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REGISTRO DE PATENTES Y MARCAS
FOLIO: 11
FECHA: 2005-06-13 16:35:00
CLASE: 01-01-01 29 MAR 2005
SOLICITUD: 2005-01-01-01 29 MAR 2005

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: **P1.- ARENA PHARMACEUTICALS, INC.- Solicitud de Patente de Invención en Fase Nacional PCT "MODULADORES DEL RECEPTOR 5HT_{2c}".- Clase C07D 223/14.- Expediente número 04-100.885.-**

1. Me refiero a mi memorial de 2 de Febrero de 2005.
2. Anexo me permito presentar a ese Despacho, documento completo de la Solicitud Europea No. EP 1 411 881 B1, la cual ha sido concedida por parte de la Oficina Europea de Patentes, junto con la traducción del capítulo reivindicatorio. Como bien lo puede notar ese Despacho, esta solicitud Europea **contiene esencialmente la misma materia objeto de la presente invención, lo cual demuestra que los compuestos reivindicados cumplen con los requisitos de patentabilidad.**
3. En consecuencia, ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,



ALICIA LLOREDA RICAURTE

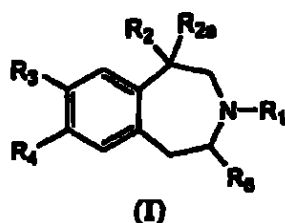
T.P. 53.215

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EP 1 411 881 B1

Reivindicaciones

1. Un compuesto de Formula (I):



donde:

R1 es: -H o

C1-8 alquilo;

R2 es: C1-8 alquilo,

-CH₂-O-C1-8 alquilo,

-C(=O)-O-C1-8 alquilo,

-C(=O)-NH-C1-8 alquilo,

-OH, o

-CH₂OH;

R2a es -H;

o R2 y R2a forman juntos -CH₂-CH₂-;

R3 es halógeno;

perhaloalquilo; o

un anillo heteroarillo de 5- miembros que tiene hasta dos heteroátomos seleccionados de O, N y S;

R4 es -H, halógeno, perhaloalquilo, -CN, -OR5, -SR5, -NHR5, -N(R5)2, -OH, arilo, o heteroarilo, donde dicho arilo puede ser sustituido opcionalmente por hasta dos sustituyentes seleccionados de C1-8 alquilo, halógeno, perhaloalquilo, y alcoxi, y dicho heteroarilo puede ser sustituido opcionalmente por hasta dos sustituyentes seleccionados del halógeno y C1-8 alquilo;

o:

R3 y R4 junto con los átomos a los cuales se juntan pueden formar un anillo heterocíclico de 5- o 6- miembros que tiene un átomo O; cada R5 es independientemente C1-8 alquilo, C1-8 alqueno, arilo, heteroarilo, arilalquilo, heteroarilalquilo o perhaloalquilo, o alilo; y

R6 es -H o C1-8 alquilo;

o una sal, solvato o hidrato farmacéuticamente aceptable, de ello;

siempre y cuando que:

si R6 es otro diferente a -H, entonces R4 no puede ser -H; y

si R1 y R2 son metilo, y R4 es -H, entonces R3 no puede ser imidazol, imidazol sustituido, o un derivado de imidazol;

y donde:

el arilo denota un grupo aromático policíclico que tiene de 3 a 14 átomos de carbono;

el heteroarilo denota un grupo aromático monocíclico o policíclico que tiene de 3 a 14 átomos de carbono, y de 1 a 4 anillos de heteroátomos seleccionados de O, N, y S; alcoxi denota -O-alquilo;

C1-8 alquilo denota un cadena abierta recta, ramificada o un grupo de hidrocarburos cíclicos que tiene de 1 a 8 átomos de carbono;

C1-8 alquenilo denota un cadena abierta recta, ramificada o un grupo de hidrocarburos cíclicos que tiene de 1 a 8 átomos de carbono y al menos una enlace doble;

alquilo, diferente a C1-8 alquilo, denota metilo, etilo, n-propilo, isopropilo, ciclopropilo, n-butilo, sec-butilo, ter-butilo, ciclobutilo, ciclopropilometilo, n-pentilo, isopentilo, tert-pentilo, ciclopentilo, ciclopentilometilo, n-hexilo, n-hexilo, o ciclohexilo.

2. Un compuesto de acuerdo con la reivindicación 1 donde R1 es -H.
3. Un compuesto de acuerdo con la reivindicación 1 donde R1 es C1-8 alquilo.
4. Un compuesto de acuerdo con la reivindicación 1 donde R1 es metilo.
5. Un compuesto de acuerdo con la reivindicación 1 donde R1 n-propilo.
6. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5 donde R2 es C1-8 alquilo.
7. Un compuesto de acuerdo con cualquiera de las reivindicaciones 9 a 5 donde R2 es metilo.
8. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5 donde R2 es etilo.
9. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5 donde R2 es isopropilo.
10. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5 donde R2 y R2a juntos forman -CH₂-CH₂-.

11. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10 donde R3 es halógeno.
12. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10 donde R3 es cloro.
13. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10 donde R3 es bromo.
14. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10 donde R3 es yodo.
15. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10 donde R3 es perhaloquillo.
16. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10 donde R3 es -CF₃.
17. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10 donde R3 es un anillo heteroarilo de 5- miembros que tiene hasta dos heteroátomos seleccionados de O, N y S.
18. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10 donde R3 es seleccionado de: tiofenilo, furanilo, pirrrollo, pirazolilo e imidazolilo.
19. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 18 donde R4 es -OR₅.
20. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 18 donde R4 es metoxi, etoxi, n-propoxi, isopropoxi o aliloxi.
21. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 18 donde R4 es perhaloalquillo.

22. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 18 donde R4 es -CF₃.
23. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 18 donde R4 es un anillo heteroarilo de 5- miembros que tiene hasta dos heteroátomos seleccionados de O, N y S y hasta dos sustituyentes seleccionados del halógeno y de C1-8 alquilo.
24. Un compuesto de acuerdo con la reivindicación 1 donde R4 es seleccionado de tiofenilo, furanilo, pirrrolilo, pirazolilo e imidazolilo opcionalmente sustituido con uno o dos sustituyentes seleccionados del halógeno y del metilo.
25. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 18 donde R4 es fenilo opcionalmente sustituido con hasta dos sustituyentes seleccionados de C1-8 alquilo, halógeno y alcoxi.
26. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10 donde R3 y R4 tomados en conjunto forman -O-CH=C(CH₃)-.
27. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10 donde:
R3 es halógeno; y
R4 es -OH5 donde R5 es C1-8 alquilo.
28. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10 donde:
R3 es halógeno; y
R4 es metoxi.

29. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10 donde:

R3 es cloro o bromo; y

R4 es metoxi.

30. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10 donde:

R3 es halógeno; y

R4 es aliloxi.

31. Un compuesto de acuerdo con la reivindicación 1 donde:

R2 es metilo, etilo, isopropilo, o -CH₂OH; o

R2 y R2a tomadas en conjunto forman -CH₂-CH₂-;

R3 es halógeno, o un anillo heteroarilo de 5- miembros que tiene hasta dos heteroátomos seleccionados de O, N y S, y hasta dos sustituyentes seleccionados del halógeno y C1-8 alquilo;

R4 es -H, alcoxi, un anillo heteroarilo de 5- miembros que tiene hasta dos heteroátomos seleccionados de O, N y S y hasta dos sustituyentes seleccionados del halógeno y C1-8 alquilo, o fenilo opcionalmente sustituidos con hasta dos sustituyentes seleccionados de C1-8 alquilo, halógeno, y alcoxi;

o R3 y R4 tomados en conjunto forman -O-CH=C(CH₃)-; y

R6 es -H o metilo.

32. Un compuesto de acuerdo con la reivindicación 1 donde:

R2 es metilo, etilo, isopropilo, o -CH₂OH; o

R2 y R2a tomadas en conjunto forman -CH₂-CH₂-;

R3 es cloro, bromo, o yodo;

R4 es alcoxi; y

R6 es -H o metilo.

33. Un compuesto de acuerdo con la reivindicación 1 donde:

R1 es -H;

R2 es metilo;

R3 es cloro, bromo, o tiofeno;

R4 es alcoxi, pirazoli-3-ilo o fenilo donde dicho pirazol opcionalmente tiene hasta dos sustituyentes seleccionados del halógeno y C1-8 alcoxi, y dicho fenilo opcionalmente tiene un solo halógeno sustituyente; y

R6 es -H.

34. Un compuesto de la reivindicación 1 seleccionado de:

8-bromo-7-hidroxi-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

7-aliloxi-8-bromo-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

7-benziloxi-8-bromo-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

8-bromo-7-etoxi-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

8-bromo-7-isopropoxi-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

N-propilo-8-bromo-7-metoxi-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

7-hidroxi-8-yodo-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

7-aliloxi-8-yodo-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

7-aliloxi-8-cloro-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

7-metoxi-1-metilo-8-(2-tienilo)-2,3,4,5-tetrahidro-1H-3-benzazepina;

8-bromo-1-ciclopropilo-7-metoxi-2,3,4,5-tetrahidro-1H-3-benzazepina;

8-bromo-1-hidroxi-metilo-7-metoxi-2,3,4,5-tetrahidro-1H-3-benzazepina;

8-bromo-1-isopropilo-7-metoxi-2,3,4,5-tetrahidro-1H-3-benzazepina;

8-bromo-7-hidroxi-1-isopropilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

7-aliloxi-8-bromo-1-isopropilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

8-bromo-7-metoxi-1,4-dimetilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

7-aliloxi-8-bromo-1,4-dimetilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

8-cloro-1-hidroxi-2,3,4,5-tetrahidro-1H-3-benzazepina;

8-bromo-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

8-fluoruro-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

7,8-bicloruro-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

N-metilo-8-cloro-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

8-yodo-1-metilo-7-trifluorometoxi-2,3,4,5-tetrahidro-1H-3-benzazepina;

N-propilo-8-yodo-7-metoxi-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

1-etilo-8-yodo-7-metoxi-2,3,4,5-tetrahidro-1H-3-benzazepina;
 7-(2-fluorofenilo)-8-cloro-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina; y
 8-bromo-1-metoximetilo-7-metoxi-2,3,4,5-tetrahidro-1H-3-benzazepina;

y sales, solvatos e hidratos farmacéuticamente aceptables de ello.

35. Un compuesto de acuerdo con la reivindicación 1 seleccionado de:

8-bromo-7-metoxi-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina;
 8-cloro-7-metoxi-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina;
 8-yodo-7-metoxi-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina;
 N-metilo-8-bromo-7-metoxi-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina;
 8-bromo-1-etilo-7-metoxi-2,3,4,5-tetrahidro-1H-3-benzazepina;
 8-cloro-1-etilo-7-metoxi-2,3,4,5-tetrahidro-1H-3-benzazepina;
 8-yodo-1-etilo-7-metoxi-2,3,4,5-tetrahidro-1H-3-benzazepina;
 7-metoxi-1-metilo-8-trifluorometilo-2,3,4,5-tetrahidro-1H-3-benzazepina; y
 7-metoxi-1-metilo-8-pentafluoroetilo-2,3,4,5-tetrahidro-1H-3-benzazepina;

y sales, solvatos e hidratos farmacéuticamente aceptables de ello.

36. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 35, donde R es un enantiomero.

37. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 35, donde S es un enantiomero.

37. Un compuesto de acuerdo con la reivindicación 1 seleccionado del siguiente compuesto, y sales, solvatos e hidratos farmacéuticamente aceptables de ello:

8-cloro-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina.

39. Un compuesto de acuerdo con la reivindicación 38, donde R es un enantiomero.
40. Un compuesto de acuerdo con la reivindicación 38, donde S es un enantiomero.

41. Un compuesto de acuerdo con la reivindicación 1 seleccionado del siguiente compuesto, y sales, solvatos e hidratos farmacéuticamente aceptables de ello:

8-bromo-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina.

42. Un compuesto de acuerdo con la reivindicación 1 seleccionado del siguiente compuesto, y sales, solvatos e hidratos farmacéuticamente aceptables de ello:

8-yodo-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina.

43. Un compuesto de acuerdo con la reivindicación 1 seleccionado del siguiente compuesto, y sales, solvatos e hidratos farmacéuticamente aceptables de ello:

8-trifluorometilo-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina.

44. Un compuesto de acuerdo con la reivindicación 43, donde R es un enantiomero.
45. Un compuesto de acuerdo con la reivindicación 43, donde S es un enantiomero.

46. Un compuesto de acuerdo con la reivindicación 1 seleccionado del siguiente compuesto, y sales, solvatos e hidratos farmacéuticamente aceptables de ello:

8-trifluorometilo-1-etilo-2,3,4,5-tetrahidro-1H-3-benzazepina.

47. Un compuesto de acuerdo con la reivindicación 1 seleccionado del siguiente compuesto, y sales, solvatos e hidratos farmacéuticamente aceptables de ello:

8-cloro-1-etilo-2,3,4,5-tetrahidro-1H-3-benzazepina.

