

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 00-052873- -00032-0000

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Tra. 2 PATENTES Eve: 1 REGDEPOSITO
Act. 329 CTOINFORMACION Folios: 72

Señor Director
DIRECCIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 002
Evento : 001
Actuación : 329

Referencia : Expediente No. 00.052.873
Asunto : Solicitud de patente para: **NUEVOS DERIVADOS DE
QUINUCLIDINA Y COMPOSICIONES FARMACÉUTICAS
QUE LOS CONTIENEN**
Solicitante : ALMIRALL, S.A.
Fecha de solicitud : 13 de julio de 2000

1. Yo, LUZ CLEMENCIA DE PÁEZ, obrando como apoderada del solicitante en el asunto antes identificado, me permito presentar un nuevo capítulo reivindicatorio del asunto en referencia.
2. La Decisión 486 en su artículo 70 establece que: "El titular de una patente podrá pedir a la oficina nacional competente que se modifique la patente para consignar cualquier cambio en el nombre, dirección, domicilio u otros datos del titular o del inventor o para modificar o limitar el alcance de una o más de las reivindicaciones. Del mismo modo podrá pedir la corrección de cualquier error material en la patente. ".
3. De acuerdo a lo anterior, solicito gentilmente se acepte este nuevo capítulo reivindicatorio teniendo en cuenta que la materia a proteger se encuentra totalmente contenida en la solicitud inicial y que se trata de una limitación del pliego reivindicatorio. En consecuencia, se cumplen todos los requisitos para que sea aceptada esta modificación.

"EXCELENCIA LEGAL EN UN MUNDO SIN FRONTERAS"

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Se han introducido las siguientes modificaciones al pliego reivindicatorio:

- Se modificó la reivindicación 32 al incorporar las limitaciones de la reivindicación 33.
 - Se reenumeraron las reivindicaciones restantes.
4. Anexo a este memorial, se encuentra la copia de la patente europea EP-B-1200431 como fue aceptada, luego de las modificaciones post- concesión, que corresponde a la modificación presentada adjunto con el presente memorial.

5. **ANEXOS**

- Capítulo reivindicatorio con 38 reivindicaciones
- Formulario de modificaciones
- Comprobante de tasa por valor de \$ 505 000
- Copia de patente europea EP-B-1200431 limitada

Señor Director,


LUZ CLEMENCIA DE PÁEZ
C.C. 35.456.344 de Usaquén
T.P.A. No. 23.555

COLO-17153-0806-001-2
COLO-06734-0804-001-4
COLO-16250-0806-001-7
FBJ\FR\ID-244601\WPC17153
No. M-2013-244601\FBJ



Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación

DELEGATURA PROPIEDAD INDUSTRIAL
INSCRIPCIÓN DE AFECTACIONES

1. Datos del Signo o Nueva Creación

☒ Patente

☐ Marca

☐ Lema

☐ Nombre comercial/enseña

☐ Diseño

☐ Esquema de trazado de circuito

☐ Denominación de Origen

☐ Patente de Modelo de utilidad

1.1. Identificación:

No. DE CERTIFICADO	VIGENCIA	NUMERO DE EXPEDIENTE
28393	13/07/2000 Hasta 13/07/2020	00.052.873

NOTA: Si el espacio anterior no es suficiente, por favor relacione los datos de los demás signos/nuevas creaciones con respecto de los que se solicita la inscripción de la afectación correspondiente en hoja anexa, o utilice un formulario sustancialmente igual a este

2. Datos del titular

Persona Natural

Persona Jurídica

Nombre o denominación /Nombre Social

Nombre del representante

ALMIRALL, S.A.

Tipo de empresa

Micro

Pequeña

Mediana

Otra

Documento de identificación:

C.C.

C.E.

NIT

Otro

Número

Nacionalidad/País de constitución	Dirección del titular		
España	Ronda General Mitre 151, 08022 Barcelona, España		
Dirección electrónica	No. Fax	Numero telefónico	
clientes@cavelier.com	2 11 86 50	3 47 36 11	

3. Datos del apoderado:

De Páez Luz Clemencia

C.C. 35.456.344

T.P. 23.5555

Apellidos y Nombre

Documento de identificación

Tarjeta profesional

Dirección del representante

Carrera 4ª No. 72 –35

Dirección Electrónica

No. Fax

No. Telefónico

Clientes@cavelier.com

2 11 86 50

3 47 36

Numero de Radicación o Protocolo de poder general.

☒ Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico.

4. Cambio de nombre, domicilio o dirección

☐ Cambio de Nombre ☐ Cambio de domicilio ☐ Cambio de dirección

De: _____
Tal como aparece actualmente en el registro

A: _____
Nuevo (Tal como debe quedar en el registro)

Nacionalidad/País de constitución	Dirección del titular		
Dirección electrónica	No. Fax	Numero teléfono	

5. ☐ Prenda ☐ Embargo ☐ Medidas cautelares

Código Postal	Dirección Electrónica	No Fax	Numero teléfono

NOTA: Si el espacio anterior no es suficiente, por favor relacione las afectaciones con respecto de las que se solicita inscripción en hoja anexa, o utilice un formulario sustancialmente igual a este.

6. Modificación o Limitación a Reivindicaciones (art. 70 Decisión 486)

Presento nuevo capítulo reivindicatorio compuesto por 38 reivindicaciones, en el que se modifico la reivindicación 32 al incorporar las limitaciones de la reivindicación 33. Todo lo anterior de conformidad con el pliego reivindicatorio modificado pos concedido en la oficina Europea de patentes.

Comprobante de pago No. 13-58.873 Fecha 2013/06/17

7. Anexos

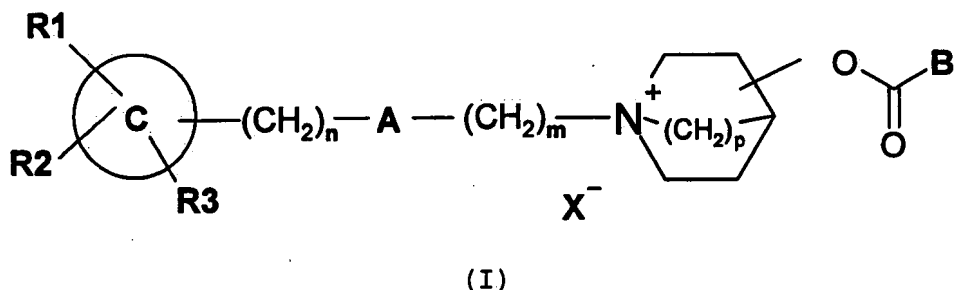
- ☒ Comprobante de pago de la tasa para la presentación de la solicitud por \$505.000:
- ☐ Poder, si fuere el caso con el que se acredita la representación
- ☐ Copia de la solicitud con sus anexos en medio magnético.

8. Firma (s)	
Nombre del Firmante	Firma
LUZ CLEMENCIA DE PAEZ	
C.C 35'456.344 de Usaquén	Tarjeta Profesional T. P 23.555

FBJ\NCA\WPC17153\ID-244635

REIVINDICACIONES

1. Un compuesto según la fórmula (I):

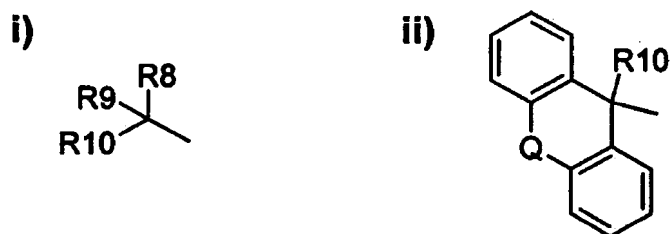


en donde:

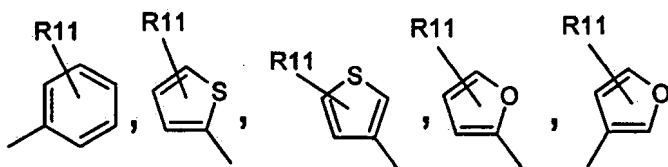
- © es un fenilo, un grupo heteroaromático de 4 a 9 átomos de carbono conteniendo uno o más heteroátomos, o un grupo naftalenilo, 5,6,7,8-tetrahidronaftalenilo o bifenilo;
- R^1 , R^2 y R^3 cada uno independientemente representan un átomo de hidrógeno o halógeno, un fenilo, un grupo $-OR^4$, $-SR^4$, $-NR^4R^5$, $-NHCOR^4$, $-CONR^4R^5$, $-CN$, $-NO_2$, $-COOR^4$ o $-CF_3$, o un grupo alquilo de 1 a 8 átomos de carbono lineal o ramificado el cual puede estar opcionalmente sustituido, por ejemplo, con un grupo hidroxilo o alcoxilo, en donde R^4 y R^5 cada uno independientemente representan un átomo de hidrógeno, un grupo alquilo de 1 a 8 átomos de carbono lineal o ramificado, o conjuntamente forman un anillo alicíclico; o R^1 y R^2 juntos forman un anillo aromático, alicíclico o heterocíclico;
- n es un número del 0 al 4;
- A representa un grupo $-CH=CR^6$, $-CR^6=CH-$, $-CR^6R^7-$, $-CO-$, $-O-$, $-S-$, $-S(O)-$, SO_2 o $-NR^6-$, en donde R^6 y R^7 cada uno independientemente representan un átomo de hidrógeno, un grupo alquilo de 1 a 8 átomos de carbono lineal o ramificado, o R^6 y R^7 juntos forman un anillo alicíclico;
- m es un número del 0 al 8; a condición de que cuando $m = 0$, A no es $-CH_2-$;
- p es un número del 1 al 2 y la sustitución en el anillo azoniabíclico puede estar en la posición 2, 3 o 4

incluyendo todas las posibles configuraciones de los carbonos asimétricos;

- B representa un grupo de fórmula i) o ii):



en donde R^{10} representa un átomo de hidrógeno, un grupo hidroxilo o metilo; y R^8 y R^9 cada uno independientemente representan



en donde R^{11} representa un átomo de hidrógeno o de halógeno o un grupo alquilo de 1 a 8 átomos de carbono lineal o ramificado; y Q representa un enlace sencillo, $-CH_2-$, $-CH_2-CH_2-$, $-O-$, $-O-CH_2-$, $-S-$, $-S-CH_2-$ o $-CH=CH-$; y

- X representa un anión farmacéuticamente aceptable de un ácido mono o polivalente.

2. Un compuesto de acuerdo a la reivindicación 1, donde R_1 , R_2 y R_3 cada uno independientemente representan un átomo de hidrógeno o halógeno, o un fenilo, o un grupo $-OR^4$, $-SR^4$, $-NR^4R^5$, $-NHCOR^4$, $-CONR^4R^5$, $-CN$, $-NO_2$, $-COOR^4$ o $-CF_3$, o un grupo alquilo de 1 a 8 átomos de carbono lineal o ramificado el cual puede estar opcionalmente sustituido con un grupo hidroxilo, en donde R^4 y R^5 cada uno independientemente representan un átomo de hidrógeno, un grupo alquilo de 1 a 8 átomos de carbono lineal o ramificado, o conjuntamente forman un anillo alicíclico de 3 a 10 átomos de carbono; o R^1 y R^2

juntos forman un anillo aromático de 6 a 14 átomos de carbono, un anillo alicíclico de 3 a 10 átomos de carbono o heterocíclico de 3 a 10 átomos de carbono.

3. Un compuesto de acuerdo a la reivindicación 1 o 2, donde A representa un grupo $-\text{CH}=\text{CR}^6$, $-\text{CR}^6=\text{CH}-$, $-\text{CR}^6\text{R}^7-$, $-\text{CO}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, SO_2 o $-\text{NR}^6-$, en donde R^6 y R^7 cada uno independientemente representan un átomo de hidrógeno, un grupo alquilo de 1 a 8 átomos de carbono lineal o ramificado, o R^6 y R^7 juntos forman un anillo alicíclico de 3 a 10 átomos de carbono.

4. Un compuesto según cualquiera de las reivindicaciones 1 a 3, en donde cualquier grupo alquilo presente en los grupos descritos desde R^1 a R^7 o R^{11} contiene de 1 a 4 átomos de carbono.

5. Un compuesto según cualquiera de las reivindicaciones 1 a 4, en donde $p=2$.

6. Un compuesto según cualquiera de las reivindicaciones precedentes en donde © representa un grupo fenilo, pirrolilo, tienilo, furilo, bifenilo, naftalenilo, 5, 6, 7, 8-tetrahidronaftalenilo, benzo[1,3] dioxolilo, imidazolilo o benzotiazolilo.

7. Un compuesto según reivindicación 6, en donde © representa un grupo fenilo, pirrolilo o tienilo.

8. Un compuesto según cualquiera de las reivindicaciones precedentes en donde R^1 , R^2 y R^3 cada uno independientemente representa un átomo de hidrógeno o halógeno o un grupo hidroxilo, metilo, terbutilobutilo, $-\text{CH}_2\text{OH}$, 3-hidroxiopropilo, $-\text{OMe}$, $-\text{NMe}_2$, $-\text{NHCOMe}$, $-\text{CONH}_2$, $-\text{CN}$, $-\text{NO}_2$, $-\text{COOMe}$ o $-\text{CF}_3$.

9. Un compuesto de acuerdo con la reivindicación 8 en donde R^1 , R^2 y R^3 cada uno independientemente representan un átomo de hidrógeno o halógeno o un grupo hidroxilo.

10. Un compuesto de acuerdo con la reivindicación 9, en donde el átomo de halógeno es flúor.

11. Un compuesto de acuerdo con cualquiera de las reivindicaciones precedentes en donde A representa un grupo $-CH_2-$, $-CH=CH-$, $-CO-$, $-NH-$, $-NMe-$, $-O-$ o $-S-$; n es 0 o 1; y m es un número del 1 al 6.

12. Un compuesto de acuerdo con la reivindicación 11, en donde A representa un grupo $-CH_2-$, $-CH=CH-$ o $-O-$ y m es 1, 2 o 3.

13. Un compuesto de acuerdo con cualquiera de las reivindicaciones precedentes en donde el grupo azoniabicyclo está sustituido en el átomo de nitrógeno seleccionado con 3-fenoxipropilo, 2-fenoxietilo, 3-fenilalilo, fenetilo, 3-fenilpropil, 4-fenilbutilo, 3-(2-hidroxifenoxi)propilo, 3-(4-fluorofenoxi)propilo, 2-benciloxietilo, 3-pirrol-1-ilpropilo, 2-tien-2-iletilo o 3-tien-2 ilpropilo.

14. Un compuesto de acuerdo con cualquiera de las reivindicaciones precedentes en donde B representa un grupo de fórmula (i) y R^8 y R^9 cada uno independientemente representan un grupo fenilo, 2-tienilo, 3-tienilo, 2-furilo, o 3-furilo y R^{11} representa un átomo de hidrógeno.

15. Un compuesto de acuerdo con cualquiera de las reivindicaciones de la 1 a la 13, en donde B representa un grupo de fórmula (ii) y Q representa un enlace sencillo, un grupo $-CH_2-$, $-CH_2-CH_2-$ o un átomo de oxígeno.

16. Un compuesto de acuerdo con cualquiera de las reivindicaciones precedentes en donde X- representa un anión bromuro, cloruro o trifluoroacetato.

17. Un compuesto de acuerdo con cualquiera de las reivindicaciones precedentes en donde el grupo azoniabicyclo está sustituido en la posición 3.

18. Un compuesto de acuerdo con la reivindicación 17, en donde el sustituyente en la posición 3 tiene configuración(R).

19. Un compuesto de acuerdo con la reivindicación 18, en donde R⁸ es diferente a R⁹ en el grupo i), y el carbono asimétrico al cual R⁸ y R⁹ están unidos tiene la configuración (R).

20. Un compuesto de acuerdo con la reivindicación 18, en donde R⁸ es diferente a R⁹ en el grupo i), y el carbono asimétrico al cual R⁸ y R⁹ están unidos tiene la configuración (S).

21. Un compuesto de acuerdo con cualquiera de las reivindicaciones precedentes que es un isómero único.

22. Un compuesto según la reivindicación 1 que es

3(R)-Difenilacetoxi-1-(3-fenoxipropil)-1-azoniabicyclo[2.2.2]octano; bromuro

3(R)-(2-Hidroxi-2,2-difenilacetoxi)-1-(3-fenoxipropil)-1-azoniabicyclo[2.2.2]octano; bromuro

3(R)-(2,2-Difenilpropioniloxi)-1-(3-fenoxipropil)-1-azoniabicyclo[2.2.2]octano; bromuro

3(R)-(2-Hidroxi-2-fenil-2-tien-2-ilacetoxi)-1-(3-fenoxipropil)-1-azoniabicyclo[2.2.2]octano; bromuro

3(R)-(2-Furan-2-il-2-hidroxi-2-fenilacetoxi)-1-(3-fenilalil)-1-azoniabicyclo[2.2.2]octano; bromuro

3(R)-(2-Furan-2-il-2-hidroxi-2-fenilacetoxi)-1-(2-fenoxietil)-lazoniabicciclo[2.2.2]octano; bromuro

3 (R)-(2-Furan-2-il-2-hidroxi-2-fenilacetoxi)-1-(3-fenoxipropil)-1-azoniabicciclo[2.2.2]octano; bromuro

3(R)-(2,2-Ditien-2-ilacetoxi)-1-(3-fenoxipropil)-1-azoniabicciclo [2.2.2]octano; bromuro

3(R)-(2-Hidroxi-2,2-ditien-2-ilacetoxi)-1-fenetil-lazoniabicciclo[2.2.2]octano, bromuro;

3 (R)-(2-Hidroxi-2,2-ditien-2-ilacetoxi)-1-(4-fenilbutil)-1-azoniabi ciclo[2.2.2]octano; bromuro

3(R)-(2-Hidroxi-2,2-ditien-2-ilacetoxi)-1-(3-fenoxipropil)-lazoniabicciclo[2.2.2]octano; bromuro

1-[3-(4-Fluorofenoxi)propil]-3(R)-(2-hidroxi-2,2-ditien-2-ilacetoxi)-1-azoniabicciclo [2.2.2]octano; cloruro

3(R)-(2-Hidroxi-2,2-ditien-2-ilacetoxi)-1-[3-(2-hidroxifenoxi) propil] -1-azoniabicciclo[2.2.2]octano; trifluoroacetato,

3 (R)-(2-Hidroxi-2,2-ditien-2-ilacetoxi)-1-(3-pirrol-1-ilpropil)-1-azoniabicciclo[2.2.2]octano; trifluoroacetato

3 (R)-(2-Hidroxi-2,2-ditien-2-ilacetoxi)-1-(2-tien-2-iletil)-1-azoniabicciclo[2.2.2]octano; bromuro

3 (R)-(2-Hidroxi-2,2-ditien-2-ilacetoxi)-1-(3-tien-2-ilpropil)-1-azoniabicciclo[2.2.2]octano; bromuro

1-(2-Benciloxietil)-3(R)-(2-hidroxi-2,2-ditien-2-ilacetoxi)-1-azonia bicciclo[2.2.2]octano; trifluoroacetato

3 (R)-(2-Hidroxi-2,2-ditien-3-ilacetoxi)-1-(3-fenoxipropil)-1-azoniabi ciclo[2.2.2]octano; bromuro

1-(3-Fenilalil)-3(R)-(9-hidroxi-9[H]-fluoren-9-carboniloxi)-1-azonia bicciclo[2.2.2]octano, bromuro;

3 (R)-(9-Hidroxi-9[H]-fluoren-9-carboniloxi)-1-(3-fenoxipropil)-1-azoniabicciclo[2.2.2]octano, bromuro;

3(R)-(9-Hidroxi-9[H]-fluoren-9-carboniloxi)-1-fenetil-1-azoniabicciclo [2.2.2]octano, bromuro;

3 (R)-(9-Hidroxi-9H-fluoren-9-carboniloxi)-1-(3-tien-2-ilpropil)-1-azoniabicciclo[2.2.2]octano, bromuro;

3 (R)-(9-Metil-9[H]-fluoren-9-carboniloxi)-1-(3-fenilalil)-1-azonia bicciclo[2.2.2]octano, bromuro;

3(R)-{9-Metil-9[H]-fluoren-9-carboniloxi)-1-{3-fenoxipropil)-1-azo niabicciclo[2.2.2]octano, bromuro;

1-{4-Fenilbutil)-3(R)-{9[H]-xanten-9-carboniloxi)-1-azoniabicciclo [2.2.2]octano, bromuro;

1-{2-Fenoxietil)-3(R)-{9[H]-xanten-9-carboniloxi)-1-azoniabicciclo [2.2.2]octano, bromuro;

1-{3-Fenoxipropil)-3(R)-{9[H]-xanten-9-carboniloxi)-1-azoniabicciclo [2.2.2]octano, bromuro;

1-Fenetil-3(R)-{9[H]-xanten-9-carboniloxi)-1-azoniabicciclo[2.2.2]octano, bromuro;

3(R)-{9-Hidroxi-9[H]-xanten-9-carboniloxi)-1-{3-fenoxipropil)-lazoniabicciclo[2.2.2]octano, bromuro;

3(R)-{9-Hidroxi-9[H]-xanten-9-carboniloxi)-1-fenetil-1-azoniabicciclo[2.2.2]octano, bromuro;

3 (R)-(9-Hidroxi-9H-xanten-9-carboniloxi)-1-(3-tien-2-ilpropil)-1-azo niabicciclo[2.2.2]octano, bromuro; o

3 (R)-(9-Metil-9[H]-xanten-9-carboniloxi)-1-(3-fenoxipropil)-1-azonia bicciclo[2.2.2]octano, bromuro;

23. Un compuesto de acuerdo la reivindicación 1 el cual es 3(R)-(2-Hidroxi-2,2-ditien-2-ilacetoxi)-1-(3-fenoxipropil)-1-azoniabicciclo[2.2.2]octano, X⁻; donde X⁻ representa un anión farmacéuticamente aceptable de un ácido mono o polivalente.

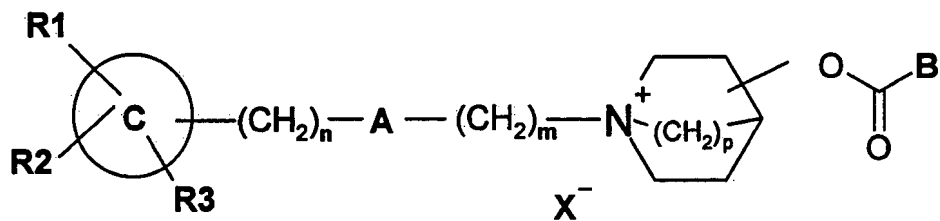
24. Un compuesto de acuerdo la reivindicación 1 el cual es 3(R)-(2-Hidroxi-2,2-ditien-2-ilacetoxi)-1-(3-fenoxipropil)-1-azoniabicciclo[2.2.2]octano, bromuro.

25. Un compuesto de acuerdo la reivindicación 1 el cual es 1-Fenetil-3(R)-{9[H]-xanten-9-carboniloxi)-1-azoniabicciclo[2.2.2]octano, X⁻; donde X⁻ representa un anión farmacéuticamente aceptable de un ácido mono o polivalente.

