 1.7-1.9 (m, 2H), 2.05 (m, 1H), 2.75 (m, 1H), 3.0 (m, 1H), 3.1-3.2 (m, 2H), 3.3-3.6 (m, 5H), 3.8 (m, 1H), 5.05 (m, 1H), 6.95-7.0 (m, 2H), 7.15-7.3 (m, 5H), 7.45 (m, 3H), 7.65 (m, 2H); MS [M-CF3COO]$^+$: 462.

EXAMPLE 142

3(R)-(9-Hydroxy-9H-xanthene-9-carbonyloxy)-1-(4-phenoxybutyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 83 mg, 37%. ^{1}H-NMR (DMSO-d6): δ 1.3 (m, 1H), 1.5-1.9 (m, 7H), 2.05 (m, 1H), 2.6 (m, 1H), 2,8 (m, 1H), 3.1-3.45 (m, 7H), 3.75 (m, 1H), 4.0 (m, 2H), 5.05 (m,1H), 6.95-7.0 (m, 3H), 7.15-7.45 (m, 9H), 7.65 (m, 2H); MS [M-CF3COO]$^+$: 500.

EXAMPLE 143

3(R)-(9-Hydroxy-9H-xanthene-9-carbonyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 102 mg, 48%. ^{1}H-NMR (DMSO-d6): δ 1.3 (m, 1H), 1.55-1.95 (m, 3H), 2.05 (m, 1H), 2,8 (m, 1H), 3.1 (m, 1H), 3.35-3.65 (m, 5H), 3.9 (m, 1H), 4.35 (m, 2H), 5.05 (m, 1H), 6.95 (d, 2H), 7.0-7.1 (m, 2H), 7.2 (m, 4H), 7.3-7.45 (m, 4H), 7.6 (t, 2H); MS [M-CF3COO]$^+$: 472.

EXEMPLE 144

1-[3-(4-Fluorophenoxy)propyl]-3(R)-(9-hydroxy-9H-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 99 mg, 44%. ^{1}H-NMR (DMSO-d6): δ 1.3 (m, 1H), 1.6 (m, 1H), 1.7-2.0 (m, 4H), 2.05 (m, 1H), 2.7 (m, 1H), 2.9 (m, 1H), 3.2-3.5 (m, 5H), 3.75-3.85 (m,1H), 3.95 (m, 2H), 5.0 (m,1H), 6.95 (m, 2H), 7.1-7.3 (m, 7H), 7.45 (t, 2H), 7.65 (t, 2H); MS [M-CF3COO]$^+$: 504.

EXEMPLE 145

3(R)-(9-Hydroxy-9H-xanthene-9-carbonyloxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 25 mg, 12%. ^{1}H-NMR (DMSO-d6): δ 1.25-1.30 (m, 1H), 1.55-1.95 (m, 3H), 2.10 (m, 1H), 2.65-2.75 (m, 1H), 2.9 (m, 1H), 3.25-3.50 (m, 2H), 3.75-3.8 (m,1H), 3.95 (m, 2H), 4.2 (d, 1H), 5.0 (m, 1H), 6.35 (m, 1H), 6.80 (d, 1H), 7.05-7.50 (m, 8H), 7.60 (m, 4H); MS [M-CF3COO]$^+$: 468.

EXAMPLE 146

3(R)-(9-Methyl-9[H]-xanthene-9-carbonyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods c and a. The yield of final step was 110 mg. ^{1}H-NMR (DMSO-d6): δ 1.4 (m, 1H), 1.65 (m, 1H), 1.75-1.95 (m, 2H), 1.9 (s, 3H), 2.05-2.15 (m, 3H), 1.8 (m, 1H), 3.15 (m, 2H), 3.25-3.5 (m, 5H), 3.85 (m, 1H), 4.0 (t, 2H), 5.05 (m, 1H), 6.95-7.0 (m, 3H), 7.15-7.2 (m, 4H), 7.3-7.4 (m, 4H), 7.45 (d, 1H), 7.55 (d, 1H); MS [M-Br]$^+$: 484; mp 195° C.