48. Un compuesto de acuerdo con la reivindicación 47, donde R es un enantiomero.

49. Un compuesto de acuerdo con la reivindicación 47, donde S es un enantiomero.

50. Un compuesto de acuerdo con la reivindicación 1 seleccionado del siguiente compuesto, y sales, solvatos e hidratos farmacéuticamente aceptables de ello:

8-bromo-1-etilo-2,3,4,5-tetrahidro-1H-3-benzazepina.

51. Un compuesto de acuerdo con la reivindicación 1 seleccionado del siguiente compuesto, y sales, solvatos e hidratos farmacéuticamente aceptables de ello:

8-yodo-1-etilo-2,3,4,5-tetrahidro-1H-3-benzazepina.

52. Un compuesto de acuerdo con la reivindicación 1 seleccionado del siguiente compuesto, y sales, solvatos e hidratos farmacéuticamente aceptables de ello:

7,8-bicloruro-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina.

53. Un compuesto de acuerdo con la reivindicación 1 seleccionado del siguiente compuesto, y sales, solvatos e hidratos farmacéuticamente aceptables de ello:

7,8-bicloruro-1-etilo-2,3,4,5-tetrahidro-1H-3-benzazepina.

54. Un compuesto de acuerdo con la reivindicación 1 seleccionado del siguiente compuesto, y sales, solvatos e hidratos farmacéuticamente aceptables de ello:

8-cloro-7-fluoruro-1-metilo-2,3,4,5-tetrahidro-1H-3-benzazepina.

55. Un compuesto de acuerdo con la reivindicación 1 seleccionado del siguiente compuesto, y sales, solvatos e hidratos farmacéuticamente aceptables de ello:

8-cloro-7-fluoruro-1-etilo-2,3,4,5-tetrahidro-1H-3-benzazepina.

56. Una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 55 y un transportador o excipiente farmacéuticamente aceptable.

57. Una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 55 y su enantiomero, y un transportador o excipiente farmacéuticamente aceptable.

58. Una composición farmacéutica que comprende un racemato de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 55 y su enantiomero, y un transportador o excipiente farmacéuticamente aceptable.

59. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 55 para uso en un método de tratamiento del cuerpo humano o animal por terapia.
60. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 55 para uso en un método de profilaxis o tratamiento de obesidad de un mamífero.
61. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 55 para uso en un método para disminuir el consumo de alimentos de un mamífero.
62. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 55 para uso en un método para inducir saciedad en un mamífero.
63. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 55 para uso en un método para controlar la ganancia de peso de un mamífero.
64. Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 55 para la fabricación de un medicamento para uso en la profilaxis o tratamiento de obesidad de un mamífero.
65. Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 55 para la fabricación de un medicamento para uso en un método para disminuir el consumo de alimentos de un mamífero.
66. Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 55 para la fabricación de un medicamento para uso en un método para inducir saciedad en un mamífero.

67. Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 55 para la fabricación de un medicamento para uso en un método para controlar la ganancia de peso de un mamífero.



(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention
of the grant of the patent:
04.05.2005 Bulletin 2005/18

(51) Int Cl.7: **C07D 223/16, C07D 223/32,
C07D 403/04, C07D 409/04,
C07D 491/04, A61K 31/55,
A61P 3/00, A61P 9/00,
A61P 25/00**

(21) Application number: **03718323.3**

(22) Date of filing: **11.04.2003**

(86) International application number:
PCT/US2003/011076

(87) International publication number:
WO 2003/086306 (23.10.2003 Gazette 2003/43)

(54) **5HT2C RECEPTOR MODULATORS**
5HT2C-REZEPTOR-MODULATOREN
MODULATEURS DU RECEPTEUR 5HT2C

(84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HU IE IT LI LU MC NL PT RO SE SI SK TR**
Designated Extension States:
AL LT LV MK

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(30) Priority: **12.04.2002 US 372058 P**
23.08.2002 US 405495 P
18.12.2002 US 434807 P
10.04.2003 US 410981

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(43) Date of publication of application:
28.04.2004 Bulletin 2004/18

(56) References cited:
GB-A- 1 268 243 **US-A- 3 652 543**
US-A- 4 111 957 **US-A- 4 988 690**
US-A- 5 015 639

(60) Divisional application:
05002888.1

(73) Proprietor: **Arena Pharmaceuticals, Inc.**
San Diego, CA 92121 (US)

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 1 411 881 B1

Description

Field of the invention

[0001] The present invention relates to compounds which act as modulators of 5HT_{2C} receptors, compositions including the compounds, and methods of using the compounds.

Background of the invention

[0002] Obesity is a life-threatening disorder in which there is an increased risk of morbidity and mortality arising from concomitant diseases such as type II diabetes, hypertension, stroke, cancer and gallbladder disease.
[0003] Obesity is now a major healthcare issue in the Western World and increasingly in some third world countries. The increase in numbers of obese people is due largely to the increasing preference for high fat content foods but also, and this can be a more important factor, the decrease in activity in most people's lives. In the last 10 years there has been a 30% increase in the incidence of obesity in the USA and that about 30% of the population of the USA is now considered obese.
[0004] Whether someone is classified as overweight or obese is generally determined on the basis of their body mass index (BMI) which is calculated by dividing body weight (kg) by height squared (m²). Thus, the units of BMI are kg/m² and it is possible to calculate the BMI range associated with minimum mortality in each decade of life. Overweight is defined as a BMI in the range 25-30 kg/m², and obesity as a BMI greater than 30 kg/m² (see TABLE below).

CLASSIFICATION OF WEIGHT BY BODY MASS INDEX (BMI)	
BMI	CLASSIFICATION
< 18.5	Underweight
18.5-24.9	Normal
25.0-29.9	Overweight
30.0-34.9	Obesity (Class I)
35.0-39.9	Obesity (Class II)
>40	Extreme Obesity (Class III)

[0005] As the BMI increases there is an increased risk of death from a variety of causes that is independent of other risk factors. The most common diseases with obesity are cardiovascular disease (particularly hypertension), diabetes (obesity aggravates the development of diabetes), gall bladder disease (particularly cancer) and diseases of reproduction. Research has shown that even a modest reduction in body weight can correspond to a significant reduction in the risk of developing coronary heart disease.
[0006] There are problems however with the BMI definition in that it does not take into account the proportion of body mass that is muscle in relation to fat (adipose tissue). To account for this, obesity can also be defined on the basis of body fat content: greater than 25% in males and 30% in females.
[0007] Obesity considerably increases the risk of developing cardiovascular diseases as well. Coronary insufficiency, atheromatous disease, and cardiac insufficiency are at the forefront of the cardiovascular complication induced by obesity. It is estimated that if the entire population had an ideal weight, the risk of coronary insufficiency would decrease by 25% and the risk of cardiac insufficiency and of cerebral vascular accidents by 35%. The incidence of coronary diseases is doubled in subjects less than 50 years of age who are 30% overweight. The diabetes patient faces a 30% reduced lifespan. After age 45, people with diabetes are about three times more likely than people without diabetes to have significant heart disease and up to five times more likely to have a stroke. These findings emphasize the interrelations between risks factors for NIDDM and coronary heart disease and the potential value of an integrated approach to the prevention of these conditions based on the prevention of obesity (Perry, I. J., et al., *BMJ* 310, 580-584 (1995)).
[0008] Diabetes has also been implicated in the development of kidney disease, eye diseases and nervous-system problems. Kidney disease, also called nephropathy, occurs when the kidney's "filter mechanism" is damaged and protein leaks into urine in excessive amounts and eventually the kidney fails. Diabetes is also a leading cause of damage to the retina at the back of the eye and increases risk of cataracts and glaucoma. Finally, diabetes is associated with nerve damage, especially in the legs and feet, which interferes with the ability to sense pain and contributes to serious infections. Taken together, diabetes complications are one of the nation's leading causes of death.
[0009] The first line of treatment is to offer diet and life style advice to patients such as reducing the fat content of

their diet and increasing their physical activity. However many patients find this difficult and need additional help from drug therapy to maintain results from these efforts.

[0010] Most currently marketed products have been unsuccessful as treatments for obesity owing to a lack of efficacy or unacceptable side-effect profiles. The most successful drug so far was the indirectly acting 5-hydroxytryptamine (5-HT) agonist d-fenfluramine (Redux™) but reports of cardiac valve defects in up to one third of patients led to its withdrawal by the FDA in 1998.

[0011] In addition, two drugs have recently been launched in the USA and Europe: Orlistat (Xenical™), a drug that prevents absorption of fat by the inhibition of pancreatic lipase, and Sibutramine (Reductil™), a 5-HT/norepinephrine re-uptake inhibitor. However, side effects associated with these products may limit their long-term utility. Treatment with Xenical™ is reported to induce gastrointestinal distress in some patients, while Sibutramine has been associated with raised blood pressure in some patients.

[0012] Serotonin (5-HT) neurotransmission plays an important role in numerous physiological processes both in health and in psychiatric disorders. 5-HT has been implicated in the regulation of feeding behavior for some time. 5-HT appears to work by inducing a feeling of fullness or satiety so eating stops earlier and fewer calories are consumed. It has been shown that a stimulatory action of 5-HT on the 5HT_{2C} receptor plays an important role in the control of eating and in the anti-obesity effect of d-fenfluramine. As the 5-HT_{2C} receptor is expressed in high density in the brain (notably in the limbic structures, extrapyramidal pathways, thalamus and hypothalamus i.e. PVN and DMH, and predominantly in the choroid plexus) and is expressed in low density or is absent in peripheral tissues, a selective 5-HT_{2C} receptor agonist can be a more effective and safe anti-obesity agent. Also, 5-HT_{2C} knockout mice are overweight with cognitive impairment and susceptibility to seizure.

[0013] It is believed that 5HT_{2C} may play a role in obsessive compulsive disorder, some forms of depression, and epilepsy. Accordingly, agonists can have anti-panic properties, and properties useful for the treatment of sexual dysfunction.

[0014] In sum, the 5HT_{2C} receptor is a validated and well-accepted receptor target for the treatment of obesity and psychiatric disorders, and it can be seen that there is a need for selective 5HT_{2C} agonists which safely decrease food intake and body weight. The present invention is directed to these, as well as other, important ends.

[0015] US 3,652,543 (Hoegerle) describes methods for the preparation of certain 1,2,4,5-tetrahydro-3-azepines which are allegedly useful as chemical intermediates. Six benzazepine compounds appear in the table at column 8, lines 25-35 (on the right hand side) therein. 7-chloro-1,2,4,5-tetrahydro-3-benzazepine hydrochloride lacks an R₂ group as required by the claimed invention (this compound has -H as R₂). 2-methyl-1,2,4,5-tetrahydro-3-benzazepine lacks R₂ and R₃ groups as required by the claimed invention (this compound has -H as R₂, and -H as R₃). 1-phenyl-1,2,4,5-tetrahydro-3-benzazepine lacks R₂ and R₃ groups as required by the claimed invention (this compound has -Ph as R₂, and -H as R₃). 1,2,3,4,4a,6,7,11b-octahydro-5H-dibenz[d,b]azepine does not have the same core structure as required by the claimed invention. 4-methyl-1,2,4,5-tetrahydro-3-benzazepine lacks R₂ and R₃ groups as required by the claimed invention (this compound has -H as R₂, and -H as R₃). 5-methyl-8-isopropyl-1,2,4,5-tetrahydro-3-benzazepine lacks R₂ and R₄ groups as required by the claimed invention (this compound has -H as R₃, and isopropyl as R₄).

[0016] US 4,111,957 (Holden et al.) describes certain 7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepines, which are alleged to have dopaminergic activity. A single benzazepine compound (used as a chemical intermediate) is shown at column 8, lines 26-27 therein. 1-hydroxy-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine lacks an R₃ group as required by the claimed invention (this compound has -OCH₃ as R₃).

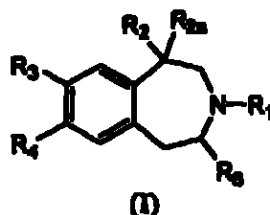
[0017] US 4,888,690 (Effland et al.) describes certain 1-aryloxy-2,3,4,5-tetrahydro-3-benzazepines which are alleged to have antidepressant, antihypertensive, and analgesic properties. All of these compounds lack R₂ and R_{2a} groups as required by the claimed invention (these compounds have aryloxy as R₂ and R_{2a}). A single benzazepine compound (used as a chemical intermediate) is shown at column 12, lines 31-32 therein. 1-hydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine lacks an R₃ group as required by the claimed invention (this compound has -H as R₃).

[0018] US 5,015,639 (Berger et al.) describes certain 1-substituted-2,3,4,5-tetrahydro-1H-benzazepines which are alleged to be useful in the treatment of psychosis, schizophrenia, depression, pain, and anxiety. A generic definition of a large number of benzazepine compounds is provided at columns 1 and 2 therein. Each of these compounds lacks an R₃ group as required by the claimed invention. In each case, the recited group R⁸ (corresponding to the group R₃ herein) is -OR¹⁰, -N(R⁶)₂, or -OC(R⁷)₂OCOR¹².