26. Un compuesto de acuerdo la reivindicación 1 el cual es 1-Fenetil-3(R)-{9[H]-xanten-9-carboniloxi)-1-azoniabicciclo[2.2.2]octano, bromuro.

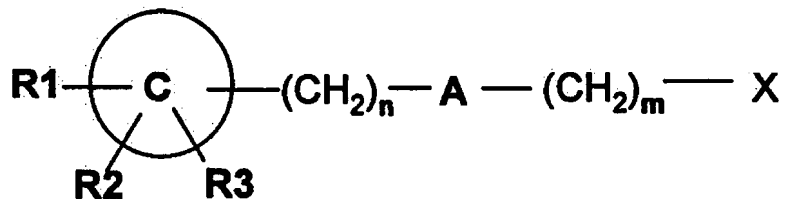
27. Un compuesto de acuerdo con cualquiera de las reivindicaciones precedentes en que la IC_{50} para los receptores muscarínicos M3 (Hm3) tiene un valor inferior a 35 nM.

28. Un procedimiento para la preparación de un compuesto de fórmula (I), como se define en cualquiera de las reivindicaciones anteriores 1 a 26,



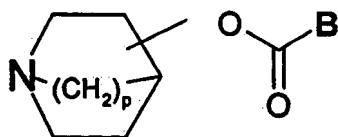
(I)

que comprende la reacción de un agente alquilante de fórmula (II)



(II)

con un compuesto de fórmula (III)

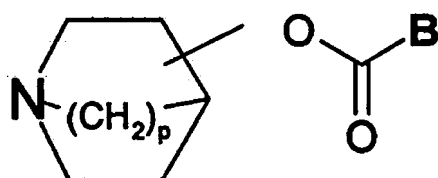


(III)

en donde, cada elemento de las fórmulas I, II Y III, R^1 , R^2 , R^3 , @, A, X, B, n, m y p son como se ha definido en cualquiera de las reivindicaciones de la 1 a la 22.

29. Un procedimiento de acuerdo con la reivindicación 28 caracterizado porque la mezcla resultante de reacción es purificada por extracción en fase sólida.

30. Un compuesto de fórmula (III)



(III)

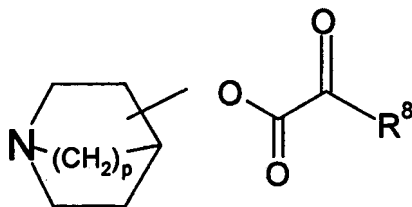
en donde B y p son como se ha definido en cualquiera de las reivindicaciones de la 1, 4, 5, 14, 15 o 17 a 22, y donde el sustituyente del grupo azabicyclo tiene la configuración (R).

31. Un compuesto de acuerdo con la reivindicación 30 que es ester 1-azabicyclo[2.2.2]oct-3(R)-ílico del ácido 9-metil-9[H] -fluoren-9-carboxílico;

ester 1-azabicyclo[2.2.2]oct-3(R)-ílico ácido 9-metil-9[H] del -xanten-9-carboxílico;o

ester 1-azabicyclo [2.2.2] oct-3 (R) -ílico del ácido 2-hidroxi-2, 2-difuran -2-ilacético;

32. Un compuesto de fórmula VII



(VII)

en donde p es como se ha definido en las reivindicaciones 1-5, R^8 es un grupo 2-tienilo o 2-furilo, y donde el sustituyente del grupo azabicyclo tiene configuración (R).

33. Un compuesto de acuerdo con la reivindicación 32 que sea ester 1-azabicyclo[2.2.2]oct-3(R)-ílico del ácido oxotien-2-ilacético; o ester 1-azabicyclo [2.2.2] oct-3 (R) -ílico del ácido oxofuran-2-ilacético.

34. Una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de las reivindicaciones de la 1 a la 27 mezclado con un vehículo o diluyente farmacéuticamente aceptable.

35. Una composición farmacéutica de acuerdo con la reivindicación 34, que además contiene un antagonista β_2 .

36. Una composición farmacéutica de acuerdo con la reivindicación 34, que además contiene un esteroide.

37. Una composición farmacéutica de acuerdo con la reivindicación 34, que además contiene un una droga anti-alérgica.

38. Una composición farmacéutica de acuerdo con la reivindicación 34, que además contiene un inhibidor de fosfodiesterasa IV.



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(12) **NEW EUROPEAN PATENT SPECIFICATION**
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(54) **QUINUCLIDINE DERIVATIVES AND THEIR USE AS MUSCARINIC M3 RECEPTORS LIGANDS**
CHINUCLIDIN-DERIVATE UND DEREN VERWENDUNG ALS MUSCARIN-M3-REZEPTOREN-LIGANDEN
DERIVES DE QUINUCLIDINE ET LEUR UTILISATION COMME LIGANDS DES RECEPTEURS M3 MUSCARINIQUES

(84) Designated Contracting States: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE Designated Extension States: AL LT LV MK RO SI (30) Priority: 14.07.1999 ES 9901580 (43) Date of publication of application: 02.05.2002 Bulletin 2002/18 (73) Proprietor: Almirall, S.A. 08022 Barcelona (ES) (72) Inventors: • FERNANDEZ FORNER, Dolors E-08025 Barcelona (ES) • PRAT QUINONES, Maria E-08003 Barcelona (ES)	• BUIL ALBERO, Maria Antonia E-08029 Barcelona (ES) (74) Representative: Srinivasan, Ravi Chandran et al J A Kemp 14 South Square Gray's Inn London WC1R 5JJ (GB) (56) References cited: EP-A- 0 424 021 FR-A- 2 012 964 • CHEMICAL ABSTRACTS, vol. 104, no. 19, 12 May 1986 (1986-05-12) Columbus, Ohio, US; abstract no. 168339g, GODOVIKOV, N. N. ET AL: "Synthesis and muscarinolytic activity of quinuclidinyl benzilate alkyl iodides" XP002128290 & KHIM.-FARM. ZH., vol. 19, no. 9, - 1985 pages 1060-1061,
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Description

[0001] This invention relates to new therapeutically useful quinuclidine derivatives, to some processes for their preparation and to pharmaceutical compositions containing them.

[0002] The novel structures according to the invention are antimuscarinic agents with a potent and long lasting effect. In particular, these compounds show high affinity for muscarinic M_3 receptors ($Hm3$).

[0003] 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, pollakiuria in neuripenia pollakiuria, neurogenic or unstable bladder, cystospasm and chronic cystitis; and gastrointestinal disorders such as irritable bowel syndrome, spastic colitis, diverticulitis and peptic ulceration.

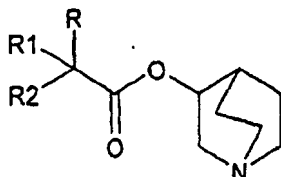
[0004] The compounds claimed are also useful for the treatment of the respiratory diseases detailed above in association with β_2 agonists, steroids, antiallergic drugs or phosphodiesterase IV inhibitors.

[0005] Compounds of the present invention may also be expected to have anti-tussive properties.

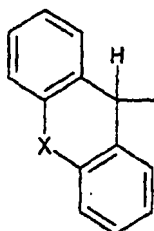
[0006] Depending on their nature the new compounds may be suitable for treating vagally induced sinus bradycardia.

[0007] Compounds with related structures have been described as antispasmodics and anti-cholinergic agents in several patents.

[0008] For example, in patent FR 2012964 are described quinuclidinol derivatives of the formula

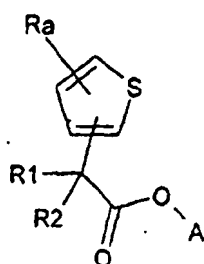


in which R is H, OH or an alkyl group having 1 to 4 carbon atoms; R_1 is a phenyl or thienyl group; and R_2 is a cyclohexyl, cyclopentyl or thienyl group, or, when R is H, R_1 and R_2 together with the carbon atom to which they are attached, form a tricyclic group of the formula:



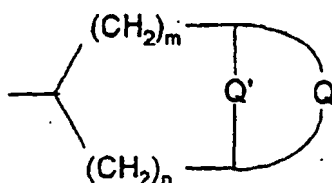
in which X is -O-, -S- or -CH₂-, or an acid addition or quaternary ammonium salt thereof.

[0009] EP- 418716 describes thienyl carboxylate esters of formula



wherein A is a group

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m and n = 1 or 2

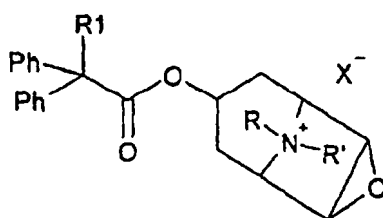
Q is a $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ or $-\text{CH}=\text{CH}-$,



group

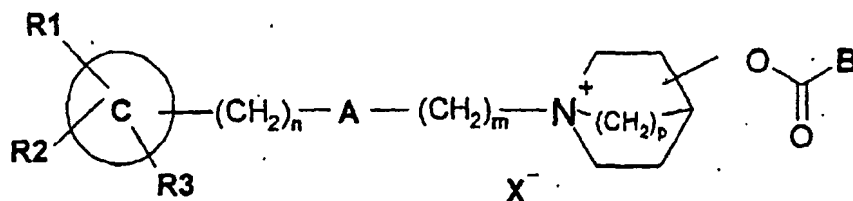
Q' is a $=\text{NR}$ or NRR' group; R_1 is a thienyl, phenyl, furyl, cyclopentyl or cyclohexyl group, optionally substituted; R_2 is H, OH, C_1-C_4 alkoxy or C_1-C_4 alkyl and R_a is H, F, Cl, CH_3 or $-\text{NR}$.

[0010] US 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, $-\text{CH}_2\text{OH}$, C_{1-4} alkyl or C_{1-4} alkoxy.

[0011] 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):



(I)

wherein:

C 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 phenyl, $-\text{OR}^4$, $-\text{SR}^4$, $-\text{NR}^4\text{R}^5$, $-\text{NHCOR}^4$, $-\text{CONR}^4\text{R}^5$, $-\text{CN}$, $-\text{NO}_2$, $-\text{COOR}^4$ or $-\text{CF}_3$ group, or a straight or branched C_1 to C_8 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 C_1 to C_8 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;

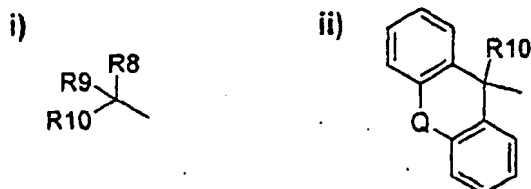
A represents a $-\text{CH}=\text{CR}^6-$, $-\text{CR}^6=\text{CH}-$, $-\text{CR}^6\text{R}^7-$, $-\text{CO}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, SO_2 or $-\text{NR}^6-$ group, wherein R^6 and R^7 each independently represent a hydrogen atom, straight or branched C_1 to C_8 alkyl group, or R^6 and R^7 together form

an alicyclic ring;

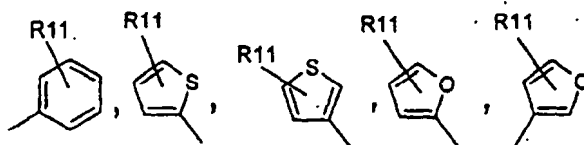
m is an integer from 0 to 8; provided that when m = 0, A is not -CH₂-;

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 R¹⁰ represents a hydrogen atom, a hydroxy or methyl group; and R⁸ and R⁹ each independently represents



wherein R¹¹ represents a hydrogen or halogen atom, or a straight or branched C₁ to C₈ alkyl group and Q represents a single bond, -CH₂-, -CH₂-CH₂-, -O-, -O-CH₂-, -S-, -S-CH₂- 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.

[0012] 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.

[0013] The compounds of the present invention represented by the formula (I) described above, which may have one or more asymmetric carbons, include all the possible stereoisomers. The single isomers and mixtures of the isomers fall within the scope of the present invention.

[0014] If any of R¹ to R⁷ or R¹¹ represents an alkyl group, 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.

[0015] 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.

[0016] 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; R¹, R² and R³ each independently represent a hydrogen or halogen atom, or a hydroxyl, methyl, tert-butyl, -CH₂OH, 3-hydroxypropyl, -OMe, -NMe₂, -NHCOMe, -CONH₂, -CN, -NO₂, -COOMe or -CF₃ 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 -CH₂-, -CH=CH-, -CO-, -NH-, -NMe-, -O- or -S- group, in particular a -CH₂-, -CH=CH- or -O- group.

[0017] 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.

[0018] 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), R⁸ and R⁹ each independently represent a phenyl, 2-thienyl, 3-thienyl, 2-furyl or 3-furyl group, wherein R¹¹ is hydrogen atom; and, if B is a group of formula (ii), Q represents a single bond, -CH₂-, -CH₂-CH₂-, -O- or -S- group, in particular a single bond, -CH₂-, -CH₂-CH₂- or -O- group, most preferably a single bond or -O- group; and in any case R¹⁰ 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.

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[0019] Most preferably 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, 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-carbenyloxy, or 5[H]-dibenze[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-carbenyloxy or 9-methyl-9[H]-xanthene-9-carbonyloxy.

[0020] 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-tolylxypropyl, 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[i,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, phenoxy]prepyl, 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.

[0021] 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-azoniabicyclo[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-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-phenoxypropyl)-1-azoniabicyclo[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-azoniabicyclo[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
 3(R)-(2-Hydroxy-2,2-dithien-3-ylacetoxy)-1-(3-phenoxypropyl)-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-9[H]-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-phenylallyl)-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-(9-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

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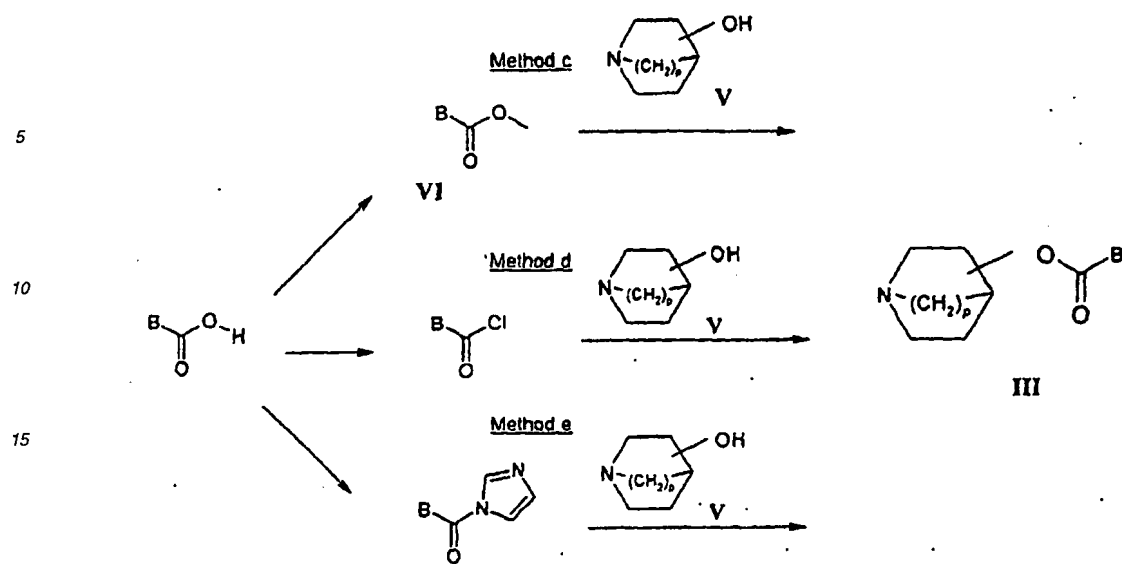
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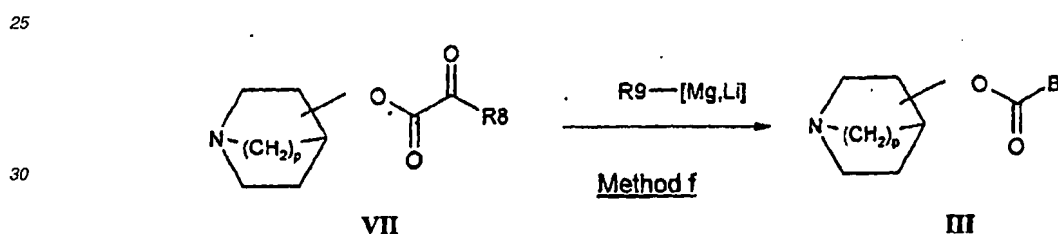
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[0026] Some compounds of general formula III where B is a group of formula i), R^8 and R^9 are as described above and R^{10} is a hydroxy group, may also be prepared from the glyoxalate esters of general formula VII by reaction with the corresponding organometallic derivative.



[0027] 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.

[0028] The following compounds are examples of compounds of general formula III and VII which have not been described before:

- 40
- 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-4g).
- 45 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).

[0029] Compounds of Formula V could be:

- 50
- 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.

55 [0030] The following examples are intended to illustrate, but not to limit, the experimental procedures that have been described above.

[0031] The structures of the prepared compounds were confirmed by $^1\text{H-NMR}$ 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

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tetramethyl silane. Their purity was determined by HPLC, using reverse phase chromatography on a Waters instrument, with values greater than 95% being obtained. Molecular ions were obtained by electrospray ionization mass spectrometry on a Hewlett Packard instrument.

5 Method - a -

Example 20- Preparation of 3(R)-(2-Furan-2-yl-2-hydroxy-2-phenyl acetoxyl)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane, bromide.

10 **[0032]** 200 mg of (Furan-2-yl)-hydroxy-phenylacetic acid 1-aza-bicyclo[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.

15 ¹H-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, 1 H), 4.05 (m, 2H), 5.20 (m, 1 H), 6.25-6.35 (double dd, 1 H), 6.45 (m, 1 H), 6.95 (m, 4H), 7.30-7.50 (m, 7H), 7.70 (m, 1 H); MS [M-Br]⁺: 462; mp 166°C.

20 Method - b -

Example 51 - Preparation of 3(R)-(2-Hydroxy-2,2-di-thien-2-yl acetoxyl)-1-[3-(naphthalen-1-yloxy)propyl]-1-azoniabicyclo[2.2.2] octane; trifluoroacetate

25 **[0033]** 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

30 neutralized with 300 mg of poly(4-vinylpyridine), filtered and evaporated to dryness. The yield was 17 mg (15%) of title compound. ¹H- 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, 1 H), 4.2 (t, 2H), 5.25 (m, 1 H), 7.0 (m 3H), 7.2 (m, 2H), 7.4 - 7.6 (m, 7H), 7.85 (d, 1 H), 8.2 (d, 1 H); MS [M-CF₃COO]⁺: 534.

35 Method - c -

[0034] 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.

45 **[0035]** 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

50 hexane and filtered. The yield was 2.5 g (54%) of a mixture of diastereoisomers, mp: 140-142 °C; GC/MS [M]⁺: 327; ¹H- NMR (CDCl₃) : δ 1.20-1.70 (m, 4H), 1.90-2.10 (m, 1 H), 2.45-2.80 (m, 5H), 3.10-3.30 (m, 1 H), 4.8 (bs, OH), 4.90-5.0 (m, 1 H), 6.20 (m, 1 H), 6.35 (m, 1 H), 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 (1) 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, [α]_D²⁵ = +5.6 (c=2, EtOH). Diastereomer 2 was hydrolysed to yield (-)-2-hydroxy-2-phenyl-2-furan-2-ylacetic acid as a pure enantiomer, [α]_D²⁵ = -5.7 (c=2, EtOH).

[0036] Diastereomer 1: 2(*)-(Furan-2-yl)hydroxyphenylacetic acid 1-azabi cyclo[2.2.2]oct-3(R)-yl ester. ¹H-

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NMR (CDCl₃): δ 1.20-1.70 (m, 4H), 1.90 (m, 1 H), 2.45-2.50 (m, 1 H), 2.50-2.80 (m, 4H), 3.10-3.20 (m, 1 H), 4.8 (bs, OH), 4.90-5.0 (m, 1 H), 6.20 (m, 1 H), 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-azabi cyclo[2.2.2]oct-3(R)-yl ester. ¹H- NMR (CDCl₃): δ 1.20-1.70 (m, 4H), 2.10 (m, 1 H), 2.50-2.80 (m, 5H), 3.20-3.30 (m, 1 H), 4.8 (bs, OH), 4.90-5.0 (m, 1 H), 6.20 (m, 1H), 6.35 (m, 1 H), 7.30-7.50 (m, 4H), 7.60-7.70 (m, 2H).

Example I-1b- Preparation of Furan-2-ylhydroxythlen-2-ylacetic acid 1-azabicyclo[2.2.2]oct-3(R)-yl ester.

[0037] Prepared as in example I-1a. The yield was 3.06 g (64.3 %) of a mixture of diastereoisomers, mp: 172°C; GC/MS[M]⁺: 333;

¹H- 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, 1 H), 6.24-6.25 (m, 1 H), 6.42-6.45 (m, 1 H), 7.01-7.06 (m, 1H), 7.11-7.14 (m, 2H), 7.51-7.54 (m, 1 H), 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.

[0038] 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: 186°C. MS [M free base + 1]⁺: 334.

Oxalate salt, ¹H- NMR (DMSO-d₆): δ 1.43-1.55 (m, 2H), 1.68-1.78 (m, 2H), 1.75 (s, 3H), 2.02 (m, 1 H), 2.70-2.90 (m, 1 H), 2.92-3.15 (m, 4H), 3.50-3.57 (m, 1 H), 4.88 (m, 1 H), 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.

[0039] 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: 152°C. MS [M free base + 1]⁺: 350.

[0040] Oxalate salt, ¹H-NMR (DMSO-d₆): δ 1.20-1.30 (m, 1 H), 1.40-1.52 (m, 1 H), 1.64-1.81 (m, 2H), 1.90 (s, 3H), 2.0 (m, 1 H), 2.53-2.66 (m, 1 H), 2.71-2.76 (m, 1 H), 2.97-3.10 (m, 3H), 3.44-3.52 (m, 1 H), 4.90-4.92 (m, 1 H), 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.

[0041] 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 5°C in N₂ 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 ¹H-NMR.

¹H- 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.

[0042] Prepared as in example I-1e. The yield was 2.65 g (47.2%). ¹H- 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.

[0043] 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 5°C in N₂ 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 0°C. 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.

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This procedure was repeated with 5 g of starting material yielding 6.04g of the same brown solid. The products were combined and purified by column chromatography (silica gel, hexane/ethyl acetate 90:10) to yield 7.60g (global Rt: 59.4%) of a pure product, structure confirmed by ¹H-NMR. ¹H- 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.

[0044] 2.15g 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:NH₄OH, 95:5:0.5). The yield was 1.5 g (48%); mp: 112-113 °C; CG/MS [M]⁻: 347; ¹H-NMR (CDCl₃): δ 1.10-1.35 (m, 2H), 1.40-1.52 (m, 1 H), 1.52-1.68 (m, 1 H), 1.90 (m, 1 H), 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.