EXAMPLE 147

3(R)-(9-Methyl-9[H]-xanthene-9-carbonyloxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 20%. ^{1}H-NMR (DMSO-d6): δ 1.4 (m, 1H), 1.65 (m, 1H), 1.8-1.95 (m, 2H), 1.9 (s, 3H), 2.15 (m, 1H), 2.8-2.95 (m, 3H), 3.15 (d, 1H), 3.3-3.5 (m, 5H), 4.9 (m, 1H), 5.1 (m, 1H), 7.15 (m, 4H), 7.25-7.4 (m, 7H), 7.45 (d, 1H), 7.55 (d, 1H); MS [M-CF_3COO]$^+$: 454.

EXAMPLE 148

3(R)-(9-Methyl-9[H]-xanthene-9-carbonyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 24 mg, 24%. ^{1}H-NMR (DMSO-d6): δ 1.4 (m, 1H), 1.65 (m, 1H), 1.8-1.95 (m, 2H), 1.9 (s, 3H), 2.15 (m, 1H), 2.95 (m, 1H), 3.25 (m, 1H), 3.4-3.65 (m, 5H), 3.85 (m, 1H), 4.35 (t, 2H), 5.05 (m, 1H), 6.95 (d, 2H), 7.05 (t, 2H), 7.15 (m, 3H), 7.25-7.45 (m, 6H); MS [M-CF_3COO]$^+$: 470.

EXAMPLE 149

3(R)-(9-Methyl-9[H]-xanthene-9-carbonyloxy)-1-(4-oxo-4-phenylbutyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 19%. ^{1}H-NMR (DMSO-d6): δ 1.4 (m, 1H), 1.65 (m, 1H), 1.75-1.95 (m, 7H), 2.15 (m, 1H), 2.8 (m, 1H), 3.05-3.25 (m, 4H), 3.3-3.5 (m, 4H), 3.85 (m, 1H), 5.05 (m, 1H), 7.15 (m, 4H), 7.35 (t, 2H), 7.45-7.6 (m, 4H), 7.7 (t, 1H), 8.0 (d, 2H); MS [M-CF_3COO]$^+$: 496.

EXAMPLE 150

1-[3-(4-Fluorophenoxy)propyl]-3(R)-(9-methyl-9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 25 mg, 24%. ^{1}H-NMR (DMSO-d6): δ 1.4 (m, 1H), 1.65 (m, 1H), 1.75-1.95 (m, 2H), 1.9 (s, 3H), 1-95-2.1 (m, 2H), 2.15 (m, 1H), 2.8 (m, 1H), 3.1

(d, 1H), 3.25-3.5 (m, 5H), 3.8 (m, 1H), 4.0 (t, 2H), 5.05 (m, 1H), 6.95 (m, 2H), 7.15 (m, 6H), 7.35 (t, 2H), 7.5 (dd, 2H); MS $[M\text{-}CF_3COO]^+$: 502.

EXAMPLE 151

1-[3-(2,4-Difluorophenoxy)propyl]-3(R)-(9-methyl-9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 16 mg, 15%. ^{1}H-NMR (DMSO-d6): δ 1.4 (m, 1H), 1.65 (m, 1H), 1.75-1.95 (m, 2H), 1.9 (s, 3H), 2.0-2.15 (m, 3H), 2.8 (m, 1H), 3.1 (d, 1H), 7.05 (t, 1H), 7.1-7.4 (m, 8H), 7.5 (dd, 2H); MS $[M\text{-}CF_3COO]^+$: 520.