[0019] GB 1 268 243 (Wallace & Tieman Inc.) describes certain 1,2,4,5-tetrahydro-3H-benzazepines which are alleged to be useful as analgesics (in the treatment of pain) and as antagonists of narcotics (in the treatment of drug addiction) and to have antihistaminic and anticholinergic activity. Twelve benzazepine compounds are shown in the table on page 23 therein. The first six compounds lack an R₃ group as required by the claimed invention (these compounds have -OH or -OCH₃ as R₃). The last six compounds lack R₁ and R₃ groups as required by the claimed invention (these compounds have various aryl-alkyl groups as R₁, and -OH or -OCH₃ as R₃).

Summary of the invention

[0020] The present invention, in one aspect, relates to compounds represented by Formula (I):



wherein:

R_1 is: -H or C_{1-8} alkyl;

R_2 is: C_{1-8} alkyl, $-CH_2-O-C_{1-8}$ alkyl, $-C(=O)-O-C_{1-8}$ alkyl, $-C(=O)-NH-C_{1-8}$ alkyl, -OH, or $-CH_2OH$;

R_{2a} is: -H;

or R_2 and R_{2a} together form $-CH_2-CH_2-$;

R_3 is: halogen; perhaloalkyl; or a 5-membered heteroaryl ring having up to two heteroatoms selected from O, N and S;

R_4 is -H, halogen, perhaloalkyl, -CN, $-OR_6$, $-SR_6$, $-NHR_6$, $-N(R_6)_2$, -OH, aryl, or heteroaryl, wherein said aryl can be optionally substituted with up to two substituents selected from C_{1-8} alkyl, halogen, perhaloalkyl, and alkoxy, and said heteroaryl can be optionally substituted with up to two substituents selected from halogen and C_{1-8} alkyl; or: R_3 and R_4 together with the atoms to which they are attached form a 5- or 6-member heterocyclic ring having one O atom;

each R_5 is independently C_{1-8} alkyl, C_{1-8} alkenyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl or perhaloalkyl, or allyl; and

R_6 is -H or C_{1-8} alkyl;

and pharmaceutically acceptable salts, solvates and hydrates thereof; provided that:

If R_5 is other than -H, then R_4 cannot be -H; and

If R_1 and R_2 are methyl, and R_4 is -H, then R_3 cannot be imidazole, substituted imidazole, or an imidazole derivative.

[0021] In some embodiments of the compounds of Formula (I), R_1 is H. In some embodiments of the compounds of Formula (I), R_1 is C_{1-8} alkyl. In some embodiments of the compounds of Formula (I), R_1 is methyl. In some embodiments of the compounds of Formula (I), R_1 is n-propyl.

[0022] In some embodiments of the compounds of Formula (I), R_2 is C_{1-8} alkyl. In some embodiments of the compounds of Formula (I), R_2 is methyl. In some embodiments of the compounds of Formula (I), R_2 is ethyl. In some embodiments of the compounds of Formula (I), R_2 is isopropyl. In some embodiments of the compounds of Formula (I), R_2 and R_{2a} together form $-CH_2-CH_2-$.

[0023] In some embodiments of the compounds of Formula (I), R_3 is halogen. In some embodiments of the compounds of Formula (I), R_3 is chlorine. In some embodiments of the compounds of Formula (I), R_3 is bromine. In some embodiments of the compounds of Formula (I), R_3 is iodine. In some embodiments of the compounds of Formula (I), R_3 is perhaloalkyl. In some embodiments of the compounds of Formula (I), R_3 is CF_3 . In some embodiments of the compounds of Formula (I), R_3 is a 5-membered heteroaryl ring having up to two heteroatoms selected from O, N and S. In some embodiments, R_3 is a radical derived from thiophenyl, furanyl, pyrrolyl, pyrazolyl or imidazolyl.

[0024] In some embodiments of the compounds of Formula (I), R_4 is perhaloalkyl. In some embodiments of the compounds of Formula (I), R_4 is CF_3 . In some embodiments of the compounds of Formula (I), R_4 is $-OR_6$. In some embodiments R_5 is methyl, ethyl, n-propyl, isopropyl or allyl. In some embodiments of the compounds of Formula (I), R_5 is methyl or allyl. In some embodiments of the compounds of Formula (I), R_4 is a 5-membered heteroaryl ring having up to two heteroatoms selected from O, N and S, and up to two substituents selected from halogen and C_{1-8} alkyl. In some embodiments, R_4 is a radical derived from thiophenyl, furanyl, pyrrolyl, pyrazolyl or imidazolyl, which can optionally be mono- or di-substituted selected from halogen or methyl. In some embodiments of the compounds of Formula (I), R_4 is phenyl optionally substituted with up to two substituents selected from C_{1-8} alkyl, halogen, and alkoxy. In some embodiments of the compounds of Formula (I), R_3 and R_4 taken together form $-O-CH=C(CH_3)-$.

[0025] In some embodiments of the compounds of Formula (I), R_3 is halogen and R_4 is $-OR_5$ wherein R_5 is C_{1-8} alkyl. In some embodiments of the compounds of Formula (I), R_3 is chlorine and R_4 is $-OR_5$ wherein R_5 is C_{1-8} alkyl. In some embodiments of the compounds of Formula (I), R_3 is bromine and R_4 is $-OR_5$ wherein R_5 is C_{1-8} alkyl. In some embodiments of the compounds of Formula (I), R_3 is iodine and R_4 is $-OR_5$ wherein R_5 is C_{1-8} alkyl. In some embodiments of the compounds of Formula (I), R_3 is halogen and R_4 is methoxy. In one embodiment, R_3 is chlorine or bromine and R_4 is methoxy. In some embodiments of the compounds of Formula (I), R_3 is halogen and R_4 is allyloxy.

[0026] In some embodiments of the compounds of Formula (I):

R_2 is methyl, ethyl, isopropyl, or CH_2OH ; or R_2 and R_{2a} taken together form $-CH_2-CH_2-$;
 R_3 is halogen, or a 5-membered heteroaryl ring having up to two heteroatoms selected from O, N and S, and up to two substituents selected from halogen and C_{1-8} alkyl;
 R_4 is H, alkoxy, a 5-membered heteroaryl ring having up to two heteroatoms selected from O, N and S and up to two substituents selected from halogen and C_{1-8} alkyl, or phenyl optionally substituted with up to two substituents selected from C_{1-8} alkyl, halogen, and alkoxy;
 or R_3 and R_4 taken together form $-O-CH=C(CH_3)-$; and
 R_5 is H or methyl; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0027] In some embodiments of the compounds of Formula (I):

R_2 is methyl, ethyl, isopropyl, or CH_2OH ; or R_2 and R_{2a} taken together form $-CH_2-CH_2-$;
 R_3 is chlorine, bromine, or iodine;
 R_4 is alkoxy; and
 R_5 is H or methyl; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0028] In some embodiments of the compounds of Formula (I):

R_1 is H;
 R_2 is methyl;
 R_3 is H, chlorine, bromine, or thiophene;
 R_4 is alkoxy, pyrazol-3-yl or phenyl wherein said pyrazole optionally has up to two substituents selected from halogen and C_{1-8} alkyl, and said phenyl optionally has a single halogen substituent; and
 R_5 is H; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0029] In some embodiments of the compounds of Formula (I), the compound is a member of the group consisting of: 8-Bromo-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-Allyloxy-8-bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-Benzoyloxy-8-bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Bromo-7-ethoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Bromo-7-isopropoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-Propyl-8-bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-Hydroxy-8-iodo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-Allyloxy-8-iodo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-Allyloxy-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-Methoxy-1-methyl-8-(2-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-bromo-1-cyclopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-bromo-1-hydroxymethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Bromo-1-isopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Bromo-7-hydroxy-1-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-Allyloxy-8-bromo-1-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Bromo-7-methoxy-1,4-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-Allyloxy-8-bromo-1,4-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Chloro-1-hydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Fluoro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7,8-Dichloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-Methyl-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-iodo-1-methyl-7-trifluoromethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; N-Propyl-8-iodo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 1-Ethyl-8-iodo-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-(2-fluorophenyl)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; and 8-bromo-1-methoxymethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0030] In some embodiments of the compounds of Formula (I), the compound is a member of the group consisting of 8-Bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Chloro-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-iodo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-Methyl-8-bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Bromo-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Chloro-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-iodo-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

rahydro-1H-3-benzazepine; 7-Methoxy-1-methyl-8-trifluoromethyl-2,3,4,5-tetrahydro-1H-3-benzazepine, and 7-Methoxy-1-methyl-8-pentafluoroethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0031] In some embodiments of the compounds of Formula (I), the compound is a member of the group consisting of: 8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Iodo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Trifluoromethyl-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Trifluoromethyl-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Chloro-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Bromo-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Iodo-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7,8-Dichloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7,8-Dichloro-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Chloro-7-fluoro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; and 8-Chloro-7-fluoro-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0032] The present invention also provides compositions comprising one or more compounds of the invention, and one or more pharmaceutically acceptable carriers.

[0033] Described herein are methods of modulating a 5HT_{2C} receptor comprising contacting said receptor with a pharmaceutically effective amount of a compound or composition of the invention. Preferably, said compound is an agonist of said receptor.

[0034] Also described herein are methods of prophylaxis or treatment of disorders of obesity.

[0035] Also described herein are methods of decreasing food intake of a mammal comprising administering to said mammal a pharmaceutically effective amount of a compound or composition of the invention.

[0036] Also described herein are methods of inducing satiety in a mammal comprising administering to said mammal a pharmaceutically effective amount of a compound or composition of the invention.

[0037] Also described herein are methods of controlling weight gain of a mammal comprising administering to said mammal a pharmaceutically effective amount of a compound or composition of the invention.

[0038] Also described herein are methods of treating obesity comprising administering to a patient in need of such treatment a pharmaceutically effective amount of a compound or composition of the invention.

[0039] In some embodiments, some of the foregoing methods further comprise the step of identifying a subject, said subject being in need of decreasing food intake, controlling weight gain, or treating obesity, wherein said identifying step is performed prior to administering to said subject said pharmaceutically effective amount of said compound or composition of the invention.

[0040] One aspect of the present invention pertains to a compound of Formula (I) for use in a method of treatment of the human or animal body by therapy.

[0041] One aspect of the present invention pertains to a compound of Formula (I) for use in a method of prophylaxis or treatment of obesity.

[0042] One aspect of the present invention pertains to a compound of Formula (I) for the manufacture of a medicament for use in the prophylaxis or treatment of obesity.

[0043] Also described herein are methods for alleviation of a symptom of any of the diseases, conditions or disorders mentioned herein.

[0044] Applicants reserve the right to exclude any one or more of the compounds from any of the embodiments of the invention. Applicant additionally reserves the right to exclude any disorder from any of the embodiments of the invention.

Brief Description of the Figures

[0045]

Figures 1A-1G illustrate the effects of seven different compounds of the invention on food intake in food-deprived rats.

Detailed Description of the Invention

[0046] The present invention relates to 5HT_{2C} receptor agonist compounds, which are useful in methods of modulating 5HT_{2C} receptors by contacting the receptors with one or more compounds of the invention, and in methods of decreasing food intake, controlling weight gain, or treating obesity, using compounds of the invention.

[0047] The term "antagonist" is intended to mean moieties that competitively bind to the receptor at the same site as agonists (for example, the endogenous ligand), but which do not activate the intracellular responses initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists or partial agonists. Antagonists do not diminish the baseline intracellular response in the absence of an agonist or partial agonist. As used herein, the term "agonist" is intended to mean moieties that activate the intracellular response when they bind to the receptor,

or enhance GTP binding to membranes. In the context of the present invention, a pharmaceutical composition comprising a 5HT_{2C} receptor agonist of the invention can be utilized for modulating the activity of the 5HT_{2C} receptor, decreasing food intake, inducing satiation (i.e., the feeling of fullness), controlling weight gain, treating obesity, decreasing body weight and/or affecting metabolism such that the recipient loses weight and/or maintains weight. Such pharmaceutical compositions can be used in the context of disorders and/or diseases where weight gain is a component of the disease and/or disorder such as, for example, obesity.

[0048] As used herein, the term "contact" or "contacting" shall mean bringing the indicated moieties together, whether in an in vitro system or an in vivo system. Thus, "contacting" an 5HT_{2C} receptor with a compound of the invention includes the administration of a compound of the invention to an animal having an 5HT_{2C} receptor, as well as, for example, introducing a compound of the invention into a sample containing a cellular or more purified preparation containing an 5HT_{2C} receptor.

[0049] Compounds of the invention include those having the Formula (I), shown above.

[0050] In one embodiment, if R₄ is OR₅, then R₂ cannot be alkyl.

[0051] In some embodiments, if R₄ is OR₅, then R₂ cannot be cyclopentyl, -CH₂-cyclohexyl, 3,3-dimethyl-2-allyl, 3,3-dimethyl-2-methylallyl, 2-methylallyl, 2-butenyl, cyclopropylmethyl, cyclohexyl, or allyl.

[0052] It will be appreciated that compounds of Formula (I) may have one or more chiral centers, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. Formula (I) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise.