[0045] Prepared as in example I-2a. The yield was 3.12 g (71 %); mp 129°C; MS [M+1]⁺: 346; ¹H-NMR (DMSO-d₆) : δ 0.90-1.10 (m, 2H), 1.30-1.50 (m, 2H), 1.58 (m, 1 H), 2.21-2.26 (m, 2H), 2.47-2.50 (m, 3H), 2.86-2.94 (m, 1 H), 4.48-4.51 (m, 1H), 5.33 (s, 1 H), 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

[0046] Prepared as in example I-2a. The yield was 0.77 g (62.6%); mp 139°C; MS [M+1]⁺: 334; ¹H- NMR (DMSO-d₆): δ 1.1-1.2 (m, 1 H), 1.25-1.40 (m, 2H), 1.40-1.55 (m, 1 H), 1.73 (m, 1 H), 2.20 (m, 1H), 2.35-2.65 (m, 4H), 2.90-2.98 (m, 1 H), 3.93-4.14 (dd, 2H, J = 1.8 Hz, J = 4.3 Hz), 4.56 (m, 1H), 5.14 (s, 1 H), 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. Mossetig; 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.

[0047] 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 imidazolid. 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 0.33g (45.6%) of oxalate of 2,2-Diphenyl-propionic acid 1-azabicyclo[2.2.2]oct-3(R)-yl ester; mp: 146°C; MS [M free base+1]⁺: 336.

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

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Method -f-

Example I-4a- Preparation of 2-Hydroxy-2,2-dithien-2-ylacetic acid 1-azabicyclo[2.2.2]oct-4-yl ester.

5 [0048] 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
 10 (56%). ¹H-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.

15 [0049] 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 0°C. 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 dissolved 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
 20 (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. ¹H-NMR (dmsO) : δ 2.0 (m, 6H), 2.9 (m, 6H), 7.35 (m, 1 H), 8.05 (m, 1 H), 8.3 (m, 1 H).

Example I-4c- Preparation of (Furan-2-yl)hydroxyphenylacetic acid 1-azabicyclo[2.2.2]oct-3(R)-yl ester.

[0050] Phenylmagnesium bromide, 0.0057 mol (5.7 ml of a solution 1 M 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 -70°C in N₂ atmosphere. The mixture was stirred at this temperature for 10 minutes, and then warmed to room
 30 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 ¹H-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 ¹H-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.

[0051] 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%). ¹H-NMR (CDCl₃):
 40 δ 1.2-1.4 (m, 1 H), 1.4-1.8 (m, 3H), 2.0 (m, 1 H), 2.6-2.85 (m, 5H), 3.2 (m, 1 H), 5.0 (m, 1 H), 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.

45 [0052] 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 0°C. 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 dissolved 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 0°C. The mixture was stirred
 50 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.

¹H-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, 1 H), 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.

[0053] The title compound was prepared as described in example I-4c from intermediate I-4g. The yield was 3 g (33%)

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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 hydrolysed 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 with $[\alpha]^{25}_D = -20$ (c=2, EtOH).

Diastereomer 1: 2(R)-2-Hydroxy-2-phenyl-2-thien-2-ylacetic acid 1-aza bicyclo[2.2.2]oct-3(R)-yl ester. ¹H-NMR (DMSO-d₆): δ 1.1-1.25 (m, 1 H), 1.3-1.6 (m, 3H), 1.83 (m, 1 H), 2.4-2.7 (m, 5H), 3.1 (m, 1 H), 4.8 (m, 1 H), 7.0 (m, 2H), 7.05 (m, 1 H), 7.3-7.4 (m, 3H), 7.4-7.45 (m, 2H), 7.5 (m, 1 H).

Diastereomer 2: 2(S)-2-Hydroxy-2-phenyl-2-thien-2-ylacetic acid 1-aza bicyclo[2.2.2]oct-3(R)-yl ester. ¹H-NMR (DMSO-d₆): δ 1.1-1.25 (m, 1 H), 1.4-1.6 (m, 3H), 1.9 (m, 1 H), 2.3-2.7 (m, 5H), 3.05 (m, 1H), 4.8 (m, 1 H), 7.0 (m, 2H), 7.05 (m, 1 H), 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.

[0054] 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 0°C. 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 dissolved in CHCl₃ (30 ml) and a solution of 3(R)-quinuclidinol (1.95g, 0.0154 mol) in CHCl₃ (30 ml) was added to this at 0°C. 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. ¹H- NMR (CDCl₃): δ 1.40-1.50 (m, 1 H), 1.50-1.70 (m, 1 H), 1.70-1.80 (m, 1 H), 1.90-2.0 (m, 1 H), 2.15 (m, 1 H), 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).

[0055] Other carboxylic acids of Formula B-C(O)OH, whose preparation (or the syntheses of their derivatives methyl ester, chloride or imidazolide) haven't been described in methods c,d,e or in the Examples I-1e, I-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.

[0056] 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.

[0057] 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.

[0058] 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.

[0059] 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 1 μ g and 1,000 μ g, preferably from 10 to 800 μ g 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 μ g and 800 μ g per day as inhalant composition.

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Pharmacological Action

[0060] 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.

[0061] The binding of [³H]-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.

[0062] For determination of IC₅₀, 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

(continued)

COMPOUNDS No	BINDING TO RECEPTOR M ₃ (IC ₅₀ nM)
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.	

[0063] Our results show that the compounds of the present invention have affinities for the M₃ receptors which are very similar to the reference compounds.

[0064] The compounds of the invention preferably have high affinities for muscarinic M₃ receptors (HM3), preferably human muscarinic receptors. Affinity levels can typically be measured by *in vitro* assays, for example, as described above.

[0065] Preferred compounds of the invention have an IC₅₀ (nM) value for M₃ 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

[0066] 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., Rössler F. Versuchsanordnung zu Untersuchungen an der bronchialmuskulatur. Arch. Exp. Path. Pharmacol. 195: 71-74 (1940)

[0067] The compounds of the present invention inhibited the bronchospasm response to acetylcholine with high potency and a long duration of action.

[0068] 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 (M₃) and thus are useful for the treatment of diseases in which the muscarinic M₃ receptor is implicated, including respiratory diseases such as chronic obstructive pulmonary disease, chronic bronchitis, asthma and rhinitis, urinary diseases such as urinary incontinence and pollakiuria in ne-ripenia pollakinuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystitis and gastrointestinal diseases such as irritable bowel syndrome, spastic colitis and diverticulitis.

[0069] 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.

[0070] 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.

[0071] 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 pharma-ceutical composition comprising a compound of formula (I).

[0072] 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)-Diphenylacetoxyl-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2] octane; bromide

[0073] The title compound was synthesised according to methods d and a. The yield of final step was 500 mg , 81%. ¹H-

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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, 1 H), 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

[0074] The title compound was synthesised according to methods c and a. The yield of final step was 280 mg , 42%. ¹H-NMR (DMSO-d₆): δ 1.5-1.7 (m, 2H), 1.9 - 2.1 (m, 4H), 2.3 (m, 1 H), 3.1 (m, 1 H), 3.2 - 3.5 (m, 6H), 3.9 - 4.1 (m, 3H), 5.25 (m, 1 H), 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

[0075] The title compound was synthesised according to methods c and a. The yield of final step was 400 mg , 85%. ¹H-NMR (DMSO-d₆): δ 1.5-1.65 (m, 1 H), 1.7-1.8 (m, 1 H), 1.85-2.0 (m, 2H), 2.05-2.2 (m, 2H), 2.3 (m, 1 H), 3.1-3.2 (m, 1 H), 3.3-3.5 (m, 6H), 3.95 (m, 1 H), 4.05 (m, 2H), 5.25 (m, 1 H), 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-azonia bicyclo[2.2.2]octane; bromide

[0076] The title compound was synthesised according to methods c and a. The yield of final step was 300 mg, 67%. ¹H-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, 1 H), 3.3-3.6 (m, 6H), 3.95-4.05 (m, 1 H), 5.25 (m, 1 H), 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-azonia bicyclo[2.2.2]octane; bromide

[0077] The title compound was synthesised according to methods c and a. The yield of final step was 500 mg , 54%. ¹H-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, 1 H), 4.05 (t, 2H), 5.2 (m, 1 H), 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

[0078] The title compound was synthesised according to methods c and a. The yield of final step was 650 mg , 74%. ¹H-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, 1 H), 3.3-3.55 (m, 6H), 3.95 (m, 1 H), 5.25 (m, 1 H), 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

[0079] The title compound was synthesised according to methods e and a. The yield of final step was 250 mg , 61%. ¹H-NMR (CDCl₃): δ 1.47-1.60 (m, 1 H), 1.8-2.0 (m, 1 H), 2.0 (s, 3H), 2.0-2.15 (m, 4H), 2.39 (s, 1 H), 2.6 (m, 1 H), 2.92 (d, 1 H), 3.6 (m, 1 H), 3.7-3.9 (m, 4H), 4.0 (m, 2H) , 4.3 (m, 1H), 5.25 (m, 1 H), 6.85 (m, 2H), 7.0 (m, 1 H), 7.3 (m, 12H); MS [M-Br]⁺: 470; mp 186 °C.

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Example 8

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

- 5 **[0080]** 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%. ¹H- NMR (DMSO-d₆): δ 1.5 - 1.95 (m, 4H), 2.1 (m, 2H), 2.3 (m, 1H), 3.1 (m, 1 H), 3.3 - 3.5(m, 6H), 3.9 (m, 1 H), 4.05 (t, 2H), 5.2 (m, 1 H), 7.0 (m, 4H), 7.15 (m, 2H), 7.35 (m, 5H), 7.5 (m, 3H); MS [M-Br]⁺: 478; mp 220°C.

10 Example 9

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

- 15 **[0081]** 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%. ¹H- NMR (DMSO-d₆): δ 1.5-1.6 (m, 1 H), 1.65-1.75 (m, 1 H), 1.8-2.0 (m, 2H), 2.05-2.1 (m, 2H), 2.3 (m, 1 H), 3.05-3.2 (m, 1 H), 3.25-3.55 (m, 6H), 3.85-3.95 (m, 1 H), 4.0 (t, 2H), 5.2 (m, 1 H), 6.95 (m, 3H), 7.03 (m, 1 H), 7.15 (dd, 1 H), 7.2 (s, OH), 7.3-7.5 (m, 5H), 7.45-7.55 (m, 3H); MS [M-CF₃COO]⁺: 478.

20 Example 10

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

- 25 **[0082]** 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%. ¹H- 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, 1 H), 3.15-3.5 (m, 6H), 3.8-3.95 (m, 1 H), 5.2 (m, 1 H), 6.92 (m, 1H), 6.96-7.03 (m, 2H), 7.1 (dd, 1 H), 7.18 (s, OH), 7.3-7.4 (m, 4H), 7.43-7.5 (m, 2H), 7.51 (dd, 1 H); MS [M-CF₃COO]⁺: 478.

30 Example 11

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

- 35 **[0083]** 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%. ¹H- NMR (DMSO-d₆): δ 1.45-1.55 (m, 1 H), 1.65-1.75 (m, 1 H), 1.85-2.05 (m, 2H), 2.3 (m, 1 H), 2.9-3.1 (m, 2H), 3.1-3.25 (m, 1 H), 3.25-3.55 (m, 6H), 3.9-4.0 (m, 1 H), 5.25 (m, 1 H), 7.05 (m, 1 H), 7.15 (m, 1 H), 7.2 (m, 1 H), 7.25-7.4 (m, 8H), 7.45 (m, 2H, 7.55 (m, 1 H); MS [M-CF₃COO]⁺: 448.

40 Example 12

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

- 45 **[0084]** 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%. ¹H- NMR (DMSO-d₆): δ 1.45-1.55 (m, 1 H), 1.6-1.75 (m, 1H), 1.8-2.0 (m, 4H), 2.25 (m, 1 H), 2.55 (t, 2H), 3.0-3.1 (m, 1 H), 3.15-3.55 (m, 6H), 3.8-3.9 (m, 1 H), 5.2 (m, 1 H), 7.0 (m, 1 H), 7.1 (m, 1 H), 7.15-7.4 (m, 9H), 7.45 (m, 2H), 7.5 (m, 1 H); MS [M-CF₃COO]⁺: 462.

50 Example 13

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

- 55 **[0085]** 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%. ¹H- NMR (DMSO-d₆): δ 1.45-1.55 (m, 1 H), 1.65-1.75 (m, 1 H), 1.8-2.0 (m, 2H), 2.3 (m, 1 H), 3.1-3.6 (m, 9H), 3.9-4.0 (m, 1 H), 5.25 (m, 1 H), 7.0 (m, 3H), 7.15 (dd, 1 H), 7.2 (s, OH), 7.3-7.4 (m, 3H), 7.45-7.55 (m, 4H); MS [M-CF₃COO]⁺: 454.

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Example 14

3(R)-[2(R)-(2-Hydroxy-2-phenyl-2-thien-2-ylacetoxy)]-1-(3-thien-2-yl propyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

[0086] 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%. ¹H-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-yl propyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

[0087] 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%. ¹H-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-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

[0088] 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%. ¹H-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

[0089] 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%. ¹H-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 (double 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

[0090] 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%. ¹H-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 (double 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-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

[0091] The title compound was synthesised according to methods c and b from intermediate I-1a, diastereomer 1. The yield of final step was 11 mg, 23%. ¹H-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.

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Example 20

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

5 [0092] The title compound has been described in method -a-.

Example 21

10 **3(R)-[2(*)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)]-1-(3-phenoxy propyl)-1-azoniabicyclo[2.2.2]octane; bromide**

[0093] The title compound was synthesised according to methods c and a from intermediate l-1a, diastereomer 1. The yield of final step was 1.15 g 99%. ¹H- 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; mp156°C.

Example 22

20 **3(R)-[2(*)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)]-1-(3-phenoxy propyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

[0094] The title compound was synthesised according to methods c and b from intermediate l-1a, diastereomer 2. The yield of final step was 10 mg, 20%. ¹H- 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

30 **3(R)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

[0095] 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%. ¹H- 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-CF₃COO]⁺: 432.

Example 24

40 **3(R)-[2(*)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)]-1-phenethyl-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

[0096] The title compound was synthesised according to methods c and b from intermediate l-1a, diastereomer 1. The yield of final step was 16 mg, 40%. ¹H- 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

50 **3(R)-[2(*)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)]-1-phenethyl-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

[0097] The title compound was synthesised according to methods c and b from intermediate l-1a, diastereomer 2. The yield of final step was 14 mg, 35%. ¹H- 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.

3A

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Example 26

3(R)-[2(*)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)]-1-(3-phenylprop yl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

5

[0098] The title compound was synthesised according to methods c and b from intermediate I-1a, diastereomer 1. The yield of final step was 10 mg, 21%. ¹H- 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, 1 H), 5.17 (m, 1 H), 6.25 (d, 1 H), 6.45 (m, 1 H), 6.95 (s, 1 H), 7.20-7.40 (m, 8H), 7.46-7.48 (m, 2H), 7.66 (m, 1 H); MS [M-CF₃COO]⁺: 446.

10

Example 27

3(R)-[2(*)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)]-1-(2-thien-2-yl ethyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

15

[0099] The title compound was synthesised according to methods c and b from intermediate I-1a, diastereomer 1. The yield of final step was 9 mg, 19%. ¹H- 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, 1 H), 5.24 (m, 1 H), 6.27 (d, 1 H), 6.47 (m, 1 H), 6.96 (s, 1 H), 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.

20

Example 28

3(R)-[2(*)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxy)]-1-(3-thien-2-yl propyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

25

[0100] The title compound was synthesised according to methods c and b from intermediate I-1a, diastereomer 1. The yield of final step was 9 mg, 19%. ¹H- NMR (DMSO-d₆): δ 1.60-1.75 (m, 2H), 1.80-2.05 (m, 4H), 2.26 (m, 1 H), 2.81 (t, 2H), 3.02 (m, 1 H), 3.10-3.45 (m, 6H), 3.85 (m, 1 H), 5.18 (m, 1 H), 6.25 (d, 1 H), 6.45 (m, 1 H), 6.90-7.0 (m, 3H), 7.32-7.42 (m, 4H), 7.45-7.51 (m, 2H), 7.66 (m, 1 H); MS [M-CF₃COO]⁺: 452.

30

Example 29

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

35

[0101] 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%. ¹H- NMR (DMSO-d₆): δ 1.65 - 2.05 (m, 4H), 2.3 (m, 1 H), 3.0 (m, 2H), 3.15 - 3.6 (m, 7H), 3.95 (m, 1 H), 5.25 (m, 1H); 6.35 (dd, 1 H), 6.45 (m, 1 H), 7.05 (m, 1 H), 7.2 (dd, 1 H), 7.25 - 7.5 (m, 6H), 7.55 (m, 1 H), 7.65 (m, 1 H); MS [M-CF₃COO]⁺: 438.

40

Example 30

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

45

[0102] 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%. ¹H- NMR (DMSO-d₆): δ 2.65 - 2.05 (m, 4H), 2.3 (m, 1 H), 3.15 - 3.65 (m, 7H), 4.05 (m, 1 H), 4.4 (m, 2H), 5.15 (m, 1 H), 6.35 (dd, 1 H), 6.45 (m, 1 H), 6.95 - 7.05 (m, 4H), 7.15 (d, 1 H), 7.3 - 7.4 (m, 3H), 7.5 (dd, 1H), 7.65 (d, 1H); MS [M-CF₃COO]⁺: 454.

50

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

55

[0103] 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%. ¹H- NMR (DMSO-d₆): δ 1.65 - 2.1 (m, 6H), 7.05 - 7.55 (m, 9H), 3.95 (m, 1 H), 5.1 (m, 1 H), 6.35 (dd, 1H), 6.5 (m, 1 H), 7.05 (m, 1 H), 7.15 (m, 1 H), 7.3 (d, 1 H), 7.55 (m, 3H), 7.7 (dd, 2H), 8.0 (d, 2H); MS [M-CF₃COO]⁺: 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

5

[0104] 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%. ¹H- NMR (DMSO-d₆): δ 1.65 - 2.05 (m, 4H), 2.1 - 2.0 (m, 2H), 2.3 (m, 1 H), 3.15 (m, 1 H), 3.25 - 3.6 (6H), 3.9 - 4.1 (m, 3H), 5.1 (m, 1 H), 6.35 (d, 1 H), 6.45 (s, 1H), 6.95 (m, 3H), 7.05 (m, 1 H), 7.2 (d, 1 H), 7.3 (m, 3H), 7.55 (d, 1 H), 7.7 (s, 1 H); MS [M-Br]⁺: 520; mp 173°C.

10

Example 33

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

15

[0105] The title compound was synthesised according to methods f and a. The yield of final step was 200 mg, 60%. ¹H- NMR (DMSO-d₆): δ 1.6-2.20 (m, 6H), 2.3 (m, 1 H), 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

20

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

25

[0106] The title compound was synthesised according to methods c and a. The yield of final step was 240 mg , 60%. ¹H- NMR (DMSO-d₆) : δ 1.85-2.10 (m, 4H), 2.30 (s, 1 H), 3.40 (m, 1 H), 3.44-3.80 (m, 6H), 4.10 (m, 1 H), 4.45 (m, 2H), 5.20 (m, 1 H), 5.90 (s, 1 H), 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

30

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

[0107] The title compound was synthesised according to methods c and a. The yield of final step was 280 mg , 83%. ¹H- NMR (DMSO-d₆): δ 1.80-2.06 (m, 4H), 2.06-2.20 (m, 2H), 2.20-2.30 (m, 1 H), 3.20-3.65 (m, 7H), 3.90-4.10 (m, 3H), 5.20 (m, 1 H), 5.90 (s, 1 H), 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.

35

Example 36

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

40

[0108] The title compound was synthesised according to methods c and a. The yield of final step was 180 mg , 59%. ¹H- NMR (DMSO-d₆): δ 1.65 - 2.0 (4H, m), 2.35 (m, 1 H), 3.0 (m, 2H), 3.2 - 3.6 (m, 7H), 3.95 (m, 1 H), 5.25 (m, 1 H), 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

45

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

[0109] The title compound was synthesised according to methods c and a. The yield of final step was 450 mg , 58%. ¹H- 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, 1 H), 5.25 (m, 1 H), 6.1 (bs, OH), 6.9 (m, 2H), 7.1 - 7.3 (m, 9H); MS [M-Br]⁺: 468; mp 64°C.

50

Example 38

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

55

[0110] The title compound was synthesised according to methods c and a.. The yield of final step was 260 mg , 34%. ¹H- NMR (CDCl₃): δ 1.8 - 2.05 (m, 4H), 2.4 (m, 1 H), 3.55 - 3.95 (m, 5H), 4.15 - 4.5 (m, 3H), 5.25 (m, 1 H), 5.9 (s, OH), 6.15 (m, 1 H), 6.85 (t, 1 H), 6.9 - 7.05 (m, 3H), 7.15 (m, 1 H), 7.2 - 7.45 (m, 7 H); MS [M-Br]⁺: 466; mp 124°C.

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Example 39

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetox)-1-(4-phenylbutyl)-1-azonia bicyclo[2.2.2]octane; bromide

5 [0111] The title compound was synthesised according to methods c and a. The yield of final step was 320 mg, 40%. ¹H-NMR (CDCl₃): δ 1.6 - 2.0 (m, 8H), 2.4 (m, 1 H), 2.6 (m, 2H), 3.4 - 3.8 (m, 7H), 4.2 (m, 1 H), 5.25 (m, 1 H), 6.05 (bs, OH), 6.95 (m, 2H), 7.1 - 7.3 (m, 9H); MS [M-Br]⁺: 482; mp 64°C.

Example 40

10

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

15 [0112] The title compound was synthesised according to methods c and b. The yield of final step was 16 mg, 15%. ¹H-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, 1 H), 5.25 (m, 1H), 7.0 (d, 2H), 7.15 (d, 2H), 7.55 (m, 5H), 7.65 (t, 1 H), 8.0 (d, 2H); MS [M-CF₃COO]⁺: 496.

Example 41

20

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

25 [0113] The title compound was synthesised according to methods c and b. The yield of final step was 14 mg, 14%. ¹H-NMR (DMSO-d₆): δ 1.7 - 2.0 (m, 5H), 2.3 (m, 1 H), 3.0 - 3.5 (m, 9H), 3.9 (m, 1 H), 5.25 (m, 1 H), 5.65 (t, 1 H), 6.55 (m, 3H), 7.0 (d, 2H), 7.1 (t, 2H), 7.15 (m, 2H), 7.5 (m, 3H); MS [M-CF₃COO]⁺: 483.

Example 42

30

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

35 [0114] The title compound was synthesised according to methods c and b. The yield of final step was 20 mg, 19%. ¹H-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, 1 H), 6.75 (d, 2H), 7.0 (m, 2H), 7, 2 (m, 4H), 7.5 (m, 3H); MS [M-CF₃COO]⁺: 497.