EXAMPLE 152

3(R)-(9-Methyl-9[H]-xanthene-9-carbonyloxy)-1-(3-phenylaminopropyl)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 16 mg, 15%. ^{1}H-NMR (DMSO-d6): δ 1.35 (m, 1H), 1.6 (m, 1H), 1.7-1.9 (m, 4H), 1.9 (s, 3H), 2.1 (m, 1H), 2.7 (m, 1H), 2.95-3.05 (m, 3H), 3.1-3.4 (m, 6H), 3.75 (m, 1H), 5.0 (m, 1H), 5.6 (m, 1H), 6.55 (m, 3H), 7.05-7.15 (m, 6H), 7.3 (m, 2H), 7.45 (t, 2H); MS $[M\text{-}CF_3COO]^+$: 483.

EXAMPLE 153

1-[3-(4-Hydroxyphenoxy)propyl]-3(R)-(9-methyl-9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 18%. ^{1}H-NMR (DMSO-d6): δ 1.4 (m, 1H), 1.65 (m, 1H), 2.75-2.05 (m, 4H), 1.9 (s, 3H), 2.15 (m, 1H), 2.8 (m, 1H), 3.1 (d, 1H), 3.25-3.5 (m, 5H), 3.8-3.95 (m, 3H), 5.05 (m, 1H), 6.65-6.8 (m, 4H), 7.2 (m, 4H), 7.35 (t, 2H), 7.5 (m, 2H), 9.0 (s, OH); MS $[M\text{-}CF_3COO]^+$: 500.

EXAMPLE 154

1-(2-Benzyloxyethyl)-3(R)-(9-methyl-9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Trifluoroacetate

The title compound was synthesised according to methods c and b. The yield of final step was 14 mg, 14%. ^{1}H-NMR (DMSO-d6): δ 1.4 (m, 1H), 1.65 (m, 1H), 1.75-1.95 (m, 2H), 1.9 (s, 3H), 2.1 (m, 1H), 2.9 (m, 1H), 3.2-3.5 (m, 6H), 3.75-3.95 (m, 3H), 4.5 (s, 2H), 5.05 (m, 1H), 7.15 (m, 4H), 7.3-7.5 (m, 9H); MS $[M\text{-}CF_3COO]^+$: 484.

EXAMPLE 155

1-(3-Phenoxypropyl)-3(R)-(9[H]-thioxanthene-9-carbonyloxy)-1-azonia-bicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods d and a. The yield of final step was 323 mg, 50%. ^{1}H-NMR (DMSO-d6): δ 1.35 (m, 1H), 1.65 (m, 1H), 1.70-1.95 (m, 2H), 2.0-2.2 (m, 3H), 2.75-2.90 (m, 1H), 3,12 (m, 1H), 3.25-3.50 (m, 5H), 3.80 (m, 1H), 4.0 (t, 2H), 5.0 (m, 1H), 5.6 (s, 1H), 6.94-7.0 (m, 3H), 7.22-7.41 (m, 6H), 7.45-7.64 (m, 4H); MS $[M\text{-}Br]^+$: 486; mp 157° C.

EXAMPLE 156

1-(3-phenylallyl)-3(R)-(10,11-Dihydro-5H-dibenzo[a,d]cycloheptene-5-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods d and a. The yield of final step was 250 mg, 94%. ^{1}H-NMR (CDCl3): δ 1.50-1.60 (m, 1H), 1.60-1.80 (m, 1H), 1.90 (m, 2H), 2.30 (m, 1H), 2.65-2.80 (m, 2H), 2.90-3.20 (m, 3H), 3.50 (d, 1H), 3.60-3.90 (m, 3H), 4.20 (m, 1H), 4.35-4.60 (doble dd, 2H), 5.10 (m, 1H), 5.15 (s, 1H), 6.05 (dd, 1H), 6.90-7.0 (m, 2H), 7.0-7.5 (m, 11H); MS $[M\text{-}Br]^+$: 464; mp 132° C.