[0053] As used herein, the term "alkyl" is intended to denote hydrocarbon groups including straight chain, branched and cyclic hydrocarbons, including for example but not limited to methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, sec-butyl, tert-butyl, cyclobutyl, cyclopropylmethyl, n-pentyl, isopentyl, tert-pentyl, cyclopentyl, cyclopentylmethyl, n-hexyl, cyclohexyl, and the like. Throughout this specification, it should be understood that the term alkyl is intended to encompass both non-cyclic hydrocarbon groups and cyclic hydrocarbon groups. In some embodiments of the compounds of the invention, alkyl groups are non-cyclic. In further embodiments, alkyl groups are cyclic, and in further embodiments, alkyl groups are both cyclic and noncyclic. Where no preference is specified, the term "alkyl" is intended to denote groups that are both cyclic and non-cyclic.

[0054] As used herein, the term "alkenyl" is intended to denote hydrocarbon compounds including straight chain, branched and cyclic hydrocarbons that contain at least one double bond, including for example allyl, 2-methyl-allyl, 4-but-3-enyl, 4-hex-5-enyl, 3-methyl-but-2-enyl, cyclohex-2-enyl and the like.

[0055] As used herein, the term "halogen" has its normal meaning of period seven elements, including F, Cl, Br and I.

[0056] The term "alkoxy" is intended to denote substituents of the formula -O-alkyl, including -O-allyl. The term "lower" when used in connection with substituents such as alkyl indicates 6 carbons or less.

[0057] The term "arylalkyl" or "aralkyl" is intended to denote an alkyl group that bears an aryl substituent, for example a benzyl group. The term "alkylaryl" or "alkaryl" is intended to denote an aryl group that bears an alkyl substituent, for example a 4-methylphenyl group.

[0058] As used herein, the term "aryl" is intended to mean monocyclic and polycyclic aromatic groups. Although aryl groups can include as few as 3 carbon atoms, preferred aryl groups have 6 to about 14 carbon atoms, more preferably 6 to about 10 carbon atoms. Examples of aryl groups include phenyl, naphthyl, anthracyl, phenanthryl and pyrenyl.

[0059] The term "heteroaryl" is intended to denote an aryl group that contains at least one, and preferably from one to four ring "hetero" (i.e., non-carbon, e.g., O, N or S) atom. Examples of "heteroaryl" groups are radicals derived from 5- and 6-member aryl ring compounds having from one to four nitrogen, sulfur and/or oxygen atoms, for example pyrrole, pyrazole, imidazole, triazole, tetrazole, pyridine, pyrimidine, furan, pyran, thiophene, benzimidazole, quinoline, isoquinoline, oxazole, thiazole, and thiadiazole.

[0060] As used herein the term heteroarylalkyl means an alkyl group that bears a heteroaryl substituent, for example a group having the structure -CH₂-pyrrole-2-yl.

[0061] The term "substituted thiazole" means a radical derived from thiazole that bears at least one substituent group. The term "thiazole derivative" means a fused ring system in which one of the fused rings is thiazole.

[0062] The term "substituted imidazole" means a radical derived from imidazole that bears at least one substituent group. The term "imidazole derivative" means a fused ring system in which one of the fused rings is imidazole.

[0063] In some embodiments of the invention, R₄ is OR₅. In some such embodiments, R₂ cannot be cyclopentyl, -CH₂-cyclohexyl, 3,3-dimethyl-2-allyl, 3,3-dimethyl-2-methylallyl, 2-methylallyl, 2-butenyl, cyclopropylmethyl, cyclohexyl, or allyl. In further such embodiments, R₂ cannot be alkyl.

[0064] In some embodiments of the compounds of Formula (I), R₃ is halogen and R₄ is

-OR₅. In some embodiments of the compounds of Formula (I), R₄ is allyl, 2-methyl-allyl, 4-but-3-enyl, 4-hex-5-enyl, 3-methyl-but-2-enyl or cyclohex-2-enyl. In some embodiments of the compounds of Formula (I), R₅ is methyl, ethyl, n-propyl, isopropyl or allyl. In some embodiments of the compounds of Formula (I), R₅ is methyl or allyl.

[0065] Certain substituents of the compounds disclosed herein can optionally be substituted, i.e., they can optionally

bear further substituent groups. Some preferred substituent groups include halogen, lower alkyl (including methyl, ethyl, isopropyl, cyclopropyl, tert-butyl, and methylcyclopropyl), alkoxy, mono-, di- or trihaloalkoxy (e.g., -OCX₃ where X is halogen), -(CH₂)₃NH₂, -(CH₂)₃NHBoc, -N(R_{4a})(R_{4b}), phenyl, methoxyphenyl and naphthyl.

[0066] At various places in the present specification substituents of compounds of the invention are disclosed in groups or in ranges. It is specifically intended that the invention include each and every individual subcombination of the members of such groups and ranges. For example, the term "C₁₋₈ alkyl" is specifically intended to individually disclose methyl, ethyl, C₃ alkyl, C₄ alkyl, C₅ alkyl, C₆ alkyl, C₇ alkyl and C₈ alkyl.

[0067] In a preferred embodiment, the compounds of Formula (I) are selected from:

8-Bromo-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-Allyloxy-8-bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-Benzoyloxy-8-bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Bromo-7-ethoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Bromo-7-isopropoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-Propyl-8-bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-Hydroxy-8-iodo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-Allyloxy-8-iodo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-Allyloxy-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-Methoxy-1-methyl-8-(2-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-bromo-1-cyclopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-bromo-1-hydroxymethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Bromo-1-isopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Bromo-7-hydroxy-1-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-Allyloxy-8-bromo-1-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Bromo-7-methoxy-1,4-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-Allyloxy-8-bromo-1,4-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Chloro-1-hydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Fluoro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7,8-Dichloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-Methyl-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-iodo-1-methyl-7-trifluoromethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; N-Propyl-8-iodo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 1-Ethyl-8-iodo-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-(2-fluorophenyl)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; and 8-bromo-1-methoxymethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0068] In a preferred embodiment, the compounds of Formula (I) are selected from:

N-methyl-8-Bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-methyl-8-Chloro-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-methyl-8-Iodo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-Methyl-8-bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-methyl-8-Bromo-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; N-methyl-8-Chloro-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; N-methyl-8-Iodo-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; N-methyl-7-Methoxy-1-methyl-8-trifluoromethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; and N-methyl-7-Methoxy-1-methyl-8-pentafluoroethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0069] In a preferred embodiment, the compounds of Formula (I) are selected from:

N-methyl-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-methyl-8-Bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-methyl-8-Iodo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-methyl-8-Trifluoromethyl-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-methyl-8-Trifluoromethyl-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-methyl-8-Chloro-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-methyl-8-Bromo-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-methyl-8-Iodo-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-methyl-7,8-Dichloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-methyl-7,8-Dichloro-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-methyl-8-Chloro-7-fluoro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; and N-methyl-8-Chloro-7-fluoro-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0070] In a preferred embodiment, the compounds of Formula (I) are selected from:

8-Bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Chloro-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Iodo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; N-Methyl-8-bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Bromo-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Chloro-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Iodo-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine; 7-Methoxy-1-methyl-8-trifluoromethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; and 7-Methoxy-1-methyl-8-pentafluoroethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0071] In a preferred embodiment, the compounds of Formula (I) are selected from:

8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Iodo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Trifluoromethyl-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Trifluoromethyl-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Chloro-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Bromo-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Iodo-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine;

3-benzazepine; 7,8-Dichloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 7,8-Dichloro-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; 8-Chloro-7-fluoro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; and 8-Chloro-7-fluoro-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0072] The compounds of the invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. The compounds can be, for example, racemates or optically active forms. The optically active forms can be obtained by resolution of the racemates or by asymmetric synthesis. In some embodiments, compounds of Formula (I) are *R* enantiomers. In some embodiments, compounds of Formula (I) are *S* enantiomers. In some embodiments, compounds of Formula (I) are varying mixtures of enantiomers.

[0073] According to a further aspect of the invention, compounds of Formula (I) are provided for use in therapy. The compounds of Formula (I) can be used in the prophylaxis or treatment of obesity.

[0074] According to a further aspect of the invention, there is provided use of a compound of Formula (I) in the manufacture of a medicament for the prophylaxis or treatment of the disorders disclosed herein. In a preferred embodiment, there is provided a use of a compound of Formula (I) in the manufacture of a medicament for the prophylaxis or treatment of obesity.

[0075] The compounds according to the invention may optionally exist as pharmaceutically acceptable salts including pharmaceutically acceptable acid addition salts prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, palmitic, pantoic, phosphoric, succinic, sulfuric, tartaric, oxalic, *p*-toluenesulfonic and the like, such as the pharmaceutically acceptable salts listed in *Journal of Pharmaceutical Science*, 66, 2 (1977).

[0076] The acid addition salts can be obtained as the direct products of compound synthesis. In the alternative, the free base can be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent. The compounds of this invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

[0077] Compositions of the invention may conveniently be administered in unit dosage form and can be prepared by any of the methods well known in the pharmaceutical art, for example, as described in *Remington's Pharmaceutical Sciences* (Mack Pub. Co., Easton, PA, 1980).

[0078] The compounds of the invention can be employed as the sole active agent in a pharmaceutical or can be used in combination with other active ingredients which could facilitate the therapeutic effect of the compound.

[0079] Compounds of the present invention or a solvate or physiologically functional derivative thereof can be used as active ingredients in pharmaceutical compositions, specifically as 5HT_{2C} receptor agonists. By the term "active ingredient" is defined in the context of a "pharmaceutical composition" and shall mean a component of a pharmaceutical composition that provides the primary pharmaceutical benefit, as opposed to an "inactive ingredient" which would generally be recognized as providing no pharmaceutical benefit. The term "pharmaceutical composition" shall mean a composition comprising at least one active ingredient and at least one ingredient that is not an active ingredient (for example and not limitation, a filler, dye, or a mechanism for slow release), whereby the composition is amenable to use for a specified, efficacious outcome in a mammal (for example, a human).

[0080] The data developed herein supports the conclusion that the presently disclosed 5HT_{2C} receptor agonists are of use for the treatment or prophylaxis of clinical obesity or overweight disorders in mammals, including humans. Compounds of the present invention can be administered by oral, sublingual, parenteral, rectal, topical administration or by a transdermal patch. Transdermal patches dispense a drug at a controlled rate by presenting the drug for absorption in an efficient manner with a minimum of degradation of the drug. Typically, transdermal patches comprise an impermeable backing layer, a single pressure sensitive adhesive and a removable protective layer with a release liner. One of ordinary skill in the art will understand and appreciate the techniques appropriate for manufacturing a desired efficacious transdermal patch based upon the needs of the artisan.

[0081] In addition to the neutral forms of compounds of the present invention, by appropriate addition of an ionizable substituent, which does not alter the receptor specificity of the compound, physiologically acceptable salts of the compounds may also be formed and used as therapeutic agents. Different amounts of the compounds of the present invention will be required to achieve the desired biological effect. The amount will depend on factors such as the specific compound, the use for which it is intended, the means of administration, and the condition of the treated individual - all of these dosing parameters are within the level of one of ordinary skill in the medicinal arts. A typical dose can be expected to fall in the range of 0.001 to 200 mg per kilogram of body weight of the mammal. Unit doses may contain from 1 to 200 mg of the compounds of the present invention and can be administered one or more times a day, individually or in multiples.

[0082] Pharmaceutical compositions, for example, pharmaceutical compositions comprising at least one compound of the present invention and/or an acceptable salt or solvate thereof (e.g., a pharmaceutically acceptable salt or solvate) as an active ingredient combined with at least one carrier or excipient (e.g., pharmaceutical carrier or excipient) can

be used in the treatment of clinical conditions for which a 5HT_{2C} receptor agonist is indicated. At least one compound of the present invention can be combined with the carrier in either solid or liquid form in a unit dose formulation. The pharmaceutical carrier must be compatible with the other ingredients in the composition and must be tolerated by the individual recipient. Other physiologically active ingredients can be incorporated into the pharmaceutical composition of the invention if desired, and if such ingredients are compatible with the other ingredients in the composition. Formulations can be prepared by any suitable method, typically by uniformly mixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions, and then, if necessary, forming the resulting mixture into a desired shape.

[0083] Conventional excipients, such as binding agents, fillers, acceptable wetting agents, tableting lubricants, and disintegrants can be used in tablets and capsules for oral administration. Liquid preparations for oral administration can be in the form of solutions, emulsions, aqueous or oily suspensions, and syrups. Alternatively, the oral preparations can be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous vehicles (including edible oils), preservatives, and flavorings and colorants can be added to the liquid preparations. Parenteral dosage forms can be prepared by dissolving the compound of the invention in a suitable liquid vehicle and filter sterilizing the solution before filling and sealing an appropriate vial or ampoule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms.

[0084] It is noted that when the 5HT_{2C} receptor agonists are utilized as active ingredients in a pharmaceutical composition, these are not intended for use only in humans, but in other non-human mammals as well. Indeed, recent advances in the area of animal health-care mandate that consideration be given for the use of 5HT_{2C} receptor agonists for the treatment of obesity in domestic animals (e.g., cats and dogs), and 5HT_{2C} receptor agonists in other domestic animals where no disease or disorder is evident (e.g., food-oriented animals such as cows, chickens, fish, etc.). Those of ordinary skill in the art are readily credited with understanding the utility of such compounds in such settings.