Example 43

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

40 [0115] The title compound was synthesised according to methods c and a. The yield of final step was 800 mg, 83%. ¹H-NMR (DMSO-d₆): δ 1.6 - 1.9 (m, 6H), 2.3 (m, 1 H), 2.95 (t, 2H), 3.05 (m, 1 H), 3.2 - 3.5 (m, 6H), 3.9 (m, 1 H), 5.2 (m, 1 H), 7.0 (m, 2H), 7.15 (m, 2H), 7.2 (m, 1 H), 7.35 (m, 4H), 7.5 (m, 2H); MS [M-Br]⁺: 500.

Example 44

45

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

50 [0116] The title compound was synthesised according to methods c and a. The yield of final step was 490 mg, 90%. ¹H-NMR (DMSO-d₆): δ 1.7 (m, 2H), 1.95 (m, 2H), 2.1 (m, 2H), 2.3 (m, 1 H), 3.2 (m, 1 H), 3.45 (m, 6H), 4.0 (m, 3H), 5.15 (m, 1 H), 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

55

3(R)-(2-Hydroxy-2,2-dithien-2-ylacetox)-1-(3-o-tolyloxypropyl)-1-azoniabicyclo[2.2.2] octane; trifluoroacetate

[0117] The title compound was synthesised according to methods c and b The yield of final step was 19 mg, 18%. ¹H-NMR (DMSO-d₆): δ 1.7- 2.0 (m, 4H), 2.1 - 2.2 (m, 5H), 2.3 (m, 1 H), 3.15 - 3.5 (m, 7H), 3.9 - 4.05 (m, 3H), 5.05 (m, 1 H), 6.85 (t, 1H), 6.9 (d, 1 H), 7.0 (m, 2H), 7.15 (m, 4H), 7.5 (m, 3H); MS [M-CF₃COO]⁺: 498.

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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

5

[0118] The title compound was synthesised according to methods c and b. The yield of final step was 22 mg , 20%. ¹H-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, 1 H), 5.25 (m, 1 H), 6.8 (s, 2H), 7.0 (m, 2H), 7.2 (m, 2H), 7.5 (m, 3H); MS [M-CF₃COO]⁺: 526.

10

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

15

[0119] The title compound was synthesised according to methods c and b. The yield of final step was 18 mg , 16%. ¹H-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, 1 H), 3.2 - 3.5 (m, 7H), 3.8 (t, 2H), 3.95 (m, 1H), 5.2 (m, 1 H), 6.9 - 7.15 (m, 7H), 7.5 (m, 3H); MS [M-CF₃COO]⁺: 554.

20

Example 48

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

25

[0120] The title compound was synthesised according to methods c and b. The yield of final step was 22 mg , 19%. ¹H-NMR (DMSO-d₆): δ 1.7 (m, 2H), 1.9 (m, 2H), 2.15 (m, 2H), 2.3(m, 1 H), 3.2 - 3.5(m, 7H), 3.95(m, 1 H), 4.1 (t, 2H), 5.25 (m, 1 H), 7.0 (m, 4H), 7.2(m, 2H), 7.3(t, 1 H), 7.45 (t, 2H), 7.5 (m, 3H), 7.6 (m, 4H); MS [M-CF₃COO]⁺: 560.

Example 49

30

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

35

[0121] The title compound was synthesised according to methods c and b. The yield of final step was 23 mg , 21%. ¹H-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, 1 H), 7.0 (m, 2H), 7.2 (m, 2H), 7.5 (m, 3H) ; MS [M-CF₃COO]⁺: 538.

Example 50

40

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

45

[0122] The title compound was synthesised according to methods c and b. The yield of final step was 17 mg , 15%. ¹H-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, 1 H), 7.0 (m, 2H), 7.15 (m, 3H), 7.35 (m, 2H), 7.5 (m, 4H), 7.85 (m, 3H); MS [M-CF₃COO]⁺: 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

50

[0123] The title compound has been described in method -b-.

Example 52

55

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

[0124] The title compound was synthesised according to methods c and b. The yield of final step was 20 mg , 18%. ¹H-

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NMR (DMSO-d₆): δ 1.65 - 2.0 (m, 6H), 2.35 (m, 1H), 3.2 (m, 1 H), 3.3 - 3.55 (m, 6H), 3.95 (m, 1 H), 4.15 (t, 2H), 5.25 (m, 2H), 7.0 (m, 3H), 7.2 (m, 3H), 7.35 (t, 1 H), 7.45 (d, 1 H), 7.55 (m, 3H); MS [M-CF₃COO]⁺: 519.

Example 53

5

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

10 **[0125]** The title compound was synthesised according to methods c and a. The yield of final step was 180 mg , 59%. ¹H-NMR (DMSO-d₆): δ 1.65 - 2.15 (m, 6H), 2.25 (m, 1 H), 3.2 (m, 1 H), 3.25 - 3.55 (m, 6H), 3.95 (m, 2H), 4.0 (t, 2H), 5.25 (m, 1 H), 7.0 (m, 4H), 7.15 (m, 4H), 7.55 (m, 3H); MS [M-Cl]⁺: 502; mp 160 °C.

Example 54

15

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

20 **[0126]** The title compound was synthesised according to methods c and b. The yield of final step was 14 mg , 13%. ¹H-NMR (DMSO-d₆): δ 1.65 - 2.0 (m, 4H), 2.15 (m, 2H), 2.35 (m, 1 H), 3.2 (m, 1 H), 3.25 - 3.35 (m, 6H), 3.95 (m, 1 H), 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-CF₃COO]⁺: 520.

Example 55

25

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

30 **[0127]** The title compound was synthesised according to methods c and b. The yield of final step was 19 mg , 17%. ¹H-NMR (DMSO-d₆): δ 1.65 - 2.1 (m, 6H), 2.35 (m, 1 H), 3.2 (m, 1 H), 3.3 - 3.55 (m, 6H), 3.95 (m, 1 H), 4.15 (t, 2H), 5.25 (m, 1 H), 7.0 (m, 2H), 7.2 (m, 2H), 7.25 - 7.35 (m, 3H), 7.5 - 7.6 (m, 4H); MS [M-CF₃COO]⁺: 552.

Example 56

35

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

[0128] The title compound was synthesised according to methods c and b. The yield of final step was 18 mg , 17%. ¹H-NMR (DMSO-d₆): δ 1.65 - 2.1 (m, 6H), 2.35 (m, 1 H), 3.2 (m, 1 H), 3.3 - 3.55 (m, 6H), 3.95 (m, 1 H), 4.15 (t, 2H), 5.25 (m, 1 H), 7.0 (m, 2H), 7.18 (m, 2H), 7.3 (d, 1 H), 7.45 (m, 2H), 7.55 (m, 4H); MS [M-CF₃COO]⁺: 509.

40

Example 57

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

45 **[0129]** The title compound was synthesised according to methods c and a. The yield of final step was 180 mg , 53%. ¹H-NMR (DMSO-d₆): δ 1.65 - 2.2 (m, 6H), 2.3 (m, 1 H), 3.2 (m, 1H), 3.3 - 3.55 (m, 6H), 3.95 (m, 1 H), 4.15 (t, 2H), 5.25 (m, 1 H), 7.0 (m, 2H), 7.1 (d, 2H), 7.15 (m, 2H), 7.5 (m, 2H), 7.8 (d, 2H); MS [M-Br]⁺ : 509; mp 158°C.

Example 58

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3(R)-(2-Hydroxy-2,2-dithien-2-ylacetox)-1-[3-(3-methoxyphenoxy)propyl]-1-azonia bicyclo[2.2.2]octane; trifluoroacetate

55 **[0130]** The title compound was synthesised according to methods c and b. The yield of final step was 19 mg , 18%. ¹H-NMR (DMSO-d₆): δ 1.65 - 2.15 (m, 6H), 2.15 (m, 1 H), 3.2 (m, 1 H), 3.3 - 3.5 (m, 6H), 3.75 (s, 3H), 3.95 (m, 1 H), 4.0 (t, 2H), 5.25 (m, 1 H), 6.55 (m, 3H), 7.0 (m, 2H), 7.2 (m, 3H), 7.55 (m, 3H); MS [M-CF₃COO]⁺: 514.

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Example 59

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

5

[0131] The title compound was synthesised according to methods c and b. The yield of final step was 14 mg, 13%. ¹H-NMR (DMSO-d₆): δ 1.65 - 2.15 (m, 6H), 2.35 (m, 1 H), 3.2 (m, 1 H), 3.3 - 3.55 (m, 6H), 3.7 (s, 3H), 3.9-4.0 (m, 3H), 5.25 (m, 1 H), 6.9 (s, 4H), 7.0 (m, 2H), 7.15 (m, 2H), 7.5 (m, 3H); MS [M-CF₃COO]⁺: 514.

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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

15

[0132] The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 17%. ¹H-NMR (DMSO-d₆): δ 1.65 - 2.15 (m, 7H), 2.3 (m, 1 H), 3.15 (m, 1 H), 3.25 - 3.5 (m, 6H), 3.9 - 4.0 (m, 3H), 5.25 (m, 1 H), 5.95 (s, 2H), 6.4 (d, 1 H), 6.65 (s, 1 H), 6.85 (d, 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.5 (m, 3H); MS [M-CF₃COO]⁺: 528.

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Example 61

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

25

[0133] The title compound was synthesised according to methods c and b. The yield of final step was 18 mg, 16%. ¹H-NMR (DMSO-d₆): δ 1.65 - 2.0 (m, 4H), 2.2 (m, 2H), 2.3 (m, 1 H), 3.15 (m, 1 H), 3.25 - 3.55 (m, 6H), 3.95 (m, 1 H), 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-CF₃COO]⁺: 527.

Example 62

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

35

[0134] The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 17%. ¹H-NMR (DMSO-d₆): δ 1.65 - 2.15 (m, 6H), 2.3 (m, 1 H), 2.85 (s, 6H), 3.1 - 3.5 (m, 7H), 3.85 - 4.0 (m, 3H), 5.25 (m, 1 H), 6.2 (m, 1 H), 6.25 (d, 1 H), 6.35 (d, 1 H), 7.0 (m, 2H), 7.1 (t, 1 H), 7.2 (m, 2H), 7.5 (m, 3H); MS [M-CF₃COO]⁺: 527.

Example 63

40

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

45

[0135] The title compound was synthesised according to methods c and b. The yield of final step was 22 mg, 20%. ¹H-NMR (DMSO-d₆): δ 1.65 - 2.0 (m, 4H), 2.2 (m, 2H), 2.3 (m, 1H), 3.2 (m, 1 H), 3.3 - 3.5 (m, 6H), 3.95 (m, 1 H), 4.2 (t, 2H), 5.25 (m, 1 H), 7.0 (m, 2H), 7.15 (m, 4H), 7.5 (m, 3H), 8.15 (d, 2H); MS [M-CF₃COO]⁺: 529.

Example 64

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

55

[0136] The title compound was synthesised according to methods c and b. The yield of final step was 18 mg, 16%. ¹H-NMR (DMSO-d₆): δ 1.65 - 2.2 (m, 6H), 2.3 (m, 1 H), 3.15 - 3.55 (m, 7H), 3.95 (m, 1 H), 4.2 (t, 2H), 5.25 (m, 1 H), 7.0 (m, 2H), 7.2 (m, 2H), 7.45 (dd, 1 H), 7.55 (m, 3H), 7.6 (t, 1 H), 7.75 (s, 1 H), 7.85 (d, 1 H); MS [M-CF₃COO]⁺: 529.

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Example 65

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

[0137] The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 17%. ¹H-NMR (DMSO-d₆): δ 1.65 - 2.15 (m, 6H), 2.0 (s, 3H), 2.3 (m, 1 H), 3.2 (m, 1 H), 3.3 - 3.55 (m, 6H), 3.9 - 4.0 (m, 3H), 5.25 (m, 1 H), 6.85 (d, 2H), 7.0 (m, 2H), 7.2 (m, 2H), 7.5 (m, 5H), 9.8 (s, 1 H); MS [M-CF₃COO]⁺: 541.

Example 66

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

[0138] The title compound was synthesised according to methods c and b. The yield of final step was 18 mg, 16%. ¹H-NMR (DMSO-d₆): δ 1.6 - 2.2 (m, 6H), 2.3 (m, 1 H), 3.2 (m, 1 H), 3.3 - 3.5 (m, 6H), 3.85 (s, 3H), 3.95 (m, 1 H), 4.1 (t, 2H), 5.25 (m, 1 H), 7.0 (m, 2H), 7.15 (m, 2H), 7.25 (dd, 1 H), 7.45 - 7.6 (m, 6H); MS [M-CF₃COO]⁺: 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

[0139] The title compound was synthesised according to methods c and b. The yield of final step was 14 mg, 13%. ¹H-NMR (DMSO-d₆): δ 1.6 - 2.15 (m, 8H), 2.3 (m, 1 H), 2.55 (t, 2H), 3.2 (m, 1 H), 3.25 - 3.55 (m, 9H), 3.85 - 4.0 (m, 3H), 4.45 (t, OH), 5.25 (m, 1 H), 7.85 (d, 2H), 7.0 (m, 2H), 7.1 (d, 2H), 7.15 (m, 2H), 7.5 (m, 2H); MS [M-CF₃COO]⁺: 542.

Example 68

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

[0140] The title compound was synthesised according to methods c and b. The yield of final step was 16 mg, 15%. ¹H-NMR (DMSO-d₆): δ 1.7 - 2.2 (m, 6H), 2.35 (m, 1 H), 3.1 - 3.5 (m, 7H), 3.9 - 4.05 (m, 3H), 4.5 (m, 2H), 5.0 (t, OH), 5.15 (m, 1 H), 6.9 - 7.05 (m, 4H), 7.2 (m, 2H), 7.4 (d, 1 H), 7.5 (m, 3H); MS [M-CF₃COO]⁺: 514.

Example 69

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

[0141] The title compound was synthesised according to methods c and b. The yield of final step was 16 mg, 15%. ¹H-NMR (DMSO-d₆): δ 1.7 - 2.2 (m, 6H), 2.35 (m, 1 H), 3.15 - 3.5 (m, 7H), 3.9 (m, 1 H), 4.05, (t, 2H), 4.45 (d, 2H), 5, 25 (m, 2H), 6.8 (d, 1 H), 6.9 (m, 2H), 7.2 (m, 2H), 7.25 (t, 1 H), 7.5 (m, 3H); MS [M-CF₃COO]⁺: 514.

Example 70

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

[0142] The title compound was synthesised according to methods c and b. The yield of final step was 17 mg, 16%. ¹H-NMR (DMSO-d₆): δ 1.65 - 2.2 (m, 6H), 2.3 (m, 1 H), 3.15 - 3.55 (m, 7H), 3.9 - 4.05 (m, 3H), 4.4 (d, 2H), 5.1 (t, OH), 5.25 (t, 1 H), 6.9 (d, 2H), 7.0 (m, 2H), 7.2 (m, 2H), 7.25 (d, 2H), 7.5 (m, 3H); MS [M-CF₃COO]⁺: 514.

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Example 71

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

5

[0143] The title compound was synthesised according to methods c and b. The yield of final step was 24 mg , 19%. ¹H-NMR (DMSO-d₆) : δ 1.65 - 2.15 (m, 6H), 2.35 (m, 1 H), 3.2 (m, 1H), 3.25 - 3.55 (m, 6H), 3.95 (m, 1 H), 4.0 (t, 2H), 5.25 (m, 1 H), 6.7 -6.85 (m, 3H), 6.95 (d, 1 H), 7.0 (m, 2H), 7.2 (m, 2H), 7.5 (m, 3H), 8.85 (s, OH); MS [M-CF₃COO]⁺: 500.

10

Example 72

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

15

[0144] The title compound was synthesised according to methods c and b. The yield of final step was 16 mg , 15%. ¹H-NMR (DMSO-d₆) : δ 1.65 -2.1 (m, 6H), 2.3 (m, 1 H), 3.2 (m, 1 H), 3.25 - 3.5 (m, 6H), 3.95 (m, 3H), 5.25 (m, 1 H), 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-CF₃COO]⁺: 500.

Example 73

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

25

[0145] The title compound was synthesised according to methods c and b. The yield of final step was 16 mg, 15%. ¹H-NMR (DMSO-d₆) : δ 1.65 - 2.15 (m, 6H), 2.3 (m, 1 H), 3.2 (m, 1 H), 3.3 -3.55 (m, 6H), 3.9 - 4.0 (m, 3H), 5.25 (m, 1 H), 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-CF₃COO]⁺: 500.

Example 74

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

35

[0146] The title compound was synthesised according to methods c and b. The yield of final step was 21 mg, 22%. ¹H-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, 1 H), 3.05-3.2 (m, 3H), 3.2-3.5 (m, 4H), 3.8-3.95 (m, 3H), 5.2 (m, 1 H), 6.05 (t, 2H), 6.75 (t, 2H), 7.0 (t, 2H), 7.15 (d, 2H), 7.55 (m, 3H); MS [M-CF₃COO]⁺: 457.

Example 75

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

[0147] The title compound was synthesised according to methods c and b. The yield of final step was 18 mg , 17%. ¹H-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, 1 H), 7.55 (m, 3H), 7.95 (d, 1 H), 8.05 (d, 1H) ; MS [M-CF₃COO]⁺: 502.

45

Example 76

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

50

[0148] The title compound was synthesised according to methods c and b. The yield of final step was 26 mg , 25%. ¹H-NMR (DMSO-d₆) : δ 1.7 (m, 2H), 1.85 - 2.05 (m, 4H), 2.3 (m, 1 H), 3.25 - 3.5 (m, 7H), 3.6 (s, 3H), 3.9 (m, 1 H), 4.2 (t, 2H), 5.2 (m, 1 H), 7.0 (m, 3H), 7.15 (m, 2H), 7.3 (m, 1H), 7.5 (m, 3H); MS [M-CF₃COO]⁺: 504.

Example 77

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

[0149] The title compound was synthesised according to methods c and a. The yield of final step was 430 mg, 54%. ¹H-

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NMR (DMSO-d₆): δ 1.6-1.8 (m, 2H), 2.3 (m, 1 H), 3.15-3.3 (m, 4H), 3.35-3.55 (m, 5H), 3.95 (m, 1 H), 5.25 (m, 1 H), 7.0 (m, 4H), 7.15 (m, 2H), 7.4-7.5 (m, 4H); MS [M-Br]⁺: 460; mp 206°C.

Example 78

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

[0150] The title compound was synthesised according to methods c and a. The yield of final step was 600 mg, 77%. ¹H-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, 1 H), 5.2 (m, 1 H), 6.9-7.05 (m, 4H), 7.15 (m, 2H), 7.4 (d, 1H), 7.5 (m, 3H); MS [M-Br]⁺: 474; mp 138°C.

Example 79

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

[0151] The title compound was synthesised according to methods c and b. The yield of final step was 23 mg, 21%. ¹H-NMR (DMSO-d₆): δ 1.65-2.1 (m, 6H), 2.3 (m, 1 H), 3.15 (m, 1 H), 3.25-3.5 (m, 6H), 3.85 (m, 1 H), 4.0 (t, 2H), 5.2 (m, 1 H), 7.0 (t, 2H), 7.15 (m, 2H), 7.25 (m, 1 H), 7.45 (m, 5H), 7.7 (d, 1 H); MS [M-CF₃COO]⁺: 541.

Example 80

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

[0152] The title compound was synthesised according to methods c and b. The yield of final step was 16 mg, 15%. ¹H-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, 1 H), 3.9 (s, 2H), 5.2 (m, 1 H), 7.0 (m, 2H), 7.15 (m, 2H), 7.35 (m, 5H), 7.5 (m, 3H); MS [M-CF₃COO]⁺: 498.

Example 81

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

[0153] The title compound was synthesised according to methods c and a. The yield of final step was 560 mg, 60%. ¹H-NMR (CDCl₃): δ 1.2-1.75 (m, 16H), 1.8-2.1 (m, 4H), 2.4 (m, 1 H), 2.6 (t, 2H), 3.3-3.75 (m, 11 H), 4.2 (m, 1 H), 5.3 (m, 1 H), 6.0 (bs, OH), 6.95 (m, 2H), 7.15-7.3 (m, 9H); MS [M-Br]⁺: 582.

Example 82

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

[0154] The title compound was synthesised according to methods c and a. The yield of final step was 240 mg, 30%. ¹H-NMR (DMSO-d₆/CDCl₃): δ 1.8-1.95 (m, 6H), 2.1 (m, 2H), 2.45 (m, 1 H), 3.18 (m, 1 H), 3.5-3.8 (m, 6H), 4.0 (t, 2H), 4.15 (m, 1 H), 5.15 (m, 1 H), 6.7 (s, OH), 6.9 (m, 5H), 7.15 (d, 1 H), 7.25 (m, 5H); MS [M-Br]⁺: 498; mp 161°C.

Example 83

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

[0155] The title compound was synthesised according to methods c and a. The yield of final step was 380 mg, 50%. ¹H-NMR (DMSO-d₆): δ 1.85 (m, 2H), 2.05 (m, 2H), 2.4 (m, 1 H), 3.6-4.1 (m, 7H), 4.35 (m, 3H), 5.25 (m, 1 H), 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-Benzoyloxyethyl)-3(R)-(2-hydroxy-2,2-dithien-2-ylacetox)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

[0156] The title compound was synthesised according to methods c and b. The yield of final step was 17 mg, 17%. ¹H-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,

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2H), 7.15 (t, 2H), 7.3 - 7.4 (m, 4H), 7.5 (m, 3H); MS [M-CF₃COO]⁺: 484.

Example 85

5 **3(S)-(2-Hydroxy-2,2-dithien-2-ylacetox)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2] octane; bromide**

[0157] The title compound was synthesised according to methods c and a. The yield of final step was 600 mg, 54%. ¹H-NMR (DMSO-d₆/CDCl₃): δ 1.85 - 2.3 (m, 6H), 2.5 (m, 1 H), 3.3 (m, 1 H), 3.4 (d, 1 H), 3.5 - 3.7 (m, 5H), 4.05 (t, 2H), 4.2 (m, 1 H), 5.25 (m, 1H), 6.85 (d, 2H), 7.0 (m, 3H), 7.15 (m, 2H), 7.2 (d, 1 H), 7.3 (m, 4H); MS [M-Br]⁺: 484; mp 230°C.

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Example 86

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

15 [0158] The title compound was synthesised according to methods f and a. The yield of final step was 290 mg, 60%. ¹H-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 168°C.

Example 87

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

[0159] The title compound was synthesised according to methods f and a. The yield of final step was 260 mg, 57%. ¹H-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 195°C.

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Example 88

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

30

[0160] The title compound was synthesised according to methods c and a. The yield of final step was 390 mg, 92%. ¹H-NMR (DMSO-d₆): δ 1.65-2.20 (m, 6H), 2.10 (s, 3H), 2.30 (bs, 1 H), 3.10 (m, 1 H), 3.30-3.60 (m, 6H), 3.95-4.10 (m, 3H), 5.20 (m, 1 H), 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.

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Example 89

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

[0161] The title compound was synthesised according to methods c and a. The yield of final step was 300 mg, 76%. ¹H-NMR (DMSO-d₆): δ 1.6 (m, 1 H), 1.75 (m, 1 H), 1.8 - 2.0 (m, 2H), 2.0 - 2.2 (m, 2H), 2.3 (m, 1 H), 3.15 (m, 1 H), 3.3 - 3.6 (m, 6H), 3.9 (m, 1 H), 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 219°C.