EXAMPLE 157

1-(3-phenoxypropyl)-3(R)-(10,11-Dihydro-5H-dibenzo[a,d]cycloheptene-5-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods d and a. The yield of final step was 290 mg, 94%. ^{1}H-NMR (CDCl3): δ 1.45-1.60 (m, 1H), 1.65-1.80 (m, 1H), 1.80-2.0 (m, 2H), 2.0-2.20 (m, 3H), 2.80-3.0 (m, 3H), 3.15-3.30 (m, 2H), 3.30-3.45 (d, 1H), 3.45-3.80 (m, 5H), 3.85-4.0 (m, 2H), 4.20 (m, 1H), 5.10 (m, 1H), 5.20 (s, 1H), 6.80-6.90 (d, 2H), 6.90-7.0 (t, 1H), 7.10-7.30 (m, 8H), 7.40 (m, 2H); MS $[M\text{-}Br]^+$: 482; mp 182° C.

EXAMPLE 158

3(R)-(5[H]-Dibenzo[a,d]cycloheptene-5-carbonyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods d and a. The yield of final step was 180 mg, 56%. ^{1}H-NMR (DMSO-d6): δ 1.2 (m, 1H), 1.6 (m, 1H), 1.7-1.9 (m, 2H), 1.95 (m, 1H), 2.1 (m, 2H), 2.8 (m, 1H), 2.95 (d, 1H), 3.25-3.45 (m, 5H), 3.8 (m, 1H), 4.05 (t, 2H), 4.9 (m, 1H), 5.45 (s, 1H), 6.9-7.1 (m, 5H), 7.3-7.5 (m, 9H), 7.55 (d, 2H); MS $[M\text{-}Br]^+$: 480; mp 1111C.

EXAMPLE 159

3(R)-(5[H]-Dibenzo[a,d]cycloheptene-5-carbonyloxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; Bromide

The title compound was synthesised according to methods d and a. The yield of final step was 210 mg, 68%. ^{1}H-NMR (DMSO-d6): δ 1.2 (m, 1H), 1.7-1.9 (m, 2H), 2.0 (m, 1H), 2.85-3.1 (m, 4H), 3.3-3.5 (m, 5H), 3.85 (m, 1H), 4.95 (m, 1H), 5.45 (s, 1H), 7.05 (m, 2H), 7.25-7.5 (m, 11H), 7.55 (m, 2H); MS $[M\text{-}Br]^+$: 450; mp 2481C.

The Examples 160 to 164 illustrate pharmaceutical compositions according to the present invention and procedure for their preparation.

EXAMPLE 160

Preparation of a pharmaceutical composition: tablets	
Formulation:	
Compound of the present invention	5.0 mg
Lactose	113.6 mg
Microcrystalline cellulose	28.4 mg
Light silicic anhydride	1.5 mg
Magnesium stearate	1.5 mg

Using a mixer machine, 15 g of the compound of the present invention was mixed with 340.8 g of lactose and 85.2 g of microcrystalline cellulose. The mixture was subjected to compression moulding using a roller compactor to give a flake-like compressed material. The flake-like compressed

material was pulverized using a hammer mill, and the pulverized material was screened through a 20 mesh screen. A 4.5 g portion of light silicic anhydride and 4.5 g of magnesium stearate were added to the screened material and mixed. The mixer product was subjected to a tablets making machine equipped with a die/punch system of 7.5 mm in diameter, thereby obtaining 3,000 tablets each having 150 mg in weight.

EXAMPLE 161

Preparation of a pharmaceutical composition: tablets coated	
Formulation:	
Compound of the present invention	5.0 mg
Lactose	95.2 mg
Corn starch	40.8 mg
Polyvinylpyrrolidone K25	7.5 mg
Magnesium stearate	1.5 mg
Hydroxypropylcellulose	2.3 mg
Polyethylene glycol 6000	0.4 mg
Titanium dioxide	1.1 mg
Purified talc	0.7 mg

Using a fluidized bed granulating machine, 15 g of the compound of the present invention was mixed with 285.6 g of lactose and 122.4 g of corn starch. Separately, 22.5 g of polyinylpyrrolidone was dissolved in 127.5 g of water to prepare a binding solution. Using a fluidized bed granulating machine, the binding solution was sprayed on the above mixture to give granulates. A 4.5 g portion of magnesium stearate was added to the obtained granulates and mixed. The obtained mixture was subjected to a tablet making machine equipped with a die/punch biconcave system of 6.5 mm in diameter, thereby obtaining 3,000 tablets, each having 150 mg in weight.