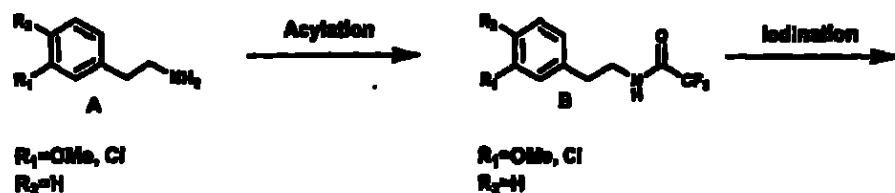
[0085] The compounds of the present invention can be readily prepared according to a variety of synthetic manipulations, all of which would be familiar to one skilled in the art. A representative general synthesis is set forth below in Scheme 1:

Scheme I

GENERAL REACTION SCHEME

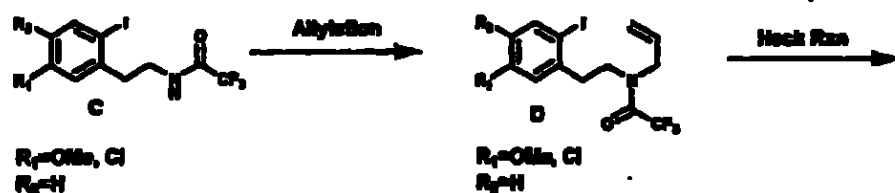
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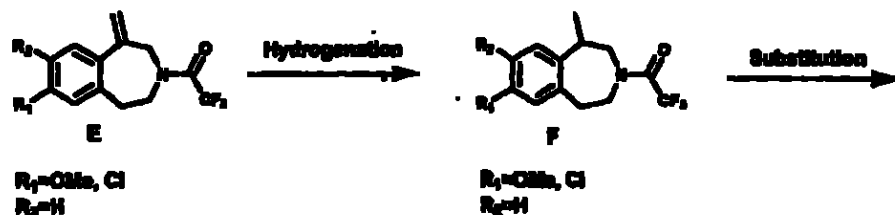
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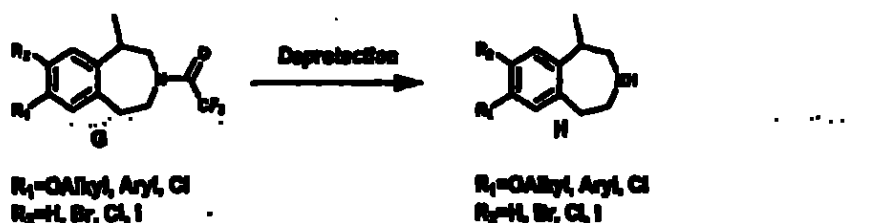
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[0085] Those of skill in the art will appreciate that a wide variety of compounds of the invention can be prepared according to Scheme I. For example, by starting with an appropriately substituted 2-phenyl ethylamine compound A having any of a wide variety of substituents R_1 and R_2 , the corresponding 7- and/or 8-substituted 1-methyl-2,3,4,5-tetrahydro-1H-3-benzazapine (compound H) can be prepared. N-alkylation can be accomplished by, for example, treatment with excess paraformaldehyde (for methylation) or a higher order aldehyde, followed by reduction with NaBH_3CN

according to the general procedure of synthetic examples 9 and 10, *infra*. In addition, by starting with an appropriately substituted 1-alkyl-2-phenyl ethylamino compound A having any of a wide variety of substituents R₁ and R₂, the corresponding 7- and/or 8-substituted 2,5-dialkyl-2,3,4,5-tetrahydro-1H-3-benzazepine compound can be prepared.

[0087] In the synthesis of many compounds of the invention, protecting groups can be required to protect various functionality or functionalities during the synthesis. Representative protecting groups suitable for a wide variety of synthetic transformations are disclosed in Greene and Wuts, *Protective Groups in Organic Synthesis*, 2d ed, John Wiley & Sons, New York, 1991.

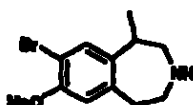
[0088] As will be recognized, the steps of the methods described herein need not be performed any particular number of times or in any particular sequence. Additional objects, advantages, and features of the invention will become apparent to those skilled in the art upon examination of the following examples thereof.

Examples

Synthetic Examples

Example 1: (R,S) 8-Bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0089]



N-Trifluoroacetyl-3-methoxyphenethylamine

[0090] A solution of 3-methoxyphenethylamine (10.0 g, 84.0 mmol) in dichloromethane (150 mL), was cooled to 0°C, and treated with pyridine (8.5 mL, 83.5 mmol) followed by the dropwise addition of trifluoroacetic anhydride (17.9 g, 83.5 mmol) and the resulting mixture stirred for 3 hours while warming to 20°C. The product mixture was diluted with EtOAc (500 mL), washed sequentially with 10% aqueous HCl (100 mL), water (100 mL), brine (100 mL), dried with Na₂SO₄ and concentrated to give 15.8 g of a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.26 (dd, J=8, 8 Hz, 1 H), 6.81 (d, J=8 Hz, 1 H), 6.77 (d, J=8 Hz, 1 H), 6.72 (s, 1 H), 6.30 (bs, 1 H), 3.80 (s, 3 H), 3.62 (dd, J=7, 7 Hz, 2 H), 2.88 (dd, J=7, 7 Hz, 2 H). MS calculated for C₁₁H₁₂F₃NO₂+H: 248, observed: 248.

N-Trifluoroacetyl-2-iodo-5-methoxyphenethylamine

[0091] A solution of *N*-trifluoroacetyl-3-methoxyphenethylamine (15.8 g, 64 mmol) in methanol (325 mL) was cooled to -78°C, and treated with CaCO₃ (14.7 g, 145 mmol), followed by a solution of ICl (29 g, 181 mmol) in methanol (40 mL). The reaction was allowed to warm to 20°C while stirring overnight and then filtered, concentrated, dissolved in EtOAc (200 mL), washed twice with 5% aqueous sodium bisulfite (100 mL), once with brine (100 mL), dried with Na₂SO₄ and concentrated to give 23.8 g of a white solid powder. ¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, J=9 Hz, 1 H), 6.78 (s, 1 H), 6.57 (d, J=9 Hz, 1 H), 6.42 (bs, 1 H), 3.77 (s, 3 H), 3.61 (dd, J=7, 7 Hz, 2 H), 2.99 (dd, J=7, 7 Hz, 2 H). MS calculated for C₁₁H₁₁F₃INO₂+H: 374, observed: 374.

N-Allyl, *N*-trifluoroacetyl-2-iodo-5-methoxyphenethylamine

[0092] A solution of *N*-trifluoroacetyl-2-iodo-5-methoxyphenethylamine (23.8 g, 63.8 mmol) in toluene (425 mL) was sequentially treated with K₂CO₃ (12.4 g, 89.8 mmol), KOH (11.8 g, 207 mmol), *n*-Bu₄NBr (2.2 g, 6.9 mmol) and allyl bromide (10.7 g, 89.8 mmol). The mixture was stirred at 80°C for 3.5 hours, cooled to 20°C, acidified with 10% aqueous HCl, separated and the aqueous phase extracted with ether (500 mL). The combined organic phases were washed with brine (200 mL), dried with Na₂SO₄ and concentrated to give 20.5 g of a brown oil. ¹H NMR (400 MHz, CDCl₃), mixture of rotamers δ 7.67 (m, 1 H), 6.80 (m, 1 H), 6.57 (m, 1 H), 5.9-5.6 (bm, 1 H), 5.27 (m, 2 H), 4.11 (d, J=6 Hz, 0.5 H), 3.85 (d, J=6 Hz, 0.5 H), 3.77 (m, 3 H), 3.55 (m, 2 H), 3.00 (m, 2 H). MS calculated for C₁₄H₁₈F₃INO₂+H: 414, observed: 414.

N-Trifluoroacetyl-7-methoxy-1-methylene-2,3,4,5-tetrahydro-1H-3-benzazepine

[0093] A solution of N-allyl, N-trifluoroacetyl-2-iodo-5-methoxyphenethylamine (20.5 g, 50 mmol) in dimethylformamide (250 mL) is treated with KOAc (14.6 g, 149 mmol), n-Bu₄NBr (16.0 g, 50 mmol), PPh₃ (1.3 g, 5.0 mmol), Pd(OAc)₂ (0.56 g, 2.5 mmol) and stirred overnight at 90°C. The product mixture was cooled to 20°C, filtered, diluted with water (500 mL) and extracted with ether (3 x 500 mL). The combined organic phases were washed with water (100 mL), brine (100 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (10% EtOAc in hexane, silica) resulted in 6.6 g of a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.26 (d, J=8 Hz, 1 H), 6.77 (d, J=8 Hz, 1 H), 6.66 (s, 1 H), 5.34-5.19 (m, 2 H), 4.40 (m, 2 H), 3.83 (m, 2 H), 3.80 (s, 3 H), 3.00 (m, 2 H). MS calculated for C₁₄H₁₄F₃NO₂+H: 285, observed: 285.

N-Trifluoroacetyl-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0094] A solution of N-trifluoroacetyl-7-methoxy-1-methylene-2,3,4,5-tetrahydro-1H-3-benzazepine (6.6 g, 23.2 mmol) in ethanol (100 mL), was treated with 10% Pd/C (0.75 g, 2.3 mmol) and stirred overnight under an atmosphere of hydrogen. The product mixture was filtered through a pad of celite and silica and the solvent removed to give 6.27 g of a white solid. ¹H NMR (400 MHz, CDCl₃, mixture of rotamers) δ 7.10 (m, 1 H), 6.74 (m, 1 H), 6.68 (m, 1 H), 4.1-3.8 (bm, 2 H), 3.8 (s, 3H), 3.5 (m, 1.5 H), 3.4 (m, 0.5 H), 3.2-2.9 (bm, 4 H), 1.32 (m, 3 H). MS calculated for C₁₄H₁₆F₃NO₂+H: 288, observed: 288.

N-Trifluoroacetyl-8-bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

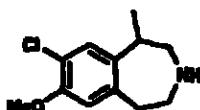
[0095] A solution of N-trifluoroacetyl-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (1.25 g, 4.35 mmol) in acetonitrile (40 mL) was treated with N-bromosuccinimide (0.852 g, 4.79 mmol) and stirred overnight at 20°C. The product mixture was diluted with EtOAc (200 mL), washed with saturated aqueous sodium bisulfite (100 mL) and brine (100 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (15% EtOAc in hexane, silica) resulted in 1.55 g of a clear oil. ¹H NMR (400 MHz, CDCl₃, mixture of rotamers) δ 7.34 (s, 1 H), 6.65 (m, 1 H), 3.87 (s, 3 H), 3.81 (m, 1 H), 3.55 (m, 1.3 H), 3.37 (m, 0.7 H), 3.2-2.9 (bm, 4 H), 1.30 (m, 3 H). MS calculated for C₁₄H₁₆BrF₃NO₂+H: 388, observed: 388.

8-Bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0096] A solution of N-trifluoroacetyl-8-bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.85 g, 2.59 mmol) in methanol (20 mL) was treated with 15% aqueous NaOH (25 mL), and stirred overnight at 20°C. The product mixture was diluted with water (100 mL), extracted twice with EtOAc (100 mL), the combined organic phases were washed with brine (100 mL), dried with Na₂SO₄ and concentrated to give 0.687 g of a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.92 (s, 1 H), 6.34 (s, 1 H), 3.87 (s, 3 H), 3.1-2.9 (m, 6 H), 2.75 (m, 1 H), 2.60 (bs, 1 H), 1.31 (d, J=7 Hz, 3 H). MS calculated for C₁₂H₁₆BrNO+H: 270, observed: 270.

Example 2: (R,S) 8-Chloro-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0097]

*N-Trifluoroacetyl-8-chloro-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine*

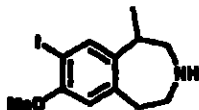
[0098] A solution of N-trifluoroacetyl-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.900 g, 2.67 mmol) in acetonitrile (30 mL) was treated with N-chlorosuccinimide (0.357 g, 2.67 mmol) and stirred overnight at 70°C. The product mixture was diluted with water (100 mL), extracted twice with EtOAc (100 mL), the combined organic phases washed with brine (100 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (20% EtOAc in hexane, silica) resulted in 0.399 g of a clear oil. ¹H NMR (400 MHz, CDCl₃, mixture of rotamers) δ 7.17 (s, 1 H), 6.68 (m, 1 H), 3.88 (s, 3 H), 3.78 (m, 1 H), 3.6-3.3 (m, 2 H), 3.2-2.9 (m, 4 H), 1.34 (m, 3 H). MS calculated for C₁₄H₁₅ClF₃NO₂+H: 322, observed: 322.

8-Chloro-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0099] A solution of N-trifluoroacetyl-8-chloro-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.399 g, 1.24 mmol) in methanol (20 mL) was treated with 15% aqueous NaOH (20 mL), and stirred overnight at 20°C. The product mixture was diluted with water (100 mL), extracted twice with EtOAc (100 mL), the combined organic phases were washed with brine (100 mL), dried with Na₂SO₄ and concentrated to give 0.308 g of a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.05 (s, 1 H), 6.59 (s, 1 H), 3.80 (s, 3 H), 3.0-2.8 (m, 6 H), 2.62 (m, 1 H), 2.16 (bs, 1 H), 1.24 (d, J=7 Hz, 3 H). MS calculated for C₁₂H₁₆ClNO+H: 226, observed: 226.