40

Example 90

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

[0162] The title compound was synthesised according to methods c and a. The yield of final step was 300 mg, 77%. ¹H-NMR (DMSO-d₆): δ 1.5-1.6 (m, 1 H), 1.6-1.75 (m, 1 H), 1.8-2.1 (m, 4H), 2.25 (m, 1 H), 2.8 (t, 2H), 3.05-3.5 (m, 7H), 3.8-3.95 (m, 1 H), 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 192°C.

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Example 91

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

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[0163] The title compound was synthesised according to methods c and b. The yield of final step. was 63 mg, 48%. ¹H-NMR (DMSO-d₆): δ 1.5-1.7 (m, 1 H), 1.7-1.85 (m, 1 H), 1.9-2.1 (m, 2H), 2.3 (m, 1 H), 2.9-3.1 (m, 2H), 3.15-3.6 (m, 7H), 3.9-4.0 (m, 1 H), 5.2 (m, 1 H), 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.

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Example 92

3(R)-(2-Hydroxy-2,2-dithien-3-yl-acetoxy)-1-(3-phenylpropyl)-1-azonia bicyclo[2.2.2]octane; trifluoroacetate

5 [0164] The title compound was synthesised according to methods c and b. The yield of final step was 75 mg, 55%. ¹H-NMR (DMSO-d₆): δ 1.5-2.0 (m, 6H), 2.25 (m, 1 H), 2.5-2.6 (m, 2H), 3.05-3.6 (m, 8H), 3.8-3.9 (m, 1H), 5.15(m, 1 H), 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

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

[0165] The title compound was synthesised according to methods c and b. The yield of final step was 68 mg, 48%. ¹H-NMR (DMSO-d₆): δ 1.5-1.8 (m, 6H), 1.8-2.0 (m, 2H), 2.25 (m, 1 H), 2.6 (m, 2H), 3.05 (m, 1 H), 3.15-3.45 (m, 6H), 3.85 (m, 1 H), 5.15(m, 1 H), 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.

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Example 94

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

20

[0166] The title compound was synthesised according to methods c and b. The yield of final step was 65 mg, 49%. ¹H-NMR (DMSO-d₆): δ 1.5-1.65 (m, 1 H), 1.65-1.78 (m, 1 H), 1.85-2.05 (m, 2H), 2.3 (m, 1 H), 3.1-3.6 (m, 9H), 3.95 (m, 1 H), 5.2 (m, 1 H), 6.75 (s, OH), 7.0 (m, 2H), 7.15 (m, 2H), 7.45 (m, 3H), 7.5 (m, 2H); MS [M-CF₃COO]⁺: 460.

25

Example 95

3(R) - (2-Hydroxy-2,2-dithien-3-ylacetoxy)-1-(4-phenoxybutyl)-1-azonia bicycle[2.2.2]octane; trifluoroacetate

[0167] The title compound was synthesised according to methods c and b. The yield of final step was 63 mg, 43%. ¹H-NMR (DMSO-d₆): δ 1.5-2.0 (m, 8H), 2.3 (m, 1 H), 3.1 (m, 1 H), 3.2-3.5 (m, 6H), 3.85 (m, 1 H), 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.

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Example 96

35 **3(R)-(2-Hydroxy-2,2-dithien-3-ylacetoxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

[0168] The title compound was synthesised according to methods c and b. The yield of final step was 72 mg, 52%. ¹H-NMR (DMSO-d₆): δ 1.55-1.65 (m, 1 H), 1.7-1.8 (m, 1 H), 1.85-2.05 (m, 2H), 2.3 (m, 1 H), 3.2-3.6 (m, 5H), 3.7 (m, 2H), 4.05 (m, 1 H), 4.4 (m, 2H), 5.2(m, 1 H), 6.75 (s, OH), 6.9-7.05 (m, 3H), 7.1 (d, 2H), 7.3-7.5 (m, 6H); MS [M-CF₃COO]⁺: 470.

40

Example 97

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

45

[0169] The title compound was synthesised according to methods c and b. The yield of final step was 79 mg, 54%. ¹H-NMR (DMSO-d₆): δ 1.55-1.65 (m, 1 H), 1.7-1.8 (m, 1 H), 1.85-2.0 (m, 2H), 2.05-2.2 (m, 2H), 2.3 (m, 1 H), 3.1-3.2 (m, 1 H), 3.25-3.55 (m, 6H), 3.85-3.95 (m, 1 H), 4.0 (t, 2H), 5.2(m, 1 H), 6.75 (s, OH), 6.95 (m, 2H), 7.15 (m, 4H), 7.4 (m, 2H), 7.5 (m, 2H); MS [M-CF₃COO]⁺: 502.

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Example 98

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

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[0170] The title compound was synthesised according to methods c and b. The yield of final step was 24 mg, 17%. ¹H-NMR (DMSO-d₆): δ 1.8 - 2.05 (m, 4H), 2.3 (m, 1 H), 3.15 (m, 1 H), 3.3 - 3.5 (m, 4H), 3.9 (m, 1 H), 4.05 (m, 2H), 5.25 (m, 1 H), 6.35 (m, 1 H), 6.75 (s, OH), 6.85 (t, 1 H), 7.1 (m, 2H), 7.3-7.5 (m, 5H), 7.55 (m, 4H); MS [M-CF₃COO]⁺: 502.

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Example 99

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

5 [0171] The title compound was synthesised according to methods c and a. The yield of final step was 400 mg, 93%. ¹H-NMR (DMSO-d₆): δ 1.35-1.50 (m, 1 H), 1.60-1.75 (m, 1 H), 1.75-1.95 (m, 2H), 2.10 (m, 1 H), 2.85 (m, 1 H), 3.10 (d, 1 H), 3.20-3.50 (m, 3H), 3.85 (m, 1H), 4.0 (dd, 2H), 5.05 (m, 1H), 6.40 (dd, 1 H), 6.80-6.90 (d, 1 H), 6.85 (s, OH), 7.20-7.50 (m, 7H), 7.60 (m, 4H), 7.80 (m, 2H); MS [M-Br]⁺: 452; mp 148°C.

10 Example 100

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

15 [0172] The title compound was synthesised according to methods c and a. The yield of final step was 690 mg, 83%. ¹H-NMR (DMSO-d₆): δ 1.47 (m, 1 H), 1.68 (m, 1 H), 1.87 (m, 2H), 2.1 (m, 3H), 2.89 (m, 1 H), 3.15 (d, 1 H), 3.4 (m, 5H), 3.9 (m, 1 H), 4.0 (m, 2H), 5.04 (m, 1 H), 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.

20 Example 101

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

25 [0173] The title compound was synthesised according to methods c and a. The yield of final step was 170 mg, 74%. ¹H-NMR (DMSO-d₆): δ 1.45 (m, 1 H), 1.65 (m, 1 H), 1.85 (m, 2H), 2.1 (m, 1 H), 2.9 (m, 3H), 3.15 (m, 1 H), 3.3 - 3.5 (m, 5H), 3.85 (m, 1 H), 5.05 (m, 1 H), 6.85 (s, OH), 7.2 - 7.4 (m, 7H), 7.45 (t, 2H), 7.55 (d, 1 H), 7.65 (d, 1 H), 7.85 (d, 2H); MS [M-Br]⁺: 440; mp 118°C.

Example 102

30 3(R)-(9-Hydroxy-9[H]-fluorene-9-carbonyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide

[0174] The title compound was synthesised according to methods c and a. The yield of final step was 460 mg, 96%. ¹H-NMR (DMSO-d₆): δ 1.42 (m, 1 H), 1.66 (m, 1 H), 1.80-1.88 (m, 2H), 2.08 (m, 1 H), 2.93 (m, 1H), 3.25-3.60 (m, 4H), 3.65 (m, 2H), 3.95 (m, 1 H), 4.35 (m, 2H), 5.02 (m, 1 H), 6.85 (s, 1 H, 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

40 3(R)-(9-Hydroxy-9[H]-fluorene-9-carbonyloxy)-1-(4-oxo-4-phenylbutyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

[0175] The title compound was synthesised according to methods c and b. The yield of final step was 15 mg, 15%. ¹H-NMR (DMSO-d₆): δ 1.45 (m, 1 H), 1.65 (m, 1 H), 1.7 - 2.0 (m, 4H), 2.1 (m, 1 H), 2.75 (m, 1 H), 3.0 - 3.2 (m, 4H), 3.25 - 3.4 (m, 4H), 3.85 (m, 1 H), 5.05 (m, 1 H), 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-CF₃COO]⁺: 482.

Example 104

50 1-[3-(4-Fluorophenoxy)propyl]-3(R)-(9-hydroxy-9[H]-fluorene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; chloride

55 [0176] The title compound was synthesised according to methods c and a. The yield of final step was 440 mg, 94%. ¹H-NMR (DMSO-d₆): δ 1.4 (m, 1 H), 1.65 (m, 2H), 1.7 - 1.95 (m, 2H), 2.0 - 2.1 (m, 3H), 2.8 (m, 1 H), 3.1 (d, 1 H), 3.2 - 3.4 (m, 5H), 3.8 (m, 1 H), 4.0 (t, 2H), 5.0 (m, 1 H), 6.85 (s, OH), 6.95 (m, 2H), 7.15 (t, 2H), 7.35 (t, 2H), 7.45 (t, 2H), 7.55 (d, 1 H), 7.65 (d, 1 H), 7.85 (d, 2H); MS [M-Br]⁺: 488; mp 142°C.

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Example 105

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

[0177] The title compound was synthesised according to methods c and b. The yield of final step was 14 mg, 13%. ¹H-NMR (DMSO-d₆): δ 1.4 (m, 1 H), 1.6 - 1.9 (m, 3H), 2.1 (m, 3H), 2.8 (m, 1 H), 3.1 (d, 1 H), 3.2 - 3.4 (m, 5H), 3.85 (m, 1 H), 4.05 (t, 2H), 5.0 (m, 1H), 6.85 (s, OH), 7.05 (t, 1 H), 7.15 - 7.4 (m, 4H), 7.45 (t, 2H), 7.55 (d, 1 H), 7.65 (d, 1 H), 7.85 (d, 2H); MS [M-CF₃COO]⁺: 506.

Example 106

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

[0178] The title compound was synthesised according to methods c and b. The yield of final step was 14 mg, 15%. ¹H-NMR (DMSO-d₆): δ 1.4 (m, 1 H), 1.6 (m, 1H), 1.8 (m, 4H), 2.05 (m, 1 H), 2.7 (m, 1 H), 3.0 (m, 3H), 3.2 - 3.4 (m, 6H), 3.8 (m, 1 H), 5.0 (m, 1 H), 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-CF₃COO]⁺: 469.

Example 107

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

[0179] The title compound was synthesised according to methods c and b. The yield of final step was 15 mg, 15%. ¹H-NMR (DMSO-d₆): δ 1.4 (m, 1H), 1.6 (m, 1 H), 1.7 - 1.9 (m, 2H), 1.95 - 2.05 (m, 2H), 2.1 (m, 1 H), 2.8 (m, 1 H), 3.1 (d, 1 H), 3.25 - 3.4 (m, 5H), 3.8 - 3.9 (m, 3H), 5.0 (m, 1 H), 6.7 (d, 2H), 6.75 (d, 2H), 6.85 (s, OH), 7.35 (t, 2H), 7.45 (t, 2H), 7.55 (d, 1 H), 7.65 (d, 1 H), 7.85 (d, 2H), 9.0 (s, OH); MS [M-CF₃COO]⁺: 486.

Example 108

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

[0180] The title compound was synthesised according to methods c and a. The yield of final step was 470 mg, 96%. ¹H-NMR (DMSO-d₆): δ 1.4 (m, 1 H), 1.65 (m, 1 H), 1.7 - 1.9 (m, 2H), 2.1 (m, 1 H), 2.9 (m, 1 H), 3.15 - 3.5 (m, 6H), 3.75 (m, 2H), 3.85 (m, 1 H), 4.5 (s, 2H), 5.0 (m, 1 H), 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

[0181] The title compound was synthesised according to methods c and a. The yield of final step was 180 mg, 70%. ¹H-NMR (DMSO-d₆): δ 1.37 (m, 1 H), 1.62 (m, 1 H), 1.75-1.95 (m, 4H), 2.06 (m, 1H), 2.72 (m, 1 H), 2.80 (m, 2H), 3.02-3.06 (m, 1 H), 3.15-3.20 (m, 2H), 3.25-3.40 (m, 3H), 3.80 (m, 1 H), 5.0 (m, 1 H), 6.85 (s, 1 H, 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

[0182] The title compound was synthesised according to methods c and b. The yield of final step was 80 mg, 40%. ¹H-NMR (DMSO-d₆): δ 1.35 (m, 1 H), 1.6 (m, 1 H), 1.7-1.90 (m, 2H), 2.05 (m, 1 H), 2.5 (m, 2H), 2.7 (m, 1 H), 3.0 (m, 1 H), 3.15 (m, 2H), 3.2-3.4 (m, 3H), 3.75 (m, 1 H), 5.0 (m, 1 H), 6.85 (s, OH), 7.20-7.50 (m, 9H), 7.55 (dd, 2H), 7.85 (d, 2H); MS [M-CF₃COO]⁺: 454.

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Example 111

3(R)-(9-Hydroxy-9H-fluorene-9-carbonyloxy)-1-(4-phenylbutyl)-1-azoni abicyclo[2.2.2]octane; trifluoroacetate

5 [0183] The title compound was synthesised according to methods c and b. The yield of final step was 74 mg, 35%. ¹H-NMR (DMSO-d₆): δ 1.35 (m, 1 H), 1.45-1.65 (m, 5H), 1.7-1.90 (m, 2H), 2.05 (m, 1 H), 2.55-2.75 (m, 3H), 3.0 (m, 1 H), 3.15-3.45 (m, 5H), 3.75 (m, 1 H), 5.0 (m, 1 H), 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.

10 Example 112

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

15 [0184] The title compound was synthesised according to methods c and b. The yield of final step was 79 mg, 39%. ¹H-NMR (DMSO-d₆): δ 1.4 (m, 1 H), 1.65 (m, 1 H), 1.8-1.95 (m, 2H), 2.1 (m, 1 H), 2.9 (m, 1 H), 3.1-3.25 (m, 4H), 3.15 -3.45 (m, 5H), 3.85 (m, 1 H), 5.05 (m, 1 H), 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, 1 H), 7.85 (d, 2H); MS[M-CF₃COO]⁺:446.

20 Example 113

3(R)-(9-Hydroxy-9H-fluorene-9-carbonyloxy)-1-(4-phenoxybutyl)-1-azon labicyclo[2.2.2]octane; trifluoroacetate

25 [0185] The title compound was synthesised according to methods c and b. The yield of final step was 72 mg, 33%. ¹H-NMR (DMSO-d₆): δ 1.4 (m, 1 H), 1.55-1.9 (m, 7H), 2.05 (m, 1H), 2.7 (m, 1H), 3.0 (m, 1 H), 3.15 -3.5 (m, 7H), 3.8 (m, 1 H), 4.0 (m, 2H), 5.05 (m, 1 H), 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.

30 Example 114

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

35 [0186] The title compound was synthesised according to methods c and a. The yield of final step was 200 mg, 76%. ¹H-NMR (DMSO-d₆): δ 1.54 (m, 1 H), 1.70-1.86 (m, 3H), 1.76 (s, 3H), 2.13 (m, 1 H), 3.06 (m, 1 H), 3.20-3.50 (m, 4H), 3.86 (m, 1 H), 4.05 (dd, 2H), 5.02 (m, 1 H), 6.43 (dd, 1H), 6.86 (d, 1 H), 7.26-7.46 (m, 7H), 7.58-7.65 (m, 3H), 7.70-7.72 (m, 1 H), 7.87-7.90 (m, 2H); MS [M-Br]⁺: 450; mp 234°C.

Example 115

40 **3(R)-(9-Methyl-9[H]-fluorene-9-carbonyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide**

[0187] The title compound was synthesised according to methods c and a. The yield of final step was 210 mg, 66%. ¹H-NMR (DMSO-d₆): δ 1.55 (m, 1 H), 1.60-2.0 (m, 3H), 1.76 (s, 3H), 2.12 (m, 1 H), 3.10-3.25 (m, 1 H), 3.40-3.80 (m, 6H), 4.0 (m, 1H), 4.41 (m, 2H), 4.98 (m, 1 H), 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

50 **3(R)-(9-Methyl-9[H]-fluorene-9-carbonyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2] octane; bromide**

[0188] The title compound was synthesised according to methods c and a. The yield of final step was 210 mg , 61%. ¹H-NMR (DMSO-d₆): δ 1.55 (m, 1 H), 1.60-2.0 (m, 3H), 1.78 (s, 3H), 2.0-2.20 (m, 3H), 3.0-3.10 (m, 1 H), 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.

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Example 117

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

5 [0189] The title compound was synthesised according to methods c and b. The yield of final step was 18 mg, 19%. ¹H-NMR (DMSO-d₆): δ 1.55 (m, 1 H), 1.65 - 1.95 (m, 3H), 1.75 (s, 3H), 2.15 (m, 1 H), 2.9 - 3.1 (m, 4H), 3.25 - 3.55 (m, 5H), 3.85 (m, 1 H), 5.05 (m, 1 H), 7.25 - 7.55 (m, 9H), 7.65 (d, 1 H), 7.75 (d, 1 H), 7.95 (d, 2H); MS [M-CF₃COO]⁺: 438.

Example 118

10

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

15 [0190] The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 19%. ¹H-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-CF₃COO]⁺: 480.

Example 119

20

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

25 [0191] The title compound was synthesised according to methods c and b. The yield of final step was 23 mg, 23%. ¹H-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-CF₃COO]⁺: 486.

Example 120

30

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

35 [0192] The title compound was synthesised according to methods c and b. The yield of final step was 20 mg, 19%. ¹H-NMR (DMSO-d₆): δ 1.55 (m, 1 H), 1.65 - 1.95 (m, 3H), 1.75 (s, 3H), 2.05 - 2.2 (m, 3H), 3.0 (m, 1 H), 3.25 - 3.55 (m, 6H), 3.85 (m, 1 H), 4.1 (t, 2H), 5.0 (m, 1 H), 7.05 (t, 1 H), 7.2 - 7.5 (m, 6H), 7.65 (d, 1 H), 7.75 /d, 1 H), 7.9 (d, 2H); MS [M-CF₃COO]⁺: 504.

Example 121

40

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

45 [0193] The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 19%. ¹H-NMR (DMSO-d₆): δ 1.55 (m, 1 H), 1.65 - 1.95 (m, 5H), 1.75 (s, 3H), 2.1 (m, 1 H), 2.95 (m, 1 H), 3.05 (m, 2H), 3.15 - 3.45 (m, 6H), 3.8 (m, 1 H), 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, 1 H), 7.75 (d, 1 H), 7.9 (d, 2H); MS [M-CF₃COO]⁺: 467.

Example 122

50

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

55 [0194] The title compound was synthesised according to methods c and b. The yield of final step was 22 mg, 22%. ¹H-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, 1 H), 3.25 - 3.5 (m, 6H), 3.8 - 3.95 (m, 3H), 5.0 (m, 1 H), 6.7 (d, 1 H), 6.75 (d, 1 H), 7.35 - 7.45 (m, 4H), 7.65 (d, 1 H), 7.75 (d, 1 H), 7.9 (d, 2H), 9.0 (s, OH); MS [M-CF₃COO]⁺: 484.

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Example 123

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

5

[0195] The title compound was synthesised according to methods c and b. The yield of final step was 17 mg, 17%. ¹H-NMR (DMSO-d₆) : δ 1.55 (m, 1 H), 1.65-1.95 (m, 4H), 1.75 (s, 3H), 2.15 (m, 1 H), 3.1 (m, 1 H), 3.3-3.55 (m, 6H), 3.8-3.95 (m, 3H), 4.5 (s, 2H), 5.0 (m, 1 H), 7.3-7.5 (m, 9H), 7.6-7.7 (m, 2H), 7.9 (d, 2H) ; MS [M-CF₃COO]⁺: 468.

10

Example 124

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

15

[0196] The title compound was synthesised according to methods d and a. The yield of final step was 420 mg, 89%. ¹H-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= 4.2Hz), 5.02 (m, 1 H), 5.25 (s, 1 H), 7.25-7.43 (m, 11 H), 7.48-7.55 (m, 2H) ; MS [M-Br]⁺: 438; mp 216°C.

20

Example 125

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

25

[0197] The title compound was synthesised according to methods d and a. The yield of final step was 450 mg, 82%. ¹H-NMR (DMSO-d₆) : δ 1.56 (m, 1 H), 1.65-1.95 (m, 3H), 2.05-2.15 (m, 3H), 3.10 (m, 1 H), 3.20-3.50 (m, 6H), 3.80 (m, 1 H), 3.94-4.14 (m, 4H), 5.0 (m, 1 H), 5.22 (s, 1 H), 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.

30

Example 126

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

35

[0198] The title compound was synthesised according to methods d and a. The yield of final step was 83 mg, 21%. ¹H-NMR (DMSO-d₆) : δ 1.50-2.0 (m, 8H), 2.15 (m, 1 H), 2.65 (m, 2H), 3.05-3.65 (m, 7H), 3.80 (m, 1 H), 5.0 (m, 1 H), 5.30 (s, 1 H), 7.10-7.45 (m, 11 H), 7.45-7.60 (m, 2H); MS [M-Br]⁺: 468; mp 95°C.

40

Example 127

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

45

[0199] The title compound was synthesised according to methods d and a. The yield of final step was 300 mg, 73%. ¹H-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, 1 H), 5.30 (s, 1 H), 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.

50

Example 128

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

55

[0200] The title compound was synthesised according to methods d and a. The yield of final step was 350 mg, 83%. ¹H-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, 1 H), 3.95-4.10 (m, 2H), 5.0 (m, 1H), 5.30 (s, 1 H), 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.

60

Example 129

65

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

[0201] The title compound was synthesised according to methods d and a. The yield of final step was 100 mg, 44% ¹H-NMR (DMSO-d₆) : δ 1.65 - 2.0 (m, 4H), 2.1 (m, 1 H), 2.9 - 3.05 (m, 2H), 3.15 - 3.6 (m, 7H), 3.85 (m, 1 H), 5.05 (m, 1 H),

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5.3 (s, 1 H)), 7.15 - 7.55 (m, 13H) ; MS [M-Br]⁺: 440.

Example 130

5 1-(4-Oxo-4-phenylbutyl)-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

[0202] The title compound was synthesised according to methods d and b. The yield of final step was 16 mg, 15%. ¹H-NMR (DMSO-d₆) : δ 1.65 - 2.05 (m, 6H), 2.1 (m, 1H), 3.1 - 3.55 (m, 9H), 3.8 (m, 1 H), 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, 1 H), 8.0 (d, 1 H); MS [M-CF₃COO]⁺: 482.