Separately, a coating solution was prepared by suspending 6.9 g of hydroxypropylmethylcellulose 2910, 1.2 g of polyethylene glycol 6000, 3.3 g of titanium dioxide and 2.1 g of purified talc in 72.6 g of water. Using a High Coated, the 3,000 tablets prepared above were coated with the coating solution to give film-coated tablets, each having 154.5 mg in weight.

EXAMPLE 162

Preparation of a pharmaceutical composition: liquid inhalant	
Formulation:	
Compound of the present invention	400 Φg
Physiological saline	1 ml

A 40 mg portion of the compound of the present invention was dissolved in 90 ml of physiological saline, and the solution was adjusted to a total volume of 100 ml with the same saline solution, dispensed in 1 ml portions into 1 ml capacity ampoule and then sterilized at 1151 for 30 minutes to give liquid inhalant.

EXAMPLE 163

Preparation of a pharmaceutical composition: powder inhalant	
Formulation:	
Compound of the present invention	200 Φg
Lactose	4,000 Φg

A 20 g portion of the compound of the present invention was uniformly mixed with 400 g of lactose, and a 200 mg portion of the mixture was packed in a powder inhaler for exclusive use to produce a powder inhalant.

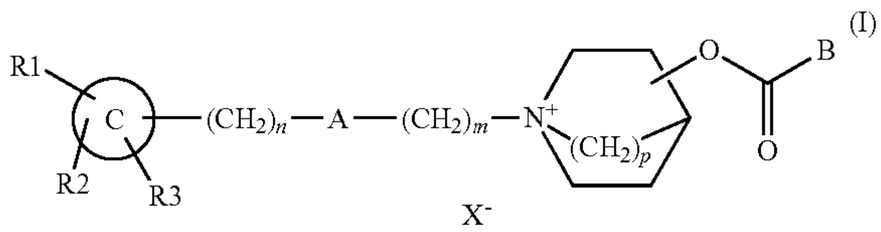
EXAMPLE 164

Preparation of a pharmaceutical composition: inhalation aerosol.	
Formulation:	
Compound of the present invention	200 Φg
Dehydrated (Absolute) ethyl alcohol USP	8,400 Φg
1,1,1,2-Tetrafluoroethane (HFC-134A)	46,810 Φg

The active ingredient concentrate is prepared by dissolving 0.0480 g of the compound of the present invention in 2.0160 g of ethyl alcohol. The concentrate is added to an appropriate filling apparatus. The active ingredient concentrate is dispensed into aerosol container, the headspace of the container is purged with Nitrogen or HFC-134A vapor (purging ingredients should not contain more than 1 ppm oxygen) and is sealed with valve. 11.2344 g of HFC-134A propellant is then pressure filled into the sealed container.

What is claimed is:

1. A compound according to formula (I)



(I)

wherein:

© is a phenyl ring, a C_4 to C_9 heteroaromatic group containing one or more heteroatoms or a naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl or biphenyl group;

R^1, R^2 and R^3 each independently represent a hydrogen atom or halogen atom, or a hydroxy group, or a phenyl, —OR^4, —SR^4, —NR^4R^5, —$NHCOR^4$, —$CONR^4R^5$, —CN, —NO_2, —$COOR^4$ or —CF_3 group, or a straight or branched **[**lower**]** *C_1 to C_4* alkyl group which may optionally be substituted**[**, for example,**]** with a hydroxy **[**or alkoxy**]** group, wherein R^4 and R^5 each independently represent a hydrogen atom, straight or branched **[**lower**]** *C_1 to C_4* alkyl group or together form an alicyclic ring; or R^1 and R^2 together form an aromatic, alicyclic or heterocyclic ring,

n is an integer from 0 to 4;