Example 3: (R,S) 8-Iodo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0100]

**N-Trifluoroacetyl-8-iodo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine**

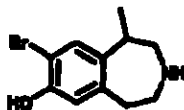
[0101] A solution of N-trifluoroacetyl-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (1.50 g, 5.22 mmol) in methanol (70 mL) was treated with CaCO₃ (1.08 g, 10.44 mmol) followed by a solution of ICl (1.70 g, 10.44 mmol) in methanol (10 mL), and stirred overnight at 20°C. The product mixture was filtered, concentrated, dissolved in EtOAc (200 mL), extracted twice with 5% aqueous sodium bisulfite (100 mL), once with brine (100 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (15% EtOAc in hexane, silica) resulted in 1.54 g of a white solid. ¹H NMR (400 MHz, CDCl₃, mixture of rotamers) δ 7.55 (m, 1 H), 6.57 (m, 1 H), 3.86 (s, 3 H), 3.80 (m, 1 H), 3.60-3.30 (m, 2 H), 3.20-2.80 (m, 4 H), 1.30 (m, 3 H). MS calculated for C₁₄H₁₆F₃INO₂+H: 414, observed: 414.

8-Iodo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0102] A solution of N-trifluoroacetyl-8-iodo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.800 g, 1.45 mmol) in methanol (20 mL) was treated with 15% aqueous NaOH (20 mL), and stirred for 3 hours at 50°C. The product mixture was diluted with water (100 mL), extracted twice with EtOAc (100 mL), the combined organic phases were washed with brine (100 mL), dried with Na₂SO₄ and concentrated to give 0.425 g of a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (s, 1 H), 6.57 (s, 1 H), 3.86 (s, 3 H), 3.12-3.06 (m, 4 H), 2.95 (m, 2 H), 2.75 (m, 1 H), 2.43 (bs, 1 H), 1.33 (d, J=6 Hz, 3 H). MS calculated for C₁₂H₁₆INO+H: 318, observed: 318.

Example 4: (R,S) 8-Bromo-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0103]

**N-Trifluoroacetyl-8-bromo-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine**

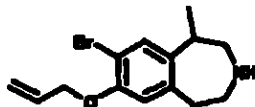
[0104] A solution of N-trifluoroacetyl-8-bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (1.50 g, 4.10 mmol) in dichloromethane (80 mL) was treated dropwise with BBr₃ (9.4 mL of a 1.0M solution in CH₂Cl₂, 9.4 mmol), and the mixture stirred overnight while warming to 20°C. The excess BBr₃ was quenched with the dropwise addition of water, the mixture diluted with ether (200 mL), washed with Na₂CO₃ (100 mL) and brine (100 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (15% EtOAc in hexane, silica) resulted in 1.25 g of a white solid foam. ¹H NMR (400 MHz, CDCl₃, mixture of rotamers) δ 7.25 (s, 1 H), 6.79 (m, 1 H), 3.78 (m, 1 H), 3.7-3.3 (m, 2 H), 3.2-2.8 (m, 4 H), 1.32 (m, 3 H).

8-Bromo-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0105] A solution of *N*-trifluoroacetyl-8-bromo-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.855 g, 1.89 mmol) in methanol (20 mL) was treated with 15% aqueous NaOH (20 mL), and stirred overnight at 20°C. The product mixture was diluted with water (100 mL), extracted twice with EtOAc (100 mL), the combined organic phases were washed with brine (100 mL), dried with Na₂SO₄ and concentrated to give 0.480 g of a clear oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.11 (s, 1 H), 6.85 (s, 1 H), 2.80 (m, 1 H), 2.73 (m, 5 H), 2.55 (m, 1 H), 1.19 (d, J=7 Hz, 3 H). MS calculated for C₁₁H₁₄BrNO+H: 256, observed: 256.

Example 5: (R,S) 7-Allyloxy-8-bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0106]

***N*-Trifluoroacetyl-7-allyloxy-8-bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine**

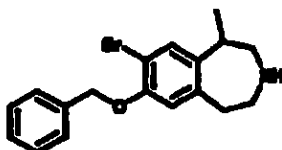
[0107] A solution of *N*-trifluoroacetyl-8-bromo-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.150 g, 0.426 mmol) in dichloromethane (5 mL) was treated with allyl bromide (0.166 g, 1.28 mmol) and DBU (0.195 g, 1.28 mmol) and then stirred 2 hours at 20°C. The product mixture was diluted with EtOAc (50 mL), washed with 5% aqueous HCl (20 mL), brine (20 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (15% EtOAc in hexane, silica) resulted in 0.149 g of a clear oil. ¹H NMR (400 MHz, CDCl₃, mixture of rotamers) δ 7.34 (s, 1 H), 6.85 (m, 1 H), 6.04 (m, 1 H), 5.47 (d, J=17 Hz, 1 H), 5.30 (d, J=9 Hz, 1 H), 4.59 (s, 2 H), 3.80 (m, 1 H), 3.8-3.3 (m, 3 H), 3.2-2.8 (m, 4 H), 1.31 (m, 3 H). MS calculated for C₁₈H₁₇BrF₃NO₂+H: 392, observed: 392.

7-Allyloxy-8-bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0108] A solution of *N*-trifluoroacetyl-7-allyloxy-8-bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (1.18 g, 3.00 mmol) in methanol (35 mL) was treated with 15% aqueous NaOH (35 mL), and stirred overnight at 20°C. The product mixture was diluted with water (200 mL), extracted twice with EtOAc (200 mL), the combined organic phases were washed with brine (100 mL), dried with Na₂SO₄ and concentrated to give 0.880 g of a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.29 (s, 1 H), 6.83 (s, 1 H), 6.04 (m, 1 H), 5.47 (d, J=17 Hz, 1 H), 5.29 (d, J=11 Hz, 1 H), 4.58 (s, 2 H), 3.01 (m, 3 H), 2.89 (m, 3 H), 2.75 (m, 1 H), 1.31 (d, J=7 Hz, 3 H). MS calculated for C₁₄H₁₈BrNO+H: 298, observed: 298.

Example 6: (R,S) 7-Benzoyloxy-8-bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0109]

***N*-Trifluoroacetyl-7-benzoyloxy-8-bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine**

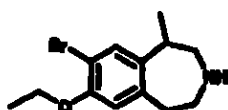
[0110] A solution of *N*-trifluoroacetyl-8-bromo-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.075 g, 0.213 mmol) in dichloromethane (5 mL) was treated with benzyl bromide (0.072 g, 0.84 mmol), DBU (0.100 g, 0.84 mmol), and stirred 2 hours at 20°C. The product mixture was diluted with EtOAc (50 mL), washed with 5% aqueous HCl (20 mL), brine (20 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (15% EtOAc in hexane, silica) resulted in 0.081 g of a clear oil. MS calculated for C₂₀H₁₉BrF₃NO₂+H: 442, observed: 442.

7-Benzoyloxy-8-bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0111] A solution of N-trifluoroacetyl-7-benzoyloxy-8-bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.81 g, 1.83 mmol) in methanol (20 mL) was treated with 15% aqueous NaOH (20 mL), and stirred overnight at 20°C. The product mixture was diluted with water (200 mL), extracted twice with EtOAc (200 mL), the combined organic phases were washed with brine (100 mL), dried with Na₂SO₄ and concentrated to give 0.412 g of a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, J=8 Hz, 2 H), 7.30 (dd, J=7, 8 Hz, 2 H), 7.23 (m, 2 H), 6.61 (s, 1 H), 5.03 (s, 2 H), 2.94 (m, 3 H), 2.81 (m, 3 H), 2.62 (m, 1 H), 2.30 (bs, 1 H), 1.24 (d, J=7 Hz, 3 H). MS calculated for C₁₈H₂₀BrNO₂+H: 346, observed: 346.

Example 7: (R,S) 8-Bromo-7-ethoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0112]

**N-Trifluoroacetyl-8-bromo-7-ethoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine**

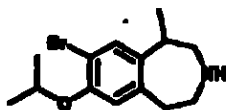
[0113] A solution of N-trifluoroacetyl-8-bromo-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.015 g, 0.043 mmol) in dichloromethane (1 mL) was treated with ethyl iodide (0.016 g, 0.102 mmol), DBU (0.016 g, 0.102 mmol) and stirred 2 hours at 20°C. The product mixture was diluted with EtOAc (10 mL), washed with 5% aqueous HCl (5 mL), brine (5 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (15% EtOAc in hexane, silica) resulted in 0.010 g of a clear oil.

8-Bromo-7-ethoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0114] A solution of N-trifluoroacetyl-8-bromo-7-ethoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.010 g, 0.028 mmol) in methanol (1 mL) was treated with 15% aqueous NaOH (1 mL), and stirred overnight at 20°C. The product mixture was diluted with water (3 mL), extracted twice with EtOAc (5 mL), the combined organic phases were washed with brine (3 mL), dried with Na₂SO₄ and concentrated to give 0.007 g of a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.29 (s, 1 H), 6.63 (s, 1 H), 4.07 (q, J=6 Hz, 2 H), 3.03 (m, 3 H), 2.91 (m, 3 H), 2.73 (m, 1 H), 2.26 (bs, 1 H), 1.46 (t, J=6 Hz, 3 H), 1.32 (d, J=7 Hz, 3 H). MS calculated for C₁₈H₁₇BrF₃NO₂+H: 380, observed: 380.

Example 8: (R,S) 8-Bromo-7-isopropoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0115]

**N-Trifluoroacetyl-8-bromo-7-isopropoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine**

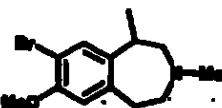
[0116] A solution of N-trifluoroacetyl-8-bromo-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.035 g, 0.099 mmol) in dichloromethane (1 mL) was treated with isopropyl bromide (0.037 g, 0.287 mmol), DBU (0.048 g, 0.205 mmol) and stirred 2 hours at 20°C. The product mixture was diluted with EtOAc (10 mL), washed with 5% aqueous HCl (5 mL), brine (5 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (15% EtOAc in hexane, silica) resulted in 0.014 g of a clear oil. MS calculated for C₁₉H₁₉BrF₃NO₂+H: 394, observed: 394.

8-Bromo-7-isopropoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0117] A solution of N-trifluoroacetyl-8-bromo-7-isopropoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.014 g, 0.035 mmol) in methanol (1 mL) was treated with 15% aqueous NaOH (1 mL), and stirred overnight at 20°C. The product mixture was diluted with water (3 mL), extracted twice with EtOAc (5 mL), the combined organic phases were washed with brine (3 mL), dried with Na₂SO₄ and concentrated to give 0.008 g of a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.24 (s, 1 H), 6.84 (s, 1 H), 4.48 (m, 1 H), 2.98 (m, 3 H), 2.87 (m, 3 H), 1.36 (m, 6 H), 1.30 (d, J=7 Hz, 3 H). MS calculated for C₁₄H₂₀BrNO+H: 298, observed: 298.

Example 9: (R,S) N-Methyl-8-bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

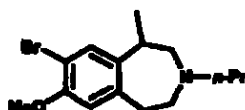
[0118]



[0119] A solution of 8-Bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (8 mg, .022 mmol) in methanol (1 mL) was treated with excess paraformaldehyde, 1.0 M HCl in ether (0.004 mL, 0.004 mmol), NaBH₃CN (1.0 mg, 0.013 mmol), and stirred overnight at 20°C. The product mixture was diluted with 5% aqueous NaOH (5 mL), extracted 3 times with CH₂Cl₂ (5 mL each), the combined organic phases were dried with Na₂SO₄ and concentrated. Flash chromatography (10% MeOH in CH₂Cl₂, silica) resulted in 5 mg of a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.31 (s, 1 H), 6.86 (s, 1 H), 3.87 (s, 3 H), 3.26 (bm, 2 H), 3.01 (bs, 1 H), 2.85 (m, 2 H), 2.45 (s, 3 H), 2.45-2.25 (m, 2 H), 1.36 (d, J=7 Hz, 3 H). MS calculated for C₁₃H₁₈BrNO+H: 284, observed: 284.

Example 10: (R,S) N-Propyl-8-bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

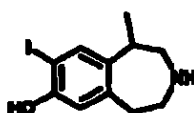
[0120]



[0121] A solution of 8-Bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-3H-3-benzazepine (8 mg, 0.022 mmol) in methanol (1 mL) was treated with propionaldehyde (5.0 mg, 0.067 mmol), 1.0 M HCl in ether (0.004 mL, 0.004 mmol), NaBH₃CN (1.0 mg, 0.013 mmol), and stirred overnight at 20°C. The product mixture was diluted with 5% aqueous NaOH (5 mL), extracted 3 times with CH₂Cl₂ (5 mL each), the combined organic phases were dried with Na₂SO₄ and concentrated. Flash chromatography (10% MeOH in CH₂Cl₂, silica) resulted in 4 mg of a clear oil. ¹H NMR (400 MHz, CD₃OD) δ 7.33 (s, 1 H), 6.87 (s, 1 H), 3.84 (s, 3 H), 3.25 (m, 2 H), 3.11 (m, 2 H), 2.97 (m, 1 H), 2.78 (bm, 2 H), 2.63 (bm, 2 H), 1.67 (m, 2 H), 1.38 (d, J=7 Hz, 3 H), 0.96 (t, J=7 Hz, 3 H). MS calculated for C₁₈H₂₂BrNO+H: 312, observed: 312.