10

Example 131

15 1-[3-(4-Fluorophenoxy)propyl]-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane, trifluoroacetate

[0203] The title compound was synthesised according to methods d and b. The yield of final step was 18 mg, 18%. ¹H-NMR (DMSO-d₆) : δ 1.7-2.1 (m, 6H), 2.15 (m, 1 H), 3.1 - 3.5 (m, 7H), 3.8 (m, 1 H), 4.0 (t, 2H), 5.0 (m, 1 H), 5.3 (s, 1H), 6.95 (m, 2H), 7.1 - 7.3 (m, 6H), 7.4 (t, 2H), 7.5 (dd, 2H); MS [M-CF₃COO]⁺: 488.

20

Example 132

25 1-[3-(2,4-Difluorophenoxy)propyl]-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

[0204] The title compound was synthesised according to methods d and b. The yield of final step was 14 mg, 14%. ¹H-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, 1 H), 4.05 (t, 2H), 5.0 (m, 1 H), 5.3 (s, 1 H), 7.05 (t, 1 H), 7.1 - 7.55 (m, 10H); MS [M-CF₃COO]⁺: 506.

30

Example 133

30 1-(3-Phenylaminopropyl)-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

[0205] The title compound was synthesised according to methods d and b. The yield of final step was 17 mg, 17%. ¹H-NMR (DMSO-d₆) : δ 1.65 - 2.0 (m, 6H), 2.15 (m, 1 H), 3.0 - 3.5 (m, 9H), 1.75 (m, 1H), 5.0 (m, 1 H), 5.3 (s, 1 H), 6.65 (t, NH), 6.55 (m, 3H), 7.05 - 7.3 (m, 6H), 7.35 - 7.55 (m, 4H); MS [M-CF₃COO]⁺: 469.

35

Example 134

40 1-[3-(4-Hydroxyphenoxy)propyl]-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

[0206] The title compound was synthesised according to methods d and b. The yield of final step was 21 mg, 20%. ¹H-NMR (DMSO-d₆) : δ 1.7 - 2.1 (m, 6H), 2.15 (m, 1 H), 3.1 - 3.5 (m, 7H), 3.7 - 3.95 (m, 3H), 5.0 (m, 1 H), 5.3 (s, 1 H), 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-CF₃COO]⁺: 486.

45

Example 135

50 1-(2-Benzoyloxyethyl)-3(R)-(9[H]-xanthene-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

[0207] The title compound was synthesised according to methods d and b. The yield of final step was 16 mg, 16%. ¹H-NMR (DMSO-d₆) : δ 1.65 - 1.95 (m, 4H), 2.1 (m, 1 H), 3.1 - 3.9 (m, 10H), 4.5 (s, 2H), 5.0 (m, 1 H), 5.3 (s, 1 H), 7.15 (m, 4H), 7.3 - 7.5 (m, 7H), 7.55 (t, 2H); MS [M-CF₃COO]⁺: 470.

55

Example 136

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

[0208] The title compound was synthesised according to methods c. and a. The yield of final step was 340 mg ,

5^

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71%. ¹H-NMR (DMSO-d₆): δ 1.30 (m, 1 H), 1.65 (m, 1 H), 1.70-1.95 (m, 2H), 1.95-2.10 (m, 3H), 2.70 (m, 1 H), 2.90 (m, 1 H), 3.2-3.5 (m, 5H), 3.80 (m, 1 H), 4.0 (t, 2H), 5.05 (m, 1 H), 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.

5 **Example 137**

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

10 **[0209]** The title compound was synthesised according to methods c and a. The yield of final step was 290 mg ; 64%. ¹H-NMR (DMSO-d₆) : δ 1.32 (m, 1 H), 1.65 (m, 1 H), 1.70-1.95 (m, 2H), 2.1 (m, 1 H), 2.75-2.90 (m, 3H), 3.05 (m, 1 H), 3.30-3.50 (m, 5H), 3.82 (m, 1 H), 5.05 (m, 1 H), 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

15

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

20 **[0210]** The title compound was synthesised according to methods c and a. The yield of final step was 310 mg , 97%. ¹H-NMR (DMSO-d₆) : δ 1.30 (m, 1 H), 1.62 (m, 1 H), 1.70-1.90 (m, 4H), 2.05 (m, 1 H), 2.60 (m, 1 H), 2.75-2.85 (m, 4H), 3.15 (m, 2H), 3.25-3.40 (m, 2H), 3.75 (m, 1 H), 5.0 (m, 1H), 6.93 (m, 1H), 7.0 (m, 1 H), 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

25

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

30 **[0211]** The title compound was synthesised according to methods c and b. The yield of final step was 85 mg , 41%. ¹H-NMR (DMSO-d₆): δ 1.30 (m, 1 H), 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

35

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

[0212] The title compound was synthesised according to methods c and b. The yield of final step was 84 mg , 38%. ¹H-NMR (DMSO-d₆): δ 1.30 (m, 1 H), 1.4-1.85 (m, 7H), 2.05 (m, 1 H), 2.5-2.6 (m, 2H), 2.80 (m, 1 H), 3.05-3.4 (m, 6H), 3.7 (m, 1 H), 5.05 (m, 1 H), 7.15-7.35 (m, 10H), 7.4 (m, 1 H), 7.65 (m, 2H); MS [M-CF₃COO]⁺: 484.

40

Example 141

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

45

[0213] The title compound was synthesised according to methods c and b. The yield of final step was 81 mg , 39%. ¹H-NMR (DMSO-d₆): δ 1.30 (m, 1H), 1.6 (m, 1 H), 1.7-1.9(m, 2H), 2.05 (m, 1 H), 2.75(m, 1 H), 3.0(m, 1 H), 3.1-3.2 (m, 2H), 3.3-3.6 (m, 5H), 3.8 (m, 1 H), 5.05 (m, 1 H), 6.95-7.0 (m, 2H), 7.15-7.3 (m, 5H), 7.45 (m, 3H), 7.65 (m, 2H); MS [M-CF₃COO]⁺: 462.

50

Example 142

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

55

[0214] The title compound was synthesised according to methods c and b. The yield of final step was 83 mg , 37%. ¹H-NMR (DMSO-d₆) : δ 1.3 (m, 1 H), 1.5-1.9 (m, 7H), 2.05 (m, 1 H), 2.6 (m, 1 H), 2,8 (m, 1H), 3.1-3.45 (m, 7H), 3.75 (m, 1 H), 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.

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Example 143

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

5

[0215] The title compound was synthesised according to methods c and b. The yield of final step was 102 mg, 48%. ¹H-NMR (DMSO-d₆): δ 1.3 (m, 1 H), 1.55-1.95 (m, 3H), 2.05 (m, 1 H), 2.8 (m, 1 H), 3.1 (m, 1 H), 3.35-3.65 (m, 5H), 3.9 (m, 1 H), 4.35 (m, 2H), 5.05 (m, 1 H), 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.

10

Example 144

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

15

[0216] The title compound was synthesised according to methods c and b. The yield of final step was 99 mg, 44%. ¹H-NMR (DMSO-d₆): δ 1.3 (m, 1 H), 1.6 (m, 1 H), 1.7-2.0 (m, 4H), 2.05 (m, 1 H), 2.7 (m, 1 H), 2.9 (m, 1 H), 3.2-3.5 (m, 5H), 3.75-3.85 (m, 1 H), 3.95 (m, 2H), 5.0 (m, 1 H), 6.95 (m, 2H), 7.1-7.3 (m, 7H), 7.45 (t, 2H), 7.65 (t, 2H); MS [M-CF₃COO]⁺: 504.

20

Example 145

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

25

[0217] The title compound was synthesised according to methods c and b. The yield of final step was 25 mg, 12%. ¹H-NMR (DMSO-d₆): δ 1.25-1.30 (m, 1 H), 1.55-1.95 (m, 3H), 2.10 (m, 1 H), 2.65-2.75 (m, 1 H), 2.9 (m, 1 H), 3.25-3.50 (m, 2H), 3.75-3.8 (m, 1 H), 3.95 (m, 2H), 4.2 (d, 1 H), 5.0 (m, 1H), 6.35 (m, 1 H), 6.80 (d, 1 H), 7.05-7.50 (m, 8H), 7.60 (m, 4H); MS [M-CF₃COO]⁺: 468.

30

Example 146

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

35

[0218] The title compound was synthesised according to methods c and a. The yield of final step was 110 mg. ¹H-NMR (DMSO-d₆): δ 1.4 (m, 1 H), 1.65 (m, 1 H), 1.75 - 1.95 (m, 2H), 1.9 (s, 3H), 2.05 - 2.15 (m, 3H), 1.8 (m, 1 H), 3.15 (m, 2H), 3.25 - 3.5 (m, 5H), 3.85 (m, 1 H), 4.0 (t, 2H), 5.05 (m, 1 H), 6.95 - 7.0 (m, 3H), 7.15 - 7.2 (m, 4H), 7.3 - 7.4 (m, 4H), 7.45 (d, 1 H), 7.55 (d, 1 H); MS [M-Br]⁺: 484; mp 195°C.

Example 147

40

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

45

[0219] The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 20%. ¹H-NMR (DMSO-d₆): δ 1.4 (m, 1 H), 1.65 (m, 1 H), 1.8 - 1.95 (m, 2H), 1.9 (s, 3H), 2.15 (m, 1 H), 2.8 - 2.95 (m, 3H), 3.15 (d, 1 H), 3.3 - 3.5 (m, 5H), 4.9 (m, 1H), 5.1 (m, 1 H), 7.15 (m, 4H), 7.25 - 7.4 (m, 7H), 7.45 (d, 1 H), 7.55 (d, 1 H); MS [M-CF₃COO]⁺: 454.

Example 148

50

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

55

[0220] The title compound was synthesised according to methods c and b. The yield of final step was 24 mg, 24%. ¹H-NMR (DMSO-d₆): δ 1.4 (m, 1 H), 1.65 (m, 1 H), 1.8 - 1.95 (m, 2H), 1.9 (s, 3H), 2.15 (m, 1 H), 2.95 (m, 1 H), 3.25 (m, 1 H), 3.4 - 3.65 (m, 5H), 3.85 (m, 1 H), 4.35 (t, 2H), 5.05 (m, 1 H), 6.95 (d, 2H), 7.05 (t, 2H), 7.15 (m, 3H), 7.25 - 7.45 (m, 6H); MS [M-CF₃COO]⁺: 470.

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Example 149

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

5

[0221] The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 19%. ¹H-NMR (DMSO-d₆): δ 1.4 (m, 1 H), 1.65 (m, 1 H), 1.75 - 1.95 (m, 7H), 2.15 (m, 1 H), 2.8 (m, 1 H), 3.05 - 3.25 (m, 4H), 3.3 - 3.5 (m, 4H), 3.85 (m, 1 H), 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-CF₃COO]⁺: 496.

10

Example 150

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

15

[0222] The title compound was synthesised according to methods c and b. The yield of final step was 25 mg, 24%. ¹H-NMR (DMSO-d₆): δ 1.4 (m, 1 H), 1.65 (m, 1 H), 1.75 - 1.95 (m, 2H), 1.9 (s, 3H), 1.95 - 2.1 (m, 2H), 2.15 (m, 1 H), 2.8 (m, 1H), 3.1 (d, 1 H), 3.25 - 3.5 (m, 5H), 3.8 (m, 1 H), 4.0 (t, 2H), 5.05 (m, 1 H), 6.95 (m, 2H), 7.15 (m, 6H), 7.35 (t, 2H), 7.5 (dd, 2H); MS [M-CF₃COO]⁺: 502.

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Example 151

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

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[0223] The title compound was synthesised according to methods c and b. The yield of final step was 16 mg, 15%. ¹H-NMR (DMSO-d₆): δ 1.4 (m, 1 H), 1.65 (m, 1 H), 1.75 - 1.95 (m, 2H), 1.9 (s, 3H), 2.0 - 2.15 (m, 3H), 2.8 (m, 1 H), 3.1 (d, 1 H), 7.05 (t, 1H), 7.1 - 7.4 (m, 8H), 7.5 (dd, 2H); MS [M-CF₃COO]⁺: 520.

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Example 152

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

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[0224] The title compound was synthesised according to methods c and b. The yield of final step was 16 mg, 15%. ¹H-NMR (DMSO-d₆): δ 1.35 (m, 1 H), 1.6 (m, 1 H), 1.7 - 1.9 (m, 4H), 1.9 (s, 3H), 2.1 (m, 1 H), 2.7 (m, 1 H), 2.95 - 3.05 (m, 3H), 3.1 - 3.4 (m, 6H), 3.75 (m, 1 H), 5.0, (m, 1 H), 5.6 (m, 1 H), 6.55 (m, 3H), 7.05 - 7.15 (m, 6H), 7.3 (m, 2H), 7.45 (t, 2H); MS [M-CF₃COO]⁺: 483.

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Example 153

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

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[0225] The title compound was synthesised according to methods c and b. The yield of final step was 19 mg, 18%. ¹H-NMR (DMSO-d₆): δ 1.4 (m, 1H), 1.65 (m, 1 H), 2.75 - 2.05 (m, 4H), 1.9 (s, 3H), 2.15 (m, 1 H), 2.8 (m, 1 H), 3.1 (d, 1 H), 3.25 - 3.5 (m, 5H), 3.8 - 3.95 (m, 3H), 5.05 (m, 1 H), 6.65 - 6.8 (m, 4H), 7.2 (m, 4H), 7.35 (t, 2H), 7.5 (m, 2H), 9.0 (s, OH); MS [M-CF₃COO]⁺: 500.

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Example 154

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

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[0226] The title compound was synthesised according to methods c and b. The yield of final step was 14 mg, 14%. ¹H-NMR (DMSO-d₆): δ 1.4 (m, 1H), 1.65 (m, 1 H), 1.75 - 1.95 (m, 2H), 1.9 (s, 3H), 2.1 (m, 1 H), 2.9 (m, 1 H), 3.2 - 3.5 (m, 6H), 3.75 - 3.95 (m, 3H), 4.5 (s, 2H), 5.05 (m, 1 H), 7.15 (m, 4H), 7.3 - 7.5 (m, 9H); MS [M-CF₃COO]⁺: 484.

Example 155

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

[0227] The title compound was synthesised according to methods d and a. The yield of final step was 323 mg, 50%. ¹H-NMR (DMSO-d6): δ 1.35 (m, 1 H), 1.65 (m, 1H), 1.70-1.95 (m, 2H), 2.0-2.2 (m, 3H), 2.75-2.90 (m, 1 H), 3.12 (m, 1 H), 3.25-3.50 (m, 5H), 3.80 (m, 1H), 4.0 (t, 2H), 5.0 (m, 1 H), 5.6 (s, 1 H), 6.94-7.0 (m, 3H), 7.22-7.41 (m, 6H), 7.45-7.64 (m, 4H) ; MS [M-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

[0228] The title compound was synthesised according to methods d and a. The yield of final step was 250 mg , 94%. ¹H-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, 1 H), 3.60-3.90 (m, 3H), 4.20 (m, 1 H), 4.35-4.60 (doble dd, 2H), 5.10 (m, 1 H), 5.15 (s, 1 H), 6.05 (dd, 1 H), 6.90-7.0 (m, 2H), 7.0-7.5 (m, 11 H); MS [M-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

[0229] The title compound was synthesised according to methods d and a. The yield of final step was 290 mg , 94%. ¹H-NMR (CDCl₃) : δ 1.45-1.60 (m, 1 H), 1.65-1.80 (m, 1 H), 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, 1 H), 3.45-3.80 (m, 5H), 3.85-4.0 (m, 2H), 4.20 (m, 1 H), 5.10 (m, 1 H), 5.20 (s, 1 H), 6.80-6.90 (d, 2H), 6.90-7.0 (t, 1 H), 7.10-7.30 (m, 8H), 7.40 (m, 2H); MS [M-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

[0230] The title compound was synthesised according to methods d and a. The yield of final step was 180 mg, 56%. ¹H-NMR (DMSO-d6) : δ 1.2 (m, 1 H), 1.6 (m, 1 H), 1.7 - 1.9 (m, 2H), 1.95 (m, 1H), 2.1 (m, 2H), 2.8 (m, 1 H), 2.95 (d, 1 H), 3.25 - 3.45 (m, 5H), 3.8 (m, 1 H), 4.05 (t, 2H), 4.9 (m, 1 H), 5.45 (s, 1 H), 6.9 - 7.1 (m, 5H), 7.3 - 7.5 (m, 9H), 7.55 (d, 2H); MS [M-Br]⁺: 480; mp 111°C.

Example 159

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

[0231] The title compound was synthesised according to methods d and a. The yield of final step was 210 mg, 68%. ¹H-NMR (DMSO-d6) : δ 1.2 (m, 1H), 1.7 - 1.9 (m, 2H), 2.0 (m, 1 H), 2.85 - 3.1 (m, 4H), 3.3 - 3.5 (m, 5H), 3.85 (m, 1 H), 4.95 (m, 1 H), 5.45 (s, 1 H), 7.05 (m, 2H), 7.25 - 7.5 (m, 11 H), 7.55 (m, 2H); MS [M-Br]⁺: 450; mp 248°C.

[0232] 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

[0233]

Formulation:	
Compound of the present invention	5.0 mg

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(continued)

Formulation:	
Lactose	113.6 mg
Microcrystalline cellulose	28.4 mg
Light silicic anhydride	1.5 mg
Magnesium stearate	1.5 mg

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[0234] 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

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Preparation of a pharmaceutical composition: tablets coated

[0235]

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

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Formulation:	
Titanium dioxide	1.1 mg
Purified talc	0.7 mg

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[0236] 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 polyvinylpyrrolidone 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

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Preparation of a pharmaceutical composition: liquid inhalant

[0237]

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Formulation:	
Compound of the present invention	400 µg
Physiological saline	1 ml

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[0238] 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 115° for 30 minutes to give liquid inhalant.

Example 163

Preparation of a pharmaceutical composition: powder inhalant

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[0239]

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Formulation:	
Compound of the present invention	200 µg
Lactose	4,000 µg

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Example 164

Preparation of a pharmaceutical composition: inhalation aerosol.

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[0241]

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Formulation:	
Compound of the present invention	200 µg
Dehydrated (Absolute) ethyl alcohol USP	8,400 µg
1,1,1,2-Tetrafluoroethane (HFC-134A)	46,810 µg

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[0242] 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.

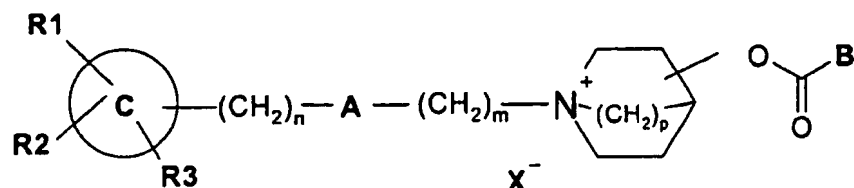
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Claims

1. A compound according to formula (I)

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(I)

wherein:

© is a phenyl ring, a C₄ to C₉ heteroaromatic group containing one or more heteroatoms or a naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl or biphenyl group;

R¹, R² and R³ each independently represent a hydrogen atom or halogen atom, or a phenyl, -OR⁴, -SR⁴, -NR⁴R⁵, -NHCOR⁴, -CONR⁴R⁵, -CN, -NO₂, -COOR⁴ or -CF₃ group, or a straight or branched C₁ to C₈ alkyl group which may optionally be substituted, for example, with a hydroxy or alkoxy group, wherein R⁴ and R⁵ each independently represent a hydrogen atom, straight or branched C₁ to C₈ alkyl group or together form an alicyclic ring; or R¹ and R² together form an aromatic, alicyclic or heterocyclic ring,

n is an integer from 0 to 4;

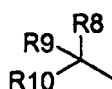
A represents a -CH=CR⁶-, -CR⁶=CH-, -CR⁶R⁷-, -CO-, -O-, -S-, -S(O)-, SO₂ or -NR⁶- group, wherein R⁶ and R⁷ each independently represent a hydrogen atom, straight or branched C₁ to C₈ alkyl group or R⁶ and R⁷ together form an alicyclic ring;

m is an integer from 0 to 8; provided that when m = 0, A is not -CH₂-;

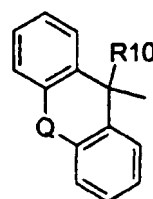
p is an integer from 1 to 2 and the substitution in the azoniabicyclic ring may be in the 2, 3 or 4 position including all possible configurations of the asymmetric carbons;

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

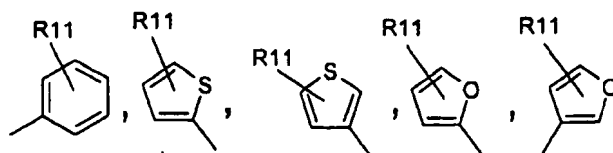
i)



ii)



wherein R¹⁰ represents a hydrogen atom, a hydroxy or methyl group; and R⁸ and R⁹ each independently represent



wherein R¹¹ represents a hydrogen or halogen atom or a straight or branched C₁ to C₈ alkyl group and Q represents a single bond, -CH₂-, -CH₂-CH₂-, -O-, -O-CH₂-, -S-, -S-CH₂- or -CH=CH-; and

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

2. A compound according to claim 1, wherein R¹, R² and R³ each independently represent a hydrogen atom or halogen atom, or a phenyl, -OR⁴-, -SR⁴-, -NR⁴R⁵-, -NHCOR⁴-, -CONR⁴R⁵-, -CN, -NO₂-, -COOR⁴ or -CF₃ group, or a straight or branched C₁ to C₈ alkyl group which may optionally be substituted with a hydroxy group, wherein R⁴ and R⁵ each independently represent a hydrogen atom, straight or branched C₁ to C₈ alkyl group or together form a C₃ to C₁₀ alicyclic ring; or R¹ and R² together form a C₆ to C₁₄ aromatic, C₃ to C₁₀ alicyclic or C₃ to C₁₀ heterocyclic ring.