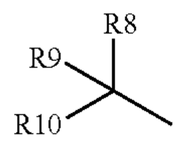
A represents a —CH_2—, —CH═CR^6—, —CR^6═CH—, —CR^6R^7—, —CO—, —O—, —S—, —S(O)—, SO_2 or —NR^6— group, wherein R^6 and R^7 each indepen-

dently represent a hydrogen atom, straight or branched [lower] C_1 *to* C_4 alkyl group or R^6 and R^7 together form an alicyclic ring;

m is an integer from 0 to 8; provided that when m=0, A is not —CH_2—;

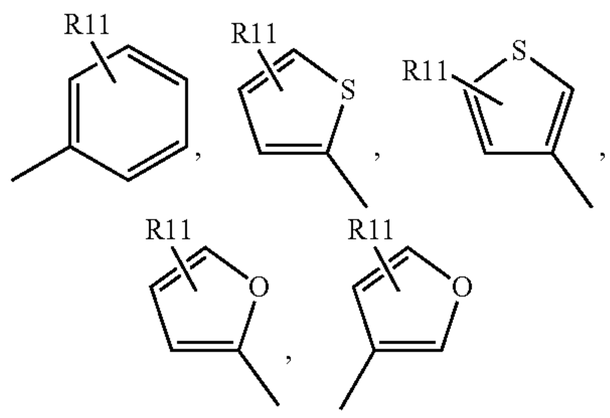
p is an integer from 1 to 2 and the substitution in the azoniabicyclic ring may be in the 2, 3 or 4 position including all possible configurations of the asymmetric carbons;

B represents a group of formula i):



i)

wherein R^{10} represents a hydrogen atom, a hydroxy or methyl group; and R^8 and R^9 each independently represent



wherein R^{11} represents a hydrogen or halogen atom or a straight or branched [lower] C_1 *to* C_4 alkyl group; and

[X] X^- represents a pharmaceutically acceptable anion of a mono or polyvalent acid.

[**2**. A compound according to claim **1**, wherein any alkyl group present as R^1 to R^7 or R^{11} contains from 1 to 4 carbon atoms.]

3. A compound according to claim **1** wherein p=2.

4. A compound according to claim **1** wherein © represents a phenyl, pyrrolyl, thienyl, furyl, biphenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl, imidazolyl or benzothiazolyl group.

5. A compound according to claim **4**, wherein © represents a phenyl, pyrrolyl or thienyl group.

6. A compound according to claim **1** wherein R^1, R^2 and R^3 each independently represent a hydrogen or halogen atom or a hydroxy, methyl, tert-butyl, —CH_2OH, 3-hydroxypropyl, —OMe, —NMe_2, —NHCOMe, —$CONH_2$, —CN, [—NO2] —NO_2, —COOMe or —CF_3 group.

7. A compound according to claim **6** wherein R^1, R^2 and R^3 each independently represent a hydrogen or halogen atom or a hydroxy group.

8. A compound according to claim **7**, wherein the halogen atom is fluorine.

9. A compound according to claim **1** wherein A represents a —CH_2—, —CH═CH—, —CO—, —NH—, —NMe—, —O— or —S— group; n is 0 or 1; and m is an integer from 1 to 6.

10. A compound according to claim **9**, wherein A represents a —CH_2—, **13** CH═CH— or —O— group and m is 1, 2 or 3.

11. A compound according to claim **1** wherein the azoniabicyclo group is substituted on the nitrogen atom with a 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, 3-(2-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 2-benzyloxyethyl, 3-pyrrol-1-ylpropyl, 2-thien-2-ylethyl or 3-thien-2-ylpropyl group.