Example 11: (R,S) 7-Hydroxy-8-iodo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0122]



EP 1 411 881 B1

N-Trifluoroacetyl-7-hydroxy-8-iodo-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine

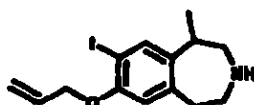
[0123] A solution of *N*-trifluoroacetyl-8-iodo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (80 mg, 0.18 mmol) in dichloromethane (3 mL) was treated with BBr₃ (0.40 mL of a 1.0M solution in CH₂Cl₂, 0.40 mmol) and stirred overnight at 20°C. The excess BBr₃ was quenched with water and the product mixture was diluted with ether (20 mL), washed with Na₂CO₃ (10 mL) and brine (10 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (15% EtOAc in hexane, silica) resulted in 74 mg of a white solid. MS calculated for C₁₃H₁₃F₃INO₂+H: 400, observed: 400.

7-Hydroxy-8-iodo-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine

[0124] A solution of *N*-trifluoroacetyl-7-hydroxy-8-iodo-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (25 mg, 0.083 mmol) in methanol (2 mL) was treated with 15% aqueous NaOH (2 mL), and stirred overnight at 20°C. The product mixture was diluted with water (5 mL), extracted twice with EtOAc (5 mL), the combined organic phases were washed with brine (5 mL), dried with Na₂SO₄ and concentrated to give 13 mg of a white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.46 (s, 1 H), 6.64 (s, 1 H), 3.16 (m, 3 H), 2.94 (m, 3 H), 2.81 (m, 1 H), 1.35 (d, J=7 Hz, 3 H). MS calculated for C₁₁H₁₄INO+H: 304, observed: 304.

Example 12: (R,S) 7-Allyloxy-8-iodo-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine

[0125]

*N*-Trifluoroacetyl-7-allyloxy-8-iodo-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine

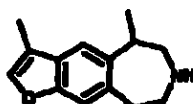
[0126] A solution of *N*-trifluoroacetyl-7-hydroxy-8-iodo-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (30 mg, 0.075 mmol) in dichloromethane (2 mL) was treated with allyl bromide (18 mg, 0.15 mmol), DBU (23 mg, 0.15 mmol) and stirred 2 hours at 20°C. The product mixture was diluted with EtOAc (10 mL), washed with 5% aqueous HCl (5 mL), brine (5 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (15% EtOAc in hexane, silica) resulted in 23 mg of a clear oil. MS calculated for C₁₆H₁₇F₃INO₂+H: 440, observed: 440.

7-Allyloxy-8-iodo-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine

[0127] A solution of *N*-trifluoroacetyl-7-allyloxy-8-iodo-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (23 mg, 0.056 mmol) in methanol (2 mL) was treated with 5% aqueous NaOH (2 mL), and stirred overnight at 20°C. The product mixture was diluted with water (5 mL), extracted twice with EtOAc (5 mL), the combined organic phases were washed with brine (5 mL), dried with Na₂SO₄ and concentrated to give 18 mg of a white solid. MS calculated for C₁₄H₁₈INO+H: 344, observed: 344.

Example 13: (R,S) 3,5-Dimethyl-6,7,8,9-tetrahydro-5*H*-1-oxa-7-aza-cyclohepta[1*b*]indene

[0128]

*N*-trifluoroacetyl-3,5-dimethyl-6,7,8,9-tetrahydro-5*H*-1-oxa-7-aza-cyclohepta[1*b*]indene

[0129] A solution of *N*-trifluoroacetyl-7-allyloxy-8-iodo-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (158 mg, 0.360 mmol) in dimethylformamide (4 mL) was treated with KOAc (106 mg, 1.08 mmol), *n*-Bu₄NBr (116 mg, 0.360 mmol), PPh₃ (13 mg, 0.036 mmol), Pd(OAc)₂ (4 mg, 0.018 mmol) and stirred overnight at 100°C. The product mixture

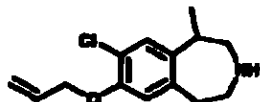
was filtered, water (10 mL) added and then extracted twice with EtOAc (10 mL). The combined organic phases were washed with brine (10 mL), dried with Na_2SO_4 and concentrated. Flash chromatography (5% EtOAc in hexane, silica) resulted in 15 mg of a clear oil. MS calculated for $\text{C}_{18}\text{H}_{18}\text{F}_3\text{NO}_2+\text{H}$: 312, observed: 312.

3,5-Dimethyl-6,7,8-tetrahydro-5H-1-oxa-7-aza-cycloheptalindene

[0130] A solution of N-trifluoroacetyl-3,5-dimethyl-6,7,8-tetrahydro-5H-1-oxa-7-aza-cycloheptalindene (15 mg, 0.048 mmol) in methanol (2 mL) was treated with 15% aqueous NaOH (2 mL), and stirred overnight at 20°C. The product mixture was diluted with water (5 mL), extracted twice with EtOAc (5 mL), the combined organic phases were washed with brine (5 mL), dried with Na_2SO_4 and concentrated to give 10 mg of a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.25 (s, 1 H), 7.12 (s, 1 H), 7.09 (s, 1 H), 3.12 (m, 1 H), 2.97 (m, 4 H), 2.85 (m, 1 H), 2.64 (bm, 1 H), 2.15 (s, 3 H), 1.34 (d, $J=8$ Hz, 3 H). MS calculated for $\text{C}_{14}\text{H}_{17}\text{NO}+\text{H}$: 216, observed: 216.

Example 14: (R,S) 7-Allyloxy-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0131]



N-Trifluoroacetyl-8-chloro-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0132] A solution of N-trifluoroacetyl-8-chloro-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (48 mg, 0.15 mmol) in dichloromethane (2 mL) was treated with BBr_3 (0.30 mL of a 1.0M solution in CH_2Cl_2 , 0.30 mmol) and stirred overnight at 20°C. The excess BBr_3 was quenched with water and the resulting mixture diluted with ether (20 mL), washed with Na_2CO_3 (10 mL) and brine (10 mL), dried with Na_2SO_4 and concentrated. Flash chromatography (15% EtOAc in hexane, silica) resulted in 24 mg of a white solid. MS calculated for $\text{C}_{13}\text{H}_{13}\text{ClF}_3\text{NO}_2+\text{H}$: 308, observed: 308.

N-Trifluoroacetyl-7-allyloxy-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

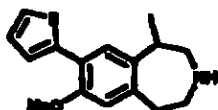
[0133] A solution of N-trifluoroacetyl-8-chloro-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (24 mg, 0.078 mmol) in dichloromethane (2 mL) was treated with allyl bromide (18 mg, 0.15 mmol), DBU (23 mg, 0.15 mmol) and stirred 2 hours at 20°C. The product mixture was diluted with EtOAc (10 mL), washed with 5% aqueous HCl (5 mL), brine (5 mL), dried with Na_2SO_4 and concentrated. Flash chromatography (15% EtOAc in hexane, silica) resulted in 23 mg of a white solid. MS calculated for $\text{C}_{18}\text{H}_{17}\text{ClF}_3\text{NO}_2+\text{H}$: 348, observed: 348.

7-Allyloxy-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0134] A solution of N-trifluoroacetyl-7-allyloxy-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (23 mg, 0.066 mmol) in methanol (2 mL) was treated with 15% aqueous NaOH (2 mL), and stirred overnight at 20°C. The product mixture was diluted with water (5 mL), extracted twice with EtOAc (5 mL), the combined organic phases were washed with brine (5 mL), dried with Na_2SO_4 and concentrated to give 19 mg of a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.12 (s, 1 H), 6.81 (s, 1 H), 6.03 (m, 1 H), 5.43 (d, $J=17$ Hz, 1 H), 5.24 (d, $J=10$ Hz, 1 H), 4.57 (d, $J=5$ Hz, 2 H), 3.1-2.9 (m, 5 H), 2.81 (m, 1 H), 2.63 (m, 1 H), 1.30 (d, $J=7$ Hz, 3 H).

Example 15: (R,S) 7-Methoxy-1-methyl-8-(2-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine

[0135]



N-Trifluoroacetyl-7-methoxy-1-methyl-8-(2-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine

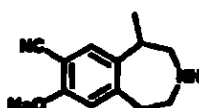
[0136] A solution of N-trifluoroacetyl-8-bromo-7-methoxy-1-methyl-1,2,4,5-tetrahydro-3H-3-benzazepine (51 mg, 0.14 mmol) in 1,4-dioxane (2 mL) was treated with thiophene-2-boronic acid (36 mg, 0.28 mmol), K_2CO_3 (58 mg, 0.42 mmol), water (0.1 mL), $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and stirred overnight at 100°C. The product mixture was diluted with EtOAc, filtered, absorbed on silica and purified by flash chromatography (10% EtOAc in hexane, silica) resulting in 28 mg of a yellow solid. MS calculated for $C_{18}H_{18}F_3NO_2S+H$: 370, observed: 370.

7-Methoxy-1-methyl-8-(2-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine

[0137] A solution of N-trifluoroacetyl-7-methoxy-1-methyl-8-(2-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (28 mg, 0.076 mmol) in methanol (2 mL) was treated with 15% aqueous NaOH (2 mL), and stirred 0.5 hours at 50°C. The product mixture was diluted with water (5 mL), extracted twice with EtOAc (5 mL), the combined organic phases were washed with brine (5 mL), dried with Na_2SO_4 and concentrated to give 18 mg of a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, $J=4$ Hz, 1 H), 7.39 (s, 1 H), 7.27 (d, $J=8$ Hz, 1 H), 7.07 (dd, $J=4, 8$ Hz, 1 H), 6.71 (s, 1 H), 3.90 (s, 3 H), 3.1-2.9 (m, 6 H), 2.80 (m, 1 H), 2.22 (bs, 1 H), 1.38 (d, $J=7$ Hz, 3 H). MS calculated for $C_{18}H_{19}NO_2S+H$: 274, observed: 274.

(Comparative) Example 16: (R,S) 8-Cyano-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0138]

*N-Trifluoroacetyl-8-cyano-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine*

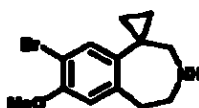
[0139] A solution of N-trifluoroacetyl-8-bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (18 mg, 0.05 mmol) in dimethylformamide (1 mL) was treated with CuCN (20 mg, 0.24 mmol) and the mixture was microwaved at 200°C for 0.5 hours. The product mixture was diluted with water (5 mL), extracted twice with EtOAc (5 mL), the combined organic phases were washed with brine (5 mL), dried with Na_2SO_4 and concentrated. Flash chromatography (35% EtOAc in hexane, silica) resulted in 10 mg of a clear oil. MS calculated for $C_{15}H_{15}F_3N_2O_2+H$: 313, observed: 313.

8-Cyano-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0140] A solution of N-trifluoroacetyl-8-cyano-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (10 mg, 0.032 mmol) in methanol (2 mL) was treated with 15% aqueous NaOH (2 mL), and stirred 1 hour at 50°C. The product mixture was diluted with water (5 mL), extracted twice with EtOAc (5 mL), the combined organic phases were washed with brine (5 mL), dried with Na_2SO_4 and concentrated to give 6.0 mg of a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.33 (s, 1 H), 6.93 (s, 1 H), 3.91 (s, 3 H), 3.18-2.97 (m, 5 H), 2.80 (m, 1 H), 2.60 (m, 1 H), 1.33 (d, $J=8$ Hz, 3 H). MS calculated for $C_{13}H_{15}N_2O+H$: 217, observed: 217.

Example 17: (R,S) 8-bromo-1-cyclopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

[0141]

*N-Trifluoroacetyl-1-cyclopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine*

[0142] A solution of diethyl zinc (1 mL, 1 M in hexanes) in dichloromethane (1 mL) at 0°C was treated with trifluor-

acetic acid in dichloromethane (0.5 mL) and the mixture stirred for 15 min. Diiodomethane (0.280 g, 1.0 mmol) in dichloromethane (0.5 mL) was then added and stirred for 15 minutes. N-Trifluoroacetyl-7-methoxy-1-methylene-2,3,4,5-tetrahydro-1H-3-benzazepine (0.075 g, 0.28 mmol) in dichloromethane (1 mL) was added and the mixture stirred for 30 minutes at 0°C and then for 2 hours at 20°C. The product mixture was quenched with aqueous saturated NH_4Cl (5 mL), extracted twice with CH_2Cl_2 (20 mL), washed with saturated aqueous NaHCO_3 (10 mL), washed with H_2O (10 mL), and concentrated. Flash chromatography (7% EtOAc in hexanes, silica) resulted in 0.050 g of a white solid. MS calculated for $\text{C}_{15}\text{H}_{16}\text{F}_3\text{NO}_2+\text{H}$: 300, observed: 300.