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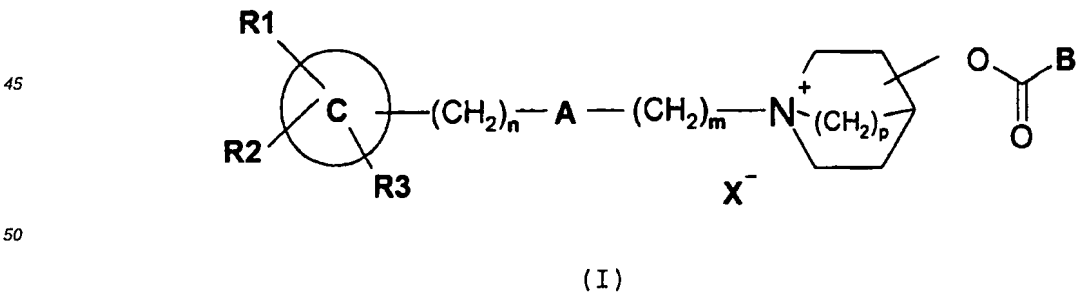
3. A compound according to claim 1 or claim 2, wherein A represents a -CH=CR⁶-, -CR⁶=CH-, -CR⁶R⁷-, -CO-, -O-, -S-, -S(O)-, SO₂ or -NR⁶- group, wherein R⁶ and R⁷ each independently represent a hydrogen atom, straight or branched C₁ to C₈ alkyl group or R⁶ and R⁷ together form a C₃ to C₁₀ alicyclic ring.
- 5 4. A compound according to any one of claims 1 to 3, wherein any alkyl group present as R¹ to R⁷ or R¹¹ contains from 1 to 4 carbon atoms.
5. A compound according to any one of claims 1 to 4 wherein p=2.
- 10 6. A compound according to any one of the preceding claims wherein © represents a phenyl, pyrrolyl, thienyl, furyl, biphenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl, benzo[1,3]dioxolyl, imidazolyl or benzothiazolyl group.
7. A compound according to claim 6, wherein © represents a phenyl, pyrrolyl or thienyl group.
- 15 8. A compound according to any one of the preceding claims wherein R¹, R² and R³ each independently represent a hydrogen or halogen atom or a hydroxy, methyl, tert-butyl, -CH₂OH, 3-hydroxypropyl, -OMe, -NMe₂, -NHCOMe, -CONH₂, -CN, -NO₂, -COOMe or -CF₃ group.
- 20 9. A compound according to claim 8 wherein R¹, R² and R³ each independently represent a hydrogen or halogen atom or a hydroxy group.
10. A compound according to claim 9, wherein the halogen atom is fluorine.
- 25 11. A compound according to any one of the preceding claims wherein A represents a -CH₂-, -CH=CH-, -CO-, -NH-, -NMe-, -O- or -S- group; n is 0 or 1; and m is an integer from 1 to 6.
12. A compound according to claim 11, wherein A represents a -CH₂-, -CH=CH- or -O- group and m is 1, 2 or 3.
- 30 13. A compound according to any one of the preceding claims 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.
- 35 14. A compound according to any one of the preceding claims wherein B represents a group of formula (i) and R⁸ and R⁹ each independently represent a phenyl, 2-thienyl, 3-thienyl, 2-furyl, or 3-furyl group and R¹¹ represents a hydrogen atom.
- 40 15. A compound according to any one of claims 1 to 13, wherein B represents a group of formula (ii) and Q represents a single bond, a -CH₂-, -CH₂-CH₂- group or an oxygen atom.
16. A compound according to any one of the preceding claims wherein X represents a bromide, chloride or trifluoroacetate anion.
- 45 17. A compound according to any one of the preceding claims wherein the azoniabicyclo group is substituted in the 3-position.
18. A compound according to claim 17, wherein the substituent in the 3 position has (R) configuration.
- 50 19. A compound according to claim 18, wherein R⁸ is different from R⁹ in group i), and the asymmetric carbon to which R⁸ and R⁹ are bonded has the (R) configuration.
20. A compound according to claim 18, wherein R⁸ is different from R⁹ in group i), and the asymmetric carbon to which R⁸ and R⁹ are bonded has the (S) configuration.
- 55 21. A compound according to any one of the preceding claims which is a single isomer.
22. A compound according to claim 1 which is

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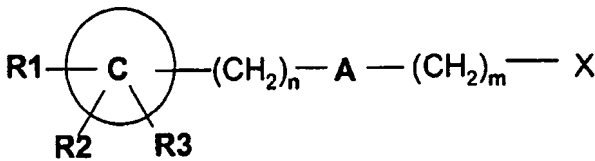
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- 3(R)-Diphenylacetoxy-1-(3-phenoxy-propyl)-1-azoniabicyclo[2.2.2]octane; bromide
- 3(R)-(2-Hydroxy-2,2-diphenyl-acetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide
- 3(R)-(2,2-Diphenylpropionyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide
- 3(R)-(2-Hydroxy-2-phenyl-2-thien-2-yl-acetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[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-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-phenoxypropyl)-1-azoniabicyclo[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-azoniabicyclo[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
- 3(R)-(2-Hydroxy-2,2-dithien-3-ylacetoxy)-1-(3-phenoxypropyl)-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-phenylallyl)-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 or
- 3(R)-(9-Methyl-9[H]-xanthene-9-carbonyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromide

- 23. A compound according to any one of the preceding claims characterised in that it has an IC₅₀ value for muscarinic M₃ receptors (Hm3) of less than 35 nM.
- 24. A process for the preparation of a compound of formula (I)

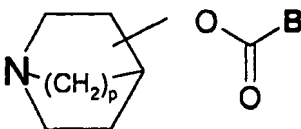


which comprises reacting an alkylating agent of formula (II)



(II)

with a compound of formula (III)

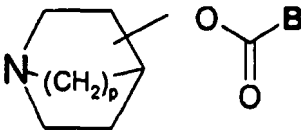


(III)

wherein, in each of formulae I, II and III, R¹, R², R³, ©, A, X, B, n, m and p are as defined in any one of claims 1 to 22.

25. A process according to claim 24 characterised in that the resulting reaction mixture is purified by solid phase extraction.

26. A compound of formula (III)

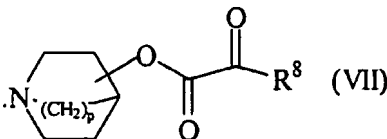


(III)

wherein B and p are as defined in any one of claims 1, 4, 5, 14, 15 or 17 to 22 and wherein the substituent on the azabicyclo group has (R)- configuration.

27. A compound according to claim 26 which is 9-Methyl-9[H]-fluorene-9-carboxylic acid 1-azabicyclo[2.2.2]oct-3(R)-yl ester; 9-Methyl-9[H]-xanthene-9-carboxylic acid 1-azabicyclo[2.2.2]oct-3(R) -yl ester; or 2-Hydroxy-2,2-difuran-2-yl-acetic acid 1-azabicyclo[2.2.2]oct-3(R)-yl ester.

28. A compound of formula (VII)

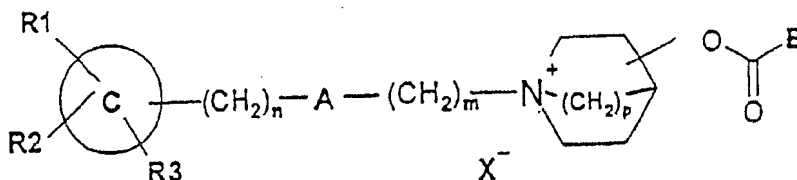


wherein p is as defined in claim 1 or 5, R⁸ is a 2-thienyl or 2-furyl group and wherein the substituent on the azabicyclo group has (R) configuration.

29. A compound according to claim 28 which is Oxothien-2-yl-acetic acid 1-azabicyclo[2.2.2]oct-3(R)-yl ester; or Oxofuran-2-yl-acetic acid 1-azabicyclo[2.2.2]oct-3(R)-yl ester.
30. Use of a compound according to any one of claims 26 to 29 in a process for producing a compound of formula (I) as defined in any one of claims 1 to 22.
31. A pharmaceutical composition comprising a compound according to any one of claims 1 to 23 in admixture with a pharmaceutically acceptable carrier or diluent.
32. A compound according to any one of claims 1 to 23, or a pharmaceutical composition according to claim 31 for use in a method of treatment of the human or animal body by therapy.
33. Use of a compound according to any one of claims 1 to 23, or a pharmaceutical composition according to claim 31 for the manufacture of a medicament for use in the treatment of respiratory, urinary or gastrointestinal disease.
34. Use of a compound according to any one of claims 1 to 23 or a pharmaceutical composition according to claim 31 for the manufacture of a medicament for use in the treatment of COPD, chronic bronchitis, asthma and rhinitis.

Patentansprüche

1. Verbindung gemäß Formel (I)



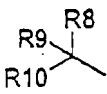
(I)

worin:

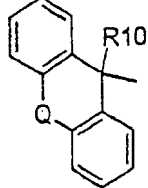
© ein Phenylring, eine C₄ bis C₉-heteroaromatische Gruppe, enthaltend ein oder mehr Heteroatome, oder eine Naphthalinyl-, 5,6,7,8-Tetrahydronaphtaliny- oder Biphenyl-Gruppe ist;
R¹, R² und R³ jeweils unabhängig voneinander für ein Wasserstoffatom oder Halogenatom oder eine Phenyl-, -OR⁴, -SR⁴, -NR⁴R⁵, -NHCOR⁴, -CONR⁴R⁵, -CN, -NO₂, -COOR⁴ oder -CF₃-Gruppe oder eine geradkettige oder verzweigte C₁ bis C₈-Alkylgruppe, die ggf. substituiert, z.B. mit einer Hydroxy- oder Alkoxygruppe sein kann, stehen, wobei R⁴ und R⁵ jeweils unabhängig voneinander für ein Wasserstoffatom eine geradkettige oder verzweigte C₁ bis C₈-Alkylgruppe stehen oder zusammen einen alicyclischen Ring bilden; oder R¹ und R² zusammen einen aromatischen, alicyclischen oder heterocyclischen Ring bilden,
n eine ganze Zahl von 0 bis 4 ist;
A für eine -CH=CR⁶-, -CR⁶=CH-, -CR⁶R⁷-, -CO-, -O-, -S-, -S(O)-, SO₂ oder -NR⁶-Gruppe steht, wobei R⁶ und R⁷ jeweils unabhängig voneinander für ein Wasserstoffatom eine geradkettige oder verzweigte C₁ bis C₈-Alkylgruppe stehen oder R⁶ und R⁷ zusammen einen alicyclischen Ring bilden;
m eine ganze Zahl von 0 bis 8 ist; vorausgesetzt, dass, wenn m = 0, A nicht -CH₂- ist;
p eine ganze Zahl von 1 bis 2 ist und die Substitution in dem azoniabicyclischen Ring in der 2-, 3- oder 4-Position sein kann, einschließlich aller möglichen Konfigurationen der asymmetrischen Kohlenstoffatome;
B für eine Gruppe der Formel i) oder ii) steht:

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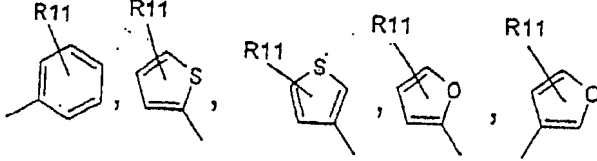
i)



ii)



worin R¹⁰ für ein Wasserstoffatom eine Hydroxy- oder Methylgruppe steht; und R⁸ und R⁹ jeweils unabhängig voneinander für



stehen, worin R¹¹ für ein Wasserstoffatom oder Halogenatom oder eine geradkettige oder verzweigte C₁ bis C₈-Alkylgruppe steht und Q für eine Einfachbindung, -CH₂-, -CH₂-CH₂-, -O-, -O-CH₂-, -S-, -S-CH₂- oder -CH=CH- steht; und X für ein pharmazeutisch annehmbares Anion einer ein- oder mehrwertigen Säure steht.

2. Verbindung nach Anspruch 1, worin R¹, R² und R³ jeweils unabhängig voneinander für ein Wasserstoffatom oder Halogenatom oder eine Phenyl-, -OR⁴-, -SR⁴-, -NR⁹R⁵-, -NHCOR⁴-, -CONR⁴R⁵-, -CN-, -NO₂-, -COOR⁴ oder -CF₃-Gruppe oder eine geradkettige oder verzweigte C₁ bis C₈-Alkylgruppe, die ggf. substituiert mit einer Hydroxygruppe sein kann, stehen, wobei R⁴ und R⁵ jeweils unabhängig voneinander für ein Wasserstoffatom eine geradkettige oder verzweigte C₁ bis C₈-Alkylgruppe stehen oder zusammen einen C₃-C₁₀-alicyclischen Ring bilden; oder R¹ und R² zusammen einen C₆-C₁₄-aromatischen, C₃-C₁₀-alicyclischen oder C₃-C₁₀-heterocyclischen Ring bilden.
3. Verbindung nach Anspruch 1 oder 2, worin A für eine -CH=CR⁶-, -CR⁶=CH-, -CR⁶R⁷-, -CO-, -O-, -S-, -S(O)-, SO₂ oder -NR⁶-Gruppe steht, wobei R⁶ und R⁷ jeweils unabhängig voneinander für ein Wasserstoffatom eine geradkettige oder verzweigte C₁ bis C₈-Alkylgruppe stehen oder R⁶ und R⁷ zusammen einen C₃-C₁₀-alicyclischen Ring bilden.
4. Verbindung nach einem der Ansprüche 1 bis 3, worin irgendeine als R¹ bis R⁷ oder R¹¹ vorhandene Alkylgruppe von 1 bis 4 Kohlenstoffatome enthält.
5. Verbindung nach einem der Ansprüche 1 bis 4, worin p = 2.
6. Verbindung nach einem der voranstehenden Ansprüche, worin © eine Phenol-, Pyrrolyl-, Thienyl-, Furyl-, Biphenyl-, Naphtaliny-, 5,6,7,8-Tetrahydronaphtaliny-, Ben-zo[1,3]dioxoly-, Imidazolyl- oder Benzothiazolyl-Gruppe steht.
7. Verbindung nach Anspruch 6, worin © für eine Phenyl-, Pyrrolyl- oder Thienyl-Gruppe steht.
8. Verbindung nach einem der voranstehenden Ansprüche, worin R¹, R² und R³ jeweils unabhängig voneinander für ein Wasserstoff- oder Halogenatom oder eine Hydroxy-, Methyl-, tert-Butyl-, -CH₂OH, 3-Hydroxypropyl-, -OMe, -NMe₂-, -NHCOMe-, -CONH₂-, -CN-, -NO₂-, -COOMe oder CF₃-Gruppe stehen.
9. Verbindung nach Anspruch 8, worin R¹, R² und R³ jeweils unabhängig voneinander für ein Wasserstoff- oder Halogenatom oder eine Hydroxygruppe stehen.
10. Verbindung nach Anspruch 9, worin das Halogenatom Fluor ist.
11. Verbindung nach einem der voranstehenden Ansprüche, worin A für eine -CH₂-, -CH=CH-, -CO-, -NH-, -NMe-, -O- oder -S-Gruppe steht; n 0 oder 1 ist; und m eine ganze Zahl von 1 bis 6 ist.

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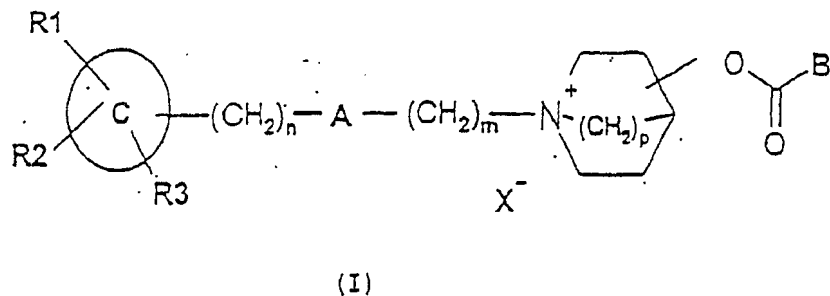
12. Verbindung nach Anspruch 11, worin A für eine $-CH_2-$, $-CH=CH-$ oder $-O-$ Gruppe steht und m 1, 2 oder 3 ist.
13. Verbindung nach einem der voranstehenden Ansprüche, worin die Azoniabicyclogruppe am Stickstoffatom substituiert ist mit einer 3-Phenoxypropyl-, 2-Phenoxyethyl-, 3-Phenylallyl-, Phenethyl-, 3-Phenylpropyl-, 4-Phenylbutyl-, 3-(2-Hydroxyphenoxy)propyl-, 3-(4-Fluorophenoxy)propyl-, 2-Benzoyloxyethyl-, 3-Pyrrol-1-ylpropyl-, 2-Thien-2-ylethyloder 3-Thien-2-ylpropyl-Gruppe.
14. Verbindung nach einem der voranstehenden Ansprüche, worin B für eine Gruppe der Formel (i) steht und R^8 und R^9 jeweils unabhängig voneinander für eine Phenyl-, 2-Thienyl-, 3-Thienyl-, 2-Furyl- oder 3-Furyl-Gruppe stehen und R^{11} für ein Wasserstoffatom steht.
15. Verbindung nach einem der Ansprüche 1 bis 13, worin B für eine Gruppe der Formel (ii) steht und Q für eine Einfachbindung, eine $-CH_2-$, $-CH_2-CH_2-$ Gruppe oder ein Sauerstoffatom steht.
16. Verbindung nach einem der voranstehenden Ansprüche, worin X für ein Bromid-, Chlorid- oder Trifluoroacetat-Anion steht.
17. Verbindung nach einem der voranstehenden Ansprüche, worin die Azoniabicyclo-Gruppe in der 3-Position substituiert ist.
18. Verbindung nach Anspruch 17, worin der Substituent in der 3-Position (R)-Konfiguration besitzt.
19. Verbindung nach Anspruch 18, worin R^8 verschieden von R^9 in Gruppe (i) ist und das asymmetrische Kohlenstoffatom an das R^8 und R^9 gebunden sind, die (R)-Konfiguration besitzt.
20. Verbindung nach Anspruch 18, worin R^8 verschieden von R^9 in Gruppe (i) ist und das asymmetrische Kohlenstoffatom an das R^8 und R^9 gebunden sind, die (S)-Konfiguration besitzt.
21. Verbindung nach einem der voranstehenden Ansprüche, die ein einzelnes Isomer ist.
22. Verbindung nach Anspruch 1, die
- 3 (R)-Diphenylacetoxyl-1-(3-phenoxy-propyl)-1-azoniabicyclo[2.2.2]octan ; Bromid
 3(R)-(2-Hydroxy-2,2-diphenyl-acetoxyl)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octan ; Bromid
 3(R)-(2,2-Diphenylpropionyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octan ; Bromid
 3(R)-(2-Hydroxy-2-phenyl-2-thien-2-yl-acetoxyl)-1-(3-phenoxypropyl)-7-azoniabicyclo[2.2.2]octan ; Bromid
 3(R)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxyl)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octan ; Bromid
 3(R)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxyl)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octan ; Bromid
 3(R)-(2-Furan-2-yl-2-hydroxy-2-phenylacetoxyl)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octan ; Bromid
 3 (R)-(2-Dithien-2-ylacetoxyl)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octan ; Bromid
 3 (R)-(2-Hydroxy-2,2-di-thien-2-ylacetoxyl)-1-phenethyl-1-azoniabicyclo[2.2.2]octan ; Bromid
 3 (R)-(2-Hydroxy-2,2-di-thien-2-ylacetoxyl)-1-(4-phenylbutyl)-1-azoniabicyclo[2.2.2]octan ; Bromid
 3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxyl)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octan ; Bromid
 1-[3-(4-Fluorophenoxy)propyl]-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxyl)-1-azoniabicyclo[2.2.2]octan ; Chlorid
 3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxyl)-1-[3-(2-hydroxyphenoxy)propyl]-1-azoniabicyclo[2.2.2]octan ; Trifluoroacetat
 3(R)-(2-Hydroxy-2,2-dithien-2-ylacetoxyl)-1-(3-pyrrol-1-ylpropyl)-1-azoniabicyclo[2.2.2]octan ; Trifluoroacetat
 3 (R)-(2-Hydroxy-2,2-dithien-2-ylacetoxyl)-1-(2-thien-2-ylethyl)-1-azoniabicyclo[2.2.2]octan ; Bromid
 3 (R)-(2-Hydroxy-2,2-dithien-2-ylacetoxyl)-1-(3-thien-2-ylpropyl)-1-azoniabicyclo[2.2.2]octan ; Bromid
 1-(2-Benzoyloxyethyl)-3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxyl)-1-azoniabicyclo[2.2.2]octan ; Trifluoroacetat
 3 (R)-(2-Hydroxy-2,2-dithien-2-ylacetoxyl)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octan ; Bromid
 1-(3-Phenylallyl)-3(R)-(9-Hydroxy-9[H]-fluoren-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octan ; Bromid
 3 (R)-(9-Hydroxy-9[H]-fluoren-9-carbonyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octan ; Bromid
 3 (R)-(9-Hydroxy-9[H]-fluoren-9-carbonyloxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octan ; Bromid
 3 (R)-(9-Hydroxy-9H-fluoren-9-carbonyloxy)-1-(3-thien-2-ylpropyl)-1-azoniabicyclo[2.2.2]octan ; Bromid
 3 (R)-(9-Methyl-9[H]-fluoren-9-carbonyloxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octan ; Bromid
 3 (R)-(9-Methyl-9[H]-fluoren-9-carbonyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octan ; Bromid
 1-(4-Phenylbutyl)-3(R)-(9[H]-xanthen-9-carbonyloxy)-1-azoniabicyclo[2.2.2]octan ; Bromid

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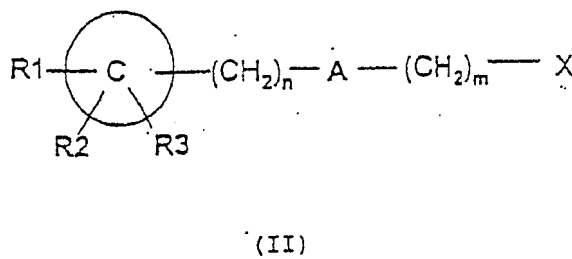
1-(2-Phenoxyethyl)-3(R)-(9[H]-xanthen-9-carbonyloxy)-1-azoniabicyclo-[2.2.2]octan ; Bromid
 1-(3-Phenoxypropyl)-3(R)-(9[H]-xanthen-9-carbonyloxy)-1-azoniabicyclo-[2.2.2] octan ; Bromid
 1-Phenethyl-3(R)-(9[H]-xanthen-9-carbonyloxy)-1-azoniabicyclo[2.2.2]-octan ; Bromid
 3 (R)-(9-Hydroxy-9[H]-xanthen-9-carbonyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octan ; Bromid
 3 (R)-(9-Hydroxy-9[H]-xanthen -9-carbonyloxy)-1-phenethyl-1-azoniabicyclo[2.2.2] octan ; Bromid

23. Verbindung nach einem der voranstehenden Ansprüche, **dadurch gekennzeichnet, dass** sie einen IC_{50} -Wert für muscarinische M_3 -Rezeptoren ($Hm3$) von weniger als 35 nM besitzt.

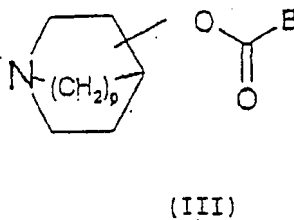
24. Verfahren zur Herstellung einer Verbindung der Formel (I)



umfassend die Umsetzung eines Alkylierungsmittels der Formel (II)



mit einer Verbindung der Formel (III)

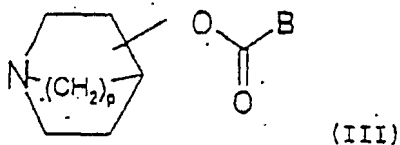


worin in jeder der Formeln I, II und III R^1 , R^2 , R^3 , $\odot$, A, X, B, n, m und p so wie in einem der Ansprüche 1 bis 22 definiert sind.

25. Verfahren nach Anspruch 24, **dadurch gekennzeichnet, dass** das resultierende Reaktionsgemisch durch Festphasenextraktion gereinigt wird.