12. A compound according to claim **1** wherein B represents a group of formula (i) and R^8 and R^9 each independently represent a phenyl, 2-thienyl, 3-thienyl, 2-furyl, or 3-furyl group and R^{11} represents a hydrogen atom.

13. A compound according to claim **1** wherein [X] X^- represents a bromide, chloride or trifluoroacetate anion.

14. A compound according to claim **1** wherein the azoniabicyclo group is substituted in the 3-position.

15. A compound according to claim **14**, wherein the substituent in the 3 position has (R) configuration.

16. A compound according to claim **15**, wherein R^8 is different from R^9 in group i), and the asymmetric carbon to which R^8 and R^9 are bonded has the (R) configuration.

17. A compound according to claim **15**, wherein R^8 is different from R^9 in group i), and the asymmetric carbon to which R^8 and R^9 are bonded has the (S) configuration.

18. A compound according to claim **1** which is a single stereoisomer.

19. A compound according to claim **1** which is

3(R)-Diphenylacetoxy-1-(3-phenoxy-propyl)-1azoniabicyclo[2.2.2]octane; bromide,

3(R)-(2-Hydroxy-2,2-diphenyl-acetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide,

3(R)-(2,2-Diphenylpropionyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide,

3(R)-(2-Hydroxy-2-phenyl-2-thien-2-yl-acetoxy)-1-(3-phenoxypropyl)-1-azonia-bicyclo [2.2.2]octane; bromide,

3(R)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)-1-(3-phenylallyl)-1-azoniabicyclo [2.2.2]octane; bromide,

3(R)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)-1-(2-phenoxyethyl)-1-azoniabicyclo [2.2.2]octane; bromide,

3(R)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo [2.2.2]octane; bromide,

3(R)-(2,2-Dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide,

[3(R)-(2-Hydroxy-2,2-di-thien-2-ylacetoxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; bromide] *3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-phenethyl-1-azoniabicyclo [2.2.2]octane; bromide,*

[3(R)-(2-Hydroxy-2,2-di-thien-2-ylacetoxy)-1-(4-phenylbutyl)-1-azoniabicyclo[2.2.2]octane; bromide] *3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(4-phenylbutyl)-1-azoniabicyclo[2.2.2]octane; bromide,*

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azonia-bicyclo[2.2.2]octane; bromide,

1-[3-(4-Fluorophenoxy)propyl]-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo [2.2.2]octane; chloride,

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-[3-(2-hydroxyphenoxy)propyl]-1-azoniabicyclo [2.2.2]octane; Trifluoroacetate,

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-pyrrol-1-ylpropyl)-1-azonia-bicyclo[2.2.2]octane; trifluoroacetate,

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(2-thien-2-ylethyl)-1-azoniabicyclo[2.2.2]octane; bromide,

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-thien-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide,

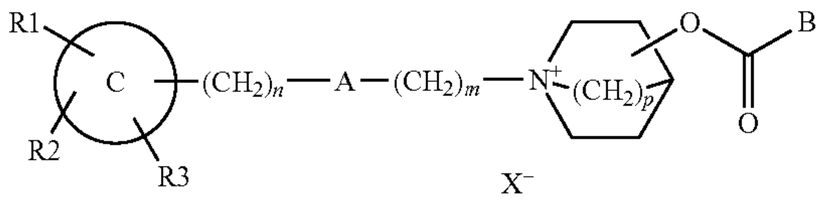
1-(2-Benzyloxyethyl)-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate, *or*

3(R)-(2-Hydroxy-2,2-dithien-3-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide.

20. A compound according to claim **1** characterised in that it has an IC_{50} value for muscarinic M_3 receptors (Hm3) of less than 35 nM.

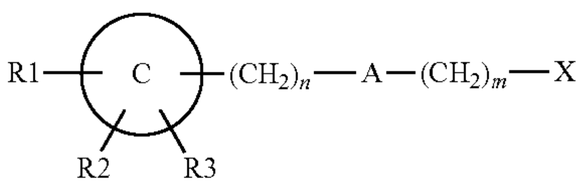
[21. A process for the preparation of a compound of formula (I)

(I)



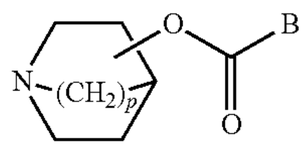
which comprises reacting an alkylating agent of formula (II)

(II)



with a compound of formula (III)

(III)



wherein, in each of formulae I, II and III, R^1, R^2 R^3, ©, A, X, B, n, m and p are as defined in any one of claims **1** to **12** or **13** to **19**.**]**

[22. A process according to claim **21** characterised in that the resulting reaction mixture is purified by solid phase extraction.**]**

23. A pharmaceutical composition comprising a compound according to claim **1** in admixture with a pharmaceutically acceptable carrier or diluent.

24. A method for treating respiratory, urinary and/or gastrointestinal disease which method comprises administering to a human or animal patient in need of such treatment an effective amount of a compound according to **[**any one of claims**]** *claim* **1** **[**to **12**, **13** to **20]** or of a pharmaceutical composition according to claim **23**.

25. A method for treating COPD, chronic bronchitis, asthma and/or **[**ehinitis**]** *rhinitis* which method comprises administering to a human or animal patient in need of such treatment an effective amount of a compound according to **[**any one of claims**]** *claim* **1** **[**to **12**, **13** to **20]** or of a pharmaceutical composition according to claim **23**.

26. A compound chosen from

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; X^-

or

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; X^-,

wherein X^- represents a pharmaceutically acceptable anion of a mono or polyvalent acid.

27. A compound chosen from

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; X^-

or

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; X^-,

wherein X^- represents chloride, bromide, iodide, sulfate, nitrate, phosphate, acetate, trifluoroacetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulfonate, or p-toluenesulfonate.

28. A compound according to claim 27, wherein X^- represents chloride, bromide, iodide, sulfate, nitrate, acetate, trifluoroacetate, maleate, oxalate, or succinate.

29. A compound according to claim 27, wherein X^- represents chloride, bromide, or trifluoroacetate.

30. A compound chosen from

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide

or

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; bromide.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : RE46,417 E
APPLICATION NO. : 15/019009
DATED : May 30, 2017
INVENTOR(S) : Dolors Fernandez Forner, Maria Prat Quiñones and Maria Antonia Buil Albero

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Claim 10, Column 49, Line 64:
"13 CH=CH-" should read as -- -CH=CH- --;

Claim 19, Column 50, Lines 25-26:
"3(R)-Diphenylacetoxy-1-(3-phenoxy-propyl)-1azoniabicyclo[2.2.2]octane;" should read as -- 3(R)-Diphenylacetoxy-1-(3-phenoxy-propyl)-1-azoniabicyclo[2.2.2]octane; --; and

Claim 19, Column 50, Lines 55-56:
"Trifluoroacetate," should read as -- trifluoroacetate, --.

Signed and Sealed this
Sixth Day of February, 2018

Joseph Matal

Joseph Matal
Performing the Functions and Duties of the
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

(68)	PATENT NO.	:	RE46417
(45)	REISSUED	:	May 30, 2017 (Originally issued June 15, 2004)
(75)	INVENTOR	:	Dolors Fernandez Forner et al.
(73)	PATENT OWNER	:	Almirall, S.A.
(95)	PRODUCT	:	TUDORZA PRESSAIR® (aclidinium bromide)

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. RE46417 based upon the regulatory review of the product TUDORZA PRESSAIR® (aclidinium bromide) by the Food and Drug Administration. According to United States Patent and Trademark Office records, the original expiration date of the patent as of the date of issuance of this certificate is July 7, 2020. Because it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 1,679 days

subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156.

I have caused the seal of the United States Patent and Trademark Office to be affixed this 15th day of March 2018.

Andrei Iancu
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office