26. Verbindung der Formel (III),

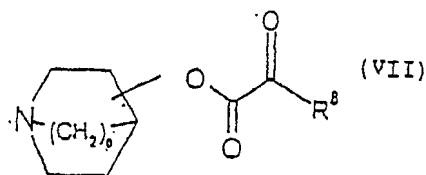
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worin B und p so wie in einem der Ansprüche 1, 4, 5, 14, 15 oder 17 bis 22 definiert sind und worin der Substituent an der Azabicyclogruppe (R)-Konfiguration besitzt.

27. Verbindung nach Anspruch 26, die
 9-Methyl-9[H]-fluoren-9-carbonsäure 1-azabicyclo[2.2.2]oct-3(R)-ylester,
 9-Methyl-9[H]-xanthen-9-carbonsäure 1-azabicyclo[2.2.2]oct-3-(R)-ylester, oder
 2-Hydroxy-2,2-difuran-2-yl-essigsäure 1-azabicyclo[2.2.2]oct-3-(R)-ylester ist.

28. Verbindung der Formel (VII)

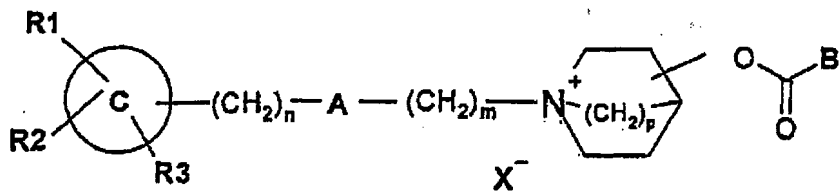


worin p so wie in Anspruch 1 oder 5 definiert ist, R⁸ eine 2-Thienyl- oder 2-Furyl-Gruppe ist und worin der Substituent an der Azabicyclogruppe (R)-Konfiguration besitzt.

29. Verbindung nach Anspruch 28, die
 Oxothien-2-yl-essigsäure 1-azabicyclo[2.2.2]oct-3(R)-ylester; oder
 Oxofuran-2-yl-essigsäure 1-azabicyclo[2.2.2]oct-3(R)-ylester ist.
30. Verwendung einer Verbindung nach einem der Ansprüche 26 bis 29 in einem Verfahren zur Herstellung einer Verbindung der Formel (I) wie in einem der Ansprüche 1 bis 22 definiert.
31. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach einem der Ansprüche 1 bis 23 im Gemisch mit einem pharmazeutisch annehmbaren Träger oder Verdünnungsmittel.
32. Verbindung nach einem der Ansprüche 1 bis 23 oder pharmazeutische Zusammensetzung nach Anspruch 31 zur Verwendung in einem Verfahren zur Behandlung des menschlichen oder tierischen Körpers durch Therapie.
33. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 23 oder einer pharmazeutischen Zusammensetzung nach Anspruch 31 zur Herstellung eines Medikaments zur Verwendung in der Behandlung von Atemwege-, Harnweg- oder Gastrointestinalerkrankungen.
34. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 23 oder einer pharmazeutischen Zusammensetzung nach Anspruch 31 zur Herstellung eines Medikaments zur Verwendung in der Behandlung von COPD, chronischer Bronchitis, Asthma und Rhinitis.

Revendications

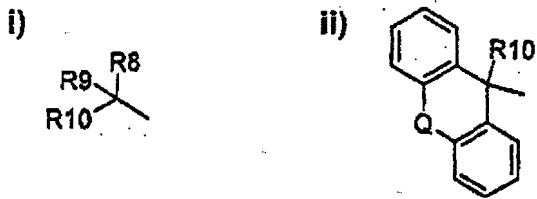
1. Composé selon la formule (I)



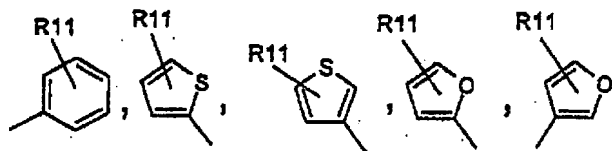
(I)

dans laquelle :

© est un cycle phényle, un groupe hétéroaromatique en C₄ à C₉ contenant un ou plusieurs hétéroatomes ou un groupe naphthalényle, 5,6,7,8-tétrahydronaphtalényle ou biphényle ;
R¹, R² et R³ représentent chacun indépendamment un atome d'hydrogène ou un atome d'halogène, ou un groupe phényle, -OR⁴, -SR⁴, -NR⁴R⁵, -NHCOR⁴, -CONR⁴R⁵, -CN, -NO₂, -COOR⁴ ou -CF₃, ou un groupe alkyle en C₁ à C₈ linéaire ou ramifié qui peut être facultativement substitué, par exemple, par un groupe hydroxy ou alcoxy, où R⁴ et R⁵ représentent chacun indépendamment atome d'hydrogène, un groupe alkyle en C₁ à C₈ linéaire ou ramifié ou forment ensemble un noyau alicyclique ; ou R¹ et R² forment ensemble un noyau aromatique, alicyclique ou hétérocyclique,
n est un entier de 0 à 4 ;
A représente un groupe -CH=CR⁶-, -CR⁶=CH-, -CR⁶R⁷-, -CO-, -O-, -S-, -S(O)-, SO₂ ou -NR⁶, où R⁶ et R⁷ représentent chacun indépendamment un atome d'hydrogène, un groupe alkyle en C₁ à C₈ linéaire ou ramifié ou R⁶ et R⁷ forment ensemble un noyau alicyclique ;
m est un entier de 0 à 8 ; étant entendu que lorsque m=0, A n'est pas -CH₂- ;
p est un entier de 1 à 2, et la substitution dans le noyau azoniabicyclique peut être en position 2, 3 ou 4, incluant toutes configurations possibles des carbones asymétriques ; B représente un groupe de formule 1) ou ii) :



dans lesquelles R¹⁰ représente un atome d'hydrogène, un groupe hydroxy ou méthyle ; et R⁸ et R⁹ représentent chacun indépendamment



où R¹¹ représente un atome d'hydrogène ou d'halogène ou un groupe alkyle en C₁ à C₈ linéaire ou ramifié et Q représente une liaison simple, -CH₂-, -CH₂-CH₂-, -O-, -O-CH₂-, -S-S-CH₂- ou -CH=CH- ; et X représente un anion pharmaceutiquement acceptable d'une acide mono ou polyvalent.

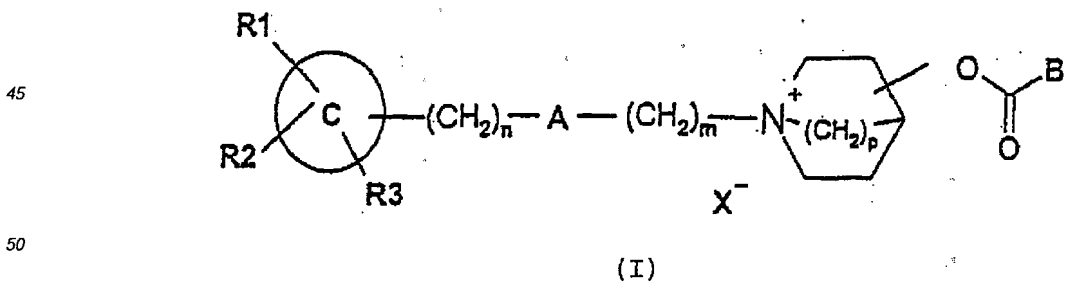
2. Composé selon la revendication 1 dans lequel R¹, R² et R³ représentent chacun indépendamment un atome d'hydrogène ou un atome d'halogène, ou un groupe phényle, -OR⁴, -SR⁴, -NR⁴R⁵, -NHCOR⁴, -CONR⁴R⁵, -CN, -NO₂, -COOR⁴ ou -CF₃, ou un groupe alkyle en C₁ à C₈ linéaire ou ramifié qui peut être facultativement substitué par un groupe hydroxy ou alcoxy, où R⁴ et R⁵ représentent chacun indépendamment un atome d'hydrogène, un groupe alkyle en C₁ à C₈ linéaire ou ramifié ou forment ensemble un noyau alicyclique en C₃ à C₁₀ ; ou R¹ et R² forment ensemble un noyau aromatique en C₆ à C₁₄, alicyclique en C₃ à C₁₀ ou hétérocyclique en C₃ à C₁₀.

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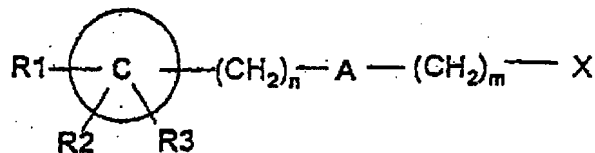
3. Composé selon la revendication 1 ou 2 dans lequel A représente un groupe $-\text{CH}=\text{CR}^6-$, $-\text{CR}^6=\text{C}-\text{H}-$, $-\text{CR}^6\text{R}^7-$, $-\text{CO}-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, SO_2 ou $-\text{NR}^6-$, où R^6 et R^7 représentent chacun indépendamment un atome d'hydrogène, un groupe alkyle en C_1 à C_8 linéaire ou ramifié ou R^6 et R^7 forment ensemble un noyau alicyclique en C_3 à C_{10} .
- 5 4. Composé selon l'une quelconque des revendications 1 à 3, dans lequel tout groupe alkyle présent en tant que R^1 à R^7 ou R^{11} contient de 1 à 4 atomes de carbone.
5. Composé selon l'une quelconque des revendications 1 à 2, dans lequel $p=2$.
- 10 6. Composé selon l'une quelconque des revendications précédentes, dans lequel C représente un groupe phényle, pyrrolyle, thiényle, furyle, diphényle, naphtalényle, 5,6,7,8-tétrahydronaphtalényle, benzo[1,3]dioxolyle, imidazolyle ou benzothiazolyle
7. Composé selon la revendication 6, dans lequel C représente un groupe phényle, pyrrolyle ou thiényle.
- 15 8. Composé selon l'une quelconque des revendications précédentes, dans lequel R^1 , R^2 et R^3 représentent chacun indépendamment un atome d'hydrogène ou d'halogène ou un groupe hydroxy, méthyle, tert-butyle, $-\text{CH}_2\text{OH}$, 3-hydroxypropyle, $-\text{OMe}$, $-\text{NMe}_2$, $-\text{NHCOMe}$, $-\text{CONH}_2$, $-\text{CN}$, $-\text{NO}_2$, $-\text{COOMe}$ ou $-\text{CF}_3$.
- 20 9. Composé selon la revendication 8, dans lequel R^1 , R^2 et R^3 représentent chacun indépendamment un atome d'hydrogène ou d'halogène ou un groupe hydroxy.
10. Composé selon la revendication 9, dans lequel l'atome d'halogène est le fluor.
- 25 11. Composé selon l'une quelconque des revendications précédentes, dans lequel A représente un groupe $-\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{CO}-$, $-\text{NH}-$, $-\text{NMe}-$, $-\text{O}-$ ou $-\text{S}-$; n est 0 ou 1; et m est un entier de 1 à 6.
12. Composé selon la revendication 11, dans lequel A représente un groupe $-\text{CH}_2-$, $-\text{CH}=\text{CH}-$ ou $-\text{O}-$ et m est 1, 2 ou 3.
- 30 13. Composé selon l'une quelconque des revendications précédentes, dans lequel le groupe azoniabicyclo est substitué sur l'atome d'azote par un groupe 3-phénoxypropyle, 2-phénoxyéthyle, 3-phénylallyle, phénéthyle, 3-phénylpropyle, 4-phénylbutyle, 3-(2-hydroxyphénoxy)propyle, 3-(4-fluorophénoxy)propyle, 2-benzyloxyéthyle, 3-pyrrol-1-ylpropyle, 2-thiën-2-yléthyle ou 3-thiën-2-ylpropyle.
- 35 14. Composé selon l'une quelconque des revendications précédentes dans lequel B représente un groupe de formule (i) et R^8 et R^9 représentent chacun indépendamment un groupe phényle, 2-thiényle, 3-thiényle, 2-furyle ou 3-furyle et R^{11} représente un atome d'hydrogène.
- 40 15. Composé selon l'une quelconque des revendications 1 à 13, dans lequel B représente un groupe de formule (ii) et Q représente une liaison simple, groupe $-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-$ ou un atome d'hydrogène.
16. Composé selon l'une quelconque des revendications précédentes, dans lequel X représente un anion bromure, chlorure ou trifluoroacétate.
- 45 17. Composé selon l'une quelconque des revendications précédentes, dans lequel le groupe azoniabicyclo est substitué en position 3.
18. Composé selon la revendication 17, dans lequel le substituant en position 3 a la configuration (R).
- 50 19. Composé selon la revendication 18, dans lequel R^8 est différent de R^9 dans le groupe i), et le carbone symétrique auquel R^8 et R^9 sont liés a la configuration (R).
20. Composé selon la revendication 18, dans lequel R^8 est différent de R^9 dans le groupe i), et le carbone asymétrique auquel R^8 et R^9 sont liés a la configuration (S).
- 55 21. Composé selon l'une quelconque des revendications précédentes, qui est un isomère unique.
22. Composé selon la revendication 1, qui est

- 3 (R) -Diphénylacétoxy-1-(3-phénoxy-propyl)-1-azoniabicyclo[2.2.2]octane; bromure
3(R)-(2-Hydroxy-2,2-diphényl-acétoxy)-1-(3-phénoxypropyl)-3-axoniabi cyclo[2.2.2]octane; bromure
3 (R)-(2,2-Diphénylpropionyloxy-1-(3-phénoxypropyl)-1-azoniabicyclo[2. 2.2]octane; bromure
3 (R)-(2-Hydroxy-2-phényl-2-thién-2-yl-acétoxy)-1-(3-phénoxypropyl)-1- azonia-bicyclo[2.2.2]octane; bromure
5 3 (R)-(2-Furan-2-yl-2-hydroxy--2-phénylacétoxy)-1-(3-phénylallyl)-1-azo niabicyclo[2.2.2]octane; bromure
3 (R)-(2-Furan-2-yl-2-hydroxy-2-phénylacétoxy)-1-(2-phénoxyéthyl)-1-azo niabicyclo[2.2.2]octane ; bromure
3 (R)-(2-Furan-2-yl-2-hydroxy-2-phénylacétoxy)-1-(3-phénoxypropyl)-1-azo niabicyclo[2.2.2]octane: bromure
3 (R)-(2,2-Dithién-2-ylacétoxy)-1-(3-phénoxypropyl)-1-azoniabicyclo [2.2.2]octane; bromure
3 (R)-(2-Hydroxy-2,2-di-thién-2-ylacétoxy)-1-phénéthyl-1-azoniabicy clo[2.2.2]octane; bromure
10 3(R)-(2-Hydroxy-2,2-di-thién-2-ylacétoxy)-1-(4-phénylbutyl)-1-axonia bicyclo[2.2.2]octane; bromure
3(R)-(2-Hydroxy-2,2-dithién-2-ylacétoxy)-1-(3-phénoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromure
1-[3-(4-Fluorophénoxy)propyl]-3(R)-(2-hydroxy-2,2-dithién-2-ylacéto xy)-1-azoniabicyclo[2.2.2]octane; chloru-
re
3(R)-(2-Hydroxy-2,2-dithién-2-ylacétoxy)-1-[3-(2-hydroxyphénoxy)pro pyl]-1-azoniabicyclo[2.2.2]octane; tri-
15 fluoroacétate
3(R)-(2-Hydroxy-2,2-dithién-2-ylacétoxy)-1-(3-pyrrol-1-ylpropyl)-1-a zonia-bicyclo[2.2.2]octane; trifluoroacéta-
te
3(R)-(2-Hydroxy-2,2-dithién-2-ylacétoxy)-1-(2-thién-2-yléthyl)-1-azo niabicyclo[2.2.2]octane; bromure
3(R)-(2-Hydroxy-2,2-dithién-2-ylacétoxy)-1-(3-thién-2-ylpropyl)-1-a zoniabicyclo[2.2.2]octane; bromure
20 1-(2-Benzyloxyéthyl)-3-(R)-(2-hydroxy-2,2-dithién-2-ylacétoxy)-1-azon iabicyclo[2.2.2]octane ; trifluoroacétate
3(R)-(2-Hydroxy-2,2-dithién-3-ylacétoxy)-1-(3-phénoxypropyl)-1-azoni abicyclo[2.2.2]octane; bromure
1-(3-phénylallyl)-3(R)-(9-Hydroxy-9[H]-fluorène-9-carbonyloxy)-1-azo niabicyclo[2.2.2]octane; bromure
3(R)-(9-Hydroxy-9[H]-fluorène-9-carbonyloxy)-1-(3-phénoxypropyl)-1-a zoniabicyclo[2.2.2]octane; bromure
3(R)-(9-Hydroxy-9[H]-fluorène-9-carbonyloxy)-1-phénéthyl-1-azoniabic yclo[2.2.2]octane; bromure
25 3(R)-(9-Hydroxy-9H-fluorène-9-carbonyloxy)-1-(3-thién-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane; bromure
3(R)-(9-Méthyl-9[H]-fluorène-9-carbonyloxy)-1-(3-phénylallyl)-1-azonia bicyclo[2.2.2]octane; bromure
3(R)-(9-Méthyl-9[H]-fluorène-9-carbonyloxy)-1-(3-phénoxypropyl)-1-azo niabicyclo[2.2.2]octane; bromure
1-(4-Phénylbutyl)-3(R)-(9[H]-xanthène-9-carbonyloxy)-1-azoniabicyclo [2.2.2]octane; bromure
1-(2-Phénoxyéthyl)-3(R)-(9[H]-xanthène-9-carbonyloxy)-1-azoniabicyclo [2.2.2]octane; bromure
30 1-(3-Phénoxypropyl)-3(R)-(9[H]-xanthène-9-carbonyloxy)-1-azoniabicyclo [2.2.2]octane; bromure
1-Phénéthyl-3(R)-(9[H]-xanthène-9-carbonyloxy)-1-azoniabicyclo[2.2.2] octane; bromure
3(R)-(9-Hydroxy-9[H]-xanthène-9-carbonyloxy)-1-(3-phénoxypropyl)-1-azoniabicyclo[2.2.2]octane; bromure
3(R)-(9-Hydroxy-9[H]-xanthène-9-carbonyloxy)-1-phénéthyl-1-azoniabic yclo[2.2.2]octane; bromure
3(R)-(9-Hydroxy-9H-xanthène-9-carbonyloxy)-1-(3-thién-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane; bromure ou
35 3(R)-(9-Méthyl-9[H]-xanthène-9-carbonyloxy)-1-(3-phénoxy-propyl)-1-a zonia-bicyclo[2.2.2]octane; bromure

23. Composé selon l'une quelconque des revendications précédentes, **caractérisé en ce qu'il a une valeur Cl_{50} pour les récepteurs M_3 muscariniques ($Hm3$) inférieure à 35 nM.**
40 24. Procédé pour la préparation d'un composé de formule (I)

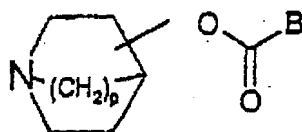


qui comprend la réaction d'un agent alkylant de formule (II)
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(II)

avec un composé de formule (III)

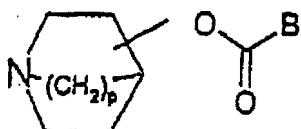


(III)

où, dans chacune des formules I, II et III, R^1 , R^2 , R^3 , A , X , B , n , m et p sont tels que définis dans l'une quelconque des revendications 1 à 22.

25. Procédé selon la revendication 24, caractérisé en ce que le mélange réactionnel résultant est purifié par extraction en phase solide

26. Composé de formule (III)



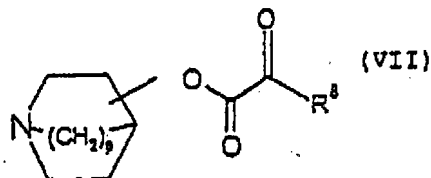
(III)

dans laquelle B et p sont tels que définis dans l'une quelconque des revendications 1, 4, 5, 14, 15 ou 17 à 22 et dans laquelle le substituant sur le groupe azabicyclo a la configuration (R).

27. Composé selon la revendication 26, qui est

un ester 1-azabicyclo[2.2.2]oct-3(R)yle d'acide 9-méthyl-9[H]-fluorène-9-carboxylique ;
un ester 1-azabicyclo[2.2.2]oct-3(R)yle d'acide 9-méthyl-[9]-xanthène-9-carboxylique ; ou
l'ester 1-azabicyclo[2.2.2]oct-3(R)yle d'acide 2-hydroxy-2,2-difuranne-2-yl-acétique.

28. Composé de formule (VII)



(VII)

dans laquelle p est tel que défini dans la revendication 1 ou 5, R^3 est un groupe 2-thiényle ou 2-furyle et dans laquelle le substituant sur le groupe azabicyclo a la configuration (R).

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29. Composé selon la revendication 28, qui est l'ester 1-azabicyclo[2.2.2]oct-3(R)-ylique de l'acide oxothién-2-yl-acétique ; ou l'ester 1-azabicyclo[2.2.2]oct-3(R)-ylique de l'acide oxofuranne-2-yl-acétique.
- 5 30. Utilisation d'un composé selon l'une quelconque des revendications 26 à 29 dans un procédé pour produire un composé de formule (I) tel que défini dans l'une quelconque des revendications 1 à 22.
31. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 23, mélangé avec un véhicule ou diluant pharmaceutiquement acceptable.
- 10 32. Composé selon l'une quelconque des revendications 1 à 23, ou composition pharmaceutique selon la revendication 31, pour l'utilisation dans une méthode de traitement du corps humain ou animal par thérapie.
33. Utilisation d'un composé selon l'une quelconque des revendications 1 à 23, ou d'une composition pharmaceutique selon la revendication 31, pour la fabrication d'un médicament pour l'utilisation dans le traitement d'une maladie respiratoire, urinaire ou gastro-intestinale.
- 15 34. Utilisation d'un composé selon l'une quelconque des revendications 1 à 23 ou d'une composition pharmaceutique selon la revendication 31, pour la fabrication d'un médicament pour l'utilisation dans le traitement d'une bronchopneumopathie chronique obstructive (BPCO), d'une bronchite chronique, de l'asthme et d'une rhinite.
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REFERENCES CITED IN THE DESCRIPTION

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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FECHA : JUNIO 17 DE 2013

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PAGO	Vr. PAGO
CAVELIER ABOGADOS	RECIBO DE CAJA			53742	04/06/2013	450,000.00
CAVELIER ABOGADOS	RECIBO DE CAJA			53772	04/06/2013	5,000.00
CAVELIER ABOGADOS	RECIBO DE CAJA			53773	04/06/2013	5,000.00
CAVELIER ABOGADOS	RECIBO DE CAJA			56031	11/06/2013	50,000.00
CAVELIER ABOGADOS	RECIBO DE CAJA			56064	11/06/2013	90,000.00
...MAS INFORMACION NO IMP			TOTAL			1,010,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILID	505,000.00
	TOTAL :	\$ 505,000.00

MON: QUINIENTOS CINCO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. COLO: 17153- 806-001-2