N-Trifluoroacetyl-8-bromo-1-cyclopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

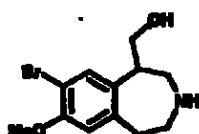
[0143] A solution of N-trifluoroacetyl-1-cyclopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (0.025 g, 0.08 mmol) in acetonitrile (1 mL) was treated with N-bromosuccinimide (0.032 g, 0.18 mmol) and stirred for 2 hrs. at 50°C. The product mixture was concentrated and then purified by flash chromatography (10% EtOAc in hexanes, silica) resulting in 0.014 g of a white solid. MS calculated for $\text{C}_{16}\text{H}_{15}\text{BrF}_3\text{NO}_2+\text{H}$: 378, observed: 378.

8-bromo-1-cyclopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

[0144] A solution of N-trifluoroacetyl-8-bromo-1-cyclopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (0.014 g, 0.037 mmol) in methanol (1 mL) was treated with 15% aqueous NaOH (1 mL), and stirred for 2 hours at 50°C. The product mixture was diluted with brine (10 mL), extracted twice with EtOAc (10 mL), dried with MgSO_4 , and concentrated to give 0.008 g of a clear oil. ^1H NMR (400 MHz, CD_3OD) δ 7.28 (s, 1 H), 6.78 (s, 1 H), 3.83 (s, 3 H), 3.02 (m, 2 H), 2.92 (m, 2 H), 2.67 (s, 2 H), 0.91 (m, 2 H), 0.85 (m, 2 H). MS calculated for $\text{C}_{13}\text{H}_{16}\text{BrNO}+\text{H}$: 282, observed: 282.

Example 18: (R,S) 8-bromo-1-hydroxymethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

[0145]



N-Trifluoroacetyl-1-hydroxymethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

[0146] A solution of N-trifluoroacetyl-7-methoxy-1-methylene-2,3,4,5-tetrahydro-1H-3-benzazepine (0.100 g, 0.35 mmol) in tetrahydrofuran (1 mL) was treated with BH_3 -THF complex (0.38 mL, 1 M in THF), and stirred for 30 min. at 20°C. Water (0.5 mL), saturated aqueous NaHCO_3 (0.5 mL), and 30% H_2O_2 (0.2 mL) were added sequentially and the reaction stirred for 30 min. at 20°C. The product mixture was diluted with EtOAc (10 mL), washed with brine (10 mL), and concentrated. Flash chromatography (33% EtOAc in hexane, silica) resulted in 0.035 g of a clear oil. MS calculated for $\text{C}_{14}\text{H}_{16}\text{F}_3\text{NO}_3+\text{H}$: 304, observed: 304.

N-Trifluoroacetyl-8-bromo-1-hydroxymethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

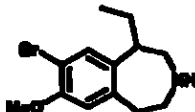
[0147] A solution of N-trifluoromethylacetyl-1-hydroxymethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (0.035 g, 0.12 mmol) in acetonitrile (1 mL) was treated with N-bromosuccinimide (0.025 g, 0.14 mmol), and stirred for 30 min. at 20°C. The product mixture was concentrated and then purified by flash chromatography (33% EtOAc in hexane, silica) resulting in 0.019 g clear oil. MS calculated for $\text{C}_{14}\text{H}_{16}\text{BrF}_3\text{NO}_3+\text{H}$: 382, observed: 382.

8-bromo-1-hydroxymethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

[0148] A solution of N-trifluoroacetyl-8-bromo-1-hydroxymethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (0.009 g, 0.024 mmol) in methanol (1 mL) was treated with 15% aqueous NaOH (1 mL), and stirred for 1 hour at 50°C. The product mixture was diluted with brine (5 mL), extracted twice with EtOAc (5 mL), dried with MgSO_4 , and concentrated to give 0.006 g clear oil. ^1H NMR (400 MHz, CD_3OD) δ 7.28 (s, 1 H), 6.79 (s, 1 H), 3.84 (m, 2 H), 3.0-2.8 (m, 7 H). MS calculated for $\text{C}_{12}\text{H}_{16}\text{BrNO}_2+\text{H}$: 286, observed: 286.

Example 19: (R,S) 8-Bromo-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

[0149]

*N-Crotyl, N-trifluoroacetyl-2-iodo-5-methoxyphenethylamine*

[0150] A solution of N-trifluoroacetyl-2-iodo-5-methoxyphenethylamine (8.88 g, 17.9 mmol) in toluene (100 mL) was treated with K_2CO_3 (3.22 g, 23.3 mmol), KOH (3.01 g, 53.7 mmol), $n-Bu_4NBr$ (0.580 g, 1.80 mmol) and crotyl bromide (3.15 g, 23.3 mmol). The mixture was stirred at 75°C for 18 hours, cooled to 20°C, diluted with Et_2O (500 mL), washed with 10% aqueous HCl (500 mL) and concentrated. Flash chromatography (10% EtOAc in hexane, silica) resulted in 5.22 g of a clear oil. MS calculated for $C_{15}H_{17}F_3INO_2+H$: 428, observed: 428.

N-Trifluoroacetyl-1-ethylene-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

[0151] A solution of N-crotyl, N-trifluoroacetyl-2-iodo-5-methoxyphenethylamine (5.20 g, 12.2 mmol) in dimethylformamide (80 mL) was treated with KOAc (3.59 g, 38.8 mmol), $n-Bu_4NBr$ (3.93 g, 12.2 mmol), PPh_3 (0.320 g, 1.22 mmol), $Pd(OAc)_2$ (0.137 g, 0.61 mmol) and stirred overnight at 90°C. The product mixture was cooled to 20°C, diluted with water (200 mL), extracted twice with ether (500 mL), the combined organic phases washed twice with brine (200 mL), and concentrated. Flash chromatography (10% EtOAc in hexane, silica) resulted in 2.29 g of a clear oil, which consists of a mixture of olefinic isomers. MS calculated for $C_{15}H_{16}F_3NO_2+H$: 300, observed: 300.

N-Trifluoroacetyl-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

[0152] A solution of N-trifluoroacetyl-1-ethylene-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (2.29 g, 7.85 mmol) in methanol (100 mL) was treated with 10% Pd/C (4.0 g, 0.77 mmol) and stirred overnight under an atmosphere of hydrogen. The product mixture was filtered through a pad of celite and silica, and the solvent removed to give 2.14 g of a clear oil. MS calculated for $C_{16}H_{18}F_3NO_2+H$: 302, observed: 302.

N-Trifluoroacetyl-8-bromo-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

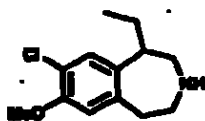
[0153] A solution of N-trifluoroacetyl-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (0.710 g, 2.36 mmol) in acetonitrile (20 mL) was treated with N-bromosuccinimide (0.504 g, 2.83 mmol), and stirred overnight at 20°C. The product mixture was concentrated, diluted with EtOAc (100 mL), washed with water (50 mL) and brine (50 mL), dried with Na_2SO_4 and concentrated. Flash chromatography (10% EtOAc in hexanes, silica) resulted in 0.581 g of a clear oil. MS calculated for $C_{15}H_{17}BrF_3NO_2+H$: 380, observed: 380.

8-Bromo-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

[0154] A solution of N-trifluoroacetyl-8-bromo-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (0.581 g, 1.48 mmol) in methanol (30 mL) was treated with 15% aqueous NaOH (30 mL), and stirred overnight at 20°C. The product mixture was diluted with brine (100 mL), extracted twice with EtOAc (200 mL), dried with $MgSO_4$, and concentrated to give 0.412 g of a clear oil. ^1H NMR (400 MHz, CD_3OD) δ 7.24 (s, 1 H), 6.78 (s, 1 H), 3.83 (s, 3 H), 3.02 (m, 3 H), 2.91 (s, 1 H), 2.85-2.76 (m, 3 H), 2.63 (m, 1 H), 1.78 (m, 1 H), 1.72 (m, 1 H), 0.94 (dd, $J=8, 6$ Hz, 3 H). MS calculated for $C_{13}H_{16}BrNO+H$: 284, observed: 284.

Example 20: (R,S) 8-Chloro-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

[0155]

***N*-Trifluoroacetyl-8-chloro-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine**

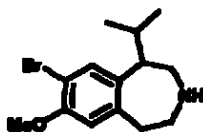
[0156] A solution of *N*-trifluoroacetyl-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (0.600 g, 1.99 mmol) in acetonitrile (20 mL) was treated with *N*-chlorosuccinimide (0.057 g, 0.32 mmol), and stirred overnight at 60°C. The product mixture was concentrated, diluted with EtOAc (100 mL), washed with water (50 mL) and brine (50 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (10% EtOAc in hexanes, silica) resulted in 0.421 g of a clear oil. MS calculated for C₁₅H₁₇ClF₃NO₂+H: 338, observed: 338.

***8*-Chloro-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine**

[0157] A solution of *N*-trifluoroacetyl-8-chloro-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (0.421 g, 1.25 mmol) in methanol (30 mL) was treated with 15% aqueous NaOH (30 mL), and stirred overnight at 20°C. The product mixture was diluted with brine (100 mL), extracted twice with EtOAc (200 mL), dried with MgSO₄, and concentrated to give 0.241 g of a clear oil. ¹H NMR (400 MHz, CD₃OD) δ 7.05 (s, 1 H), 6.79 (s, 1 H), 3.84 (s, 3 H), 3.03 (m, 3 H), 2.91 (s, 1 H), 2.88-2.76 (m, 3 H), 2.84 (m, 1 H), 1.81 (m, 1 H), 1.72 (m, 1 H), 0.93 (dd, J=8, 8 Hz, 3 H). MS calculated for C₁₃H₁₆ClNO+H: 240, observed: 240.

Example 21: (R,S) 8-Bromo-1-isopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

[0158]

***N*-(3-methylbut-2-enyl), *N*-trifluoroacetyl-2-iodo-5-methoxyphenethylamine**

[0159] A solution of *N*-trifluoroacetyl-2-iodo-5-methoxyphenethylamine (0.700 g, 1.68 mmol) in toluene (25 mL) was treated with K₂CO₃ (0.340 g, 2.4 mmol), KOH (0.210 g, 3.76 mmol), *n*-Bu₄NHr (0.060 g, 0.18 mmol) and 4-bromo-2-methyl-2-butene (0.364 g, 2.44 mmol). The mixture was stirred at 80°C for 3 hours, cooled to 20°C, diluted with ether (100 mL), washed with 10% HCl (50 mL) and concentrated. Flash chromatography (10% EtOAc in hexane, silica) resulted in 0.272 g of a clear oil. ¹H NMR (400 MHz, CDCl₃, mixture of rotamers) δ 7.85 (m, 1 H), 6.75 (m, 1 H), 6.54 (m, 1 H), 5.20 (m, 4 H), 5.0 (m, 6 H), 4.10 (m, 1 H), 3.82 (m, 1 H), 3.76 (d, 2H), 3.50 (m, 2 H), 3.02 (m, 2H), 1.75 (m, 3H), 1.66 (m, 3H).

***N*-Trifluoroacetyl-1-isopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine**

[0160] A solution of *N*-(3-methylbut-2-enyl), *N*-trifluoroacetyl-2-iodo-5-methoxyphenethylamine (0.272 g, 0.62 mmol) in dimethylformamide (12 mL) was treated with KOAc (0.183 g, 1.86 mmol), *n*-Bu₄NBr (0.200 g, 0.62 mmol), PPh₃ (0.016g, 0.062 mmol), Pd(OAc)₂ (0.183 g, 1.86 mmol) and stirred overnight at 90°C. The product mixture was cooled to 20°C, diluted with water (50 mL), extracted twice with ether (50 mL), the combined organic phases were washed with brine (50 mL), and concentrated. Flash chromatography (10% EtOAc in hexane, silica) resulted in 0.096 g of a clear oil. MS calculated for C₁₈H₁₈F₃NO₂+H: 314, observed: 314.

N-Trifluoroacetyl-1-isopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

[0161] A solution of N-trifluoroacetyl-1-isopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (0.086 g, 0.31 mmol) in ethanol (2 mL) was treated with 10% Pd/C (0.033 g, .031 mmol) and stirred overnight under an atmosphere of hydrogen. The product mixture was filtered through a pad of celite and silica, and the solvent removed to give 0.091 g of a clear oil. MS calculated for $C_{18}H_{20}F_3NO_2+H$: 318, observed: 318.

N-Trifluoroacetyl-8-bromo-1-isopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

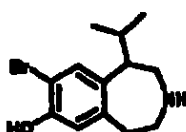
[0162] A solution of N-trifluoroacetyl-1-isopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (0.091 g, 0.29 mmol) in acetonitrile (3 mL) was treated with N-bromosuccinimide (0.057 g, 0.32 mmol), and stirred overnight at 20°C. After removing the solvent, flash chromatography (10% EtOAc in hexanes, silica) resulted in 0.056 g of a clear oil. MS calculated for $C_{18}H_{19}BrF_3NO_2+H$: 394, observed: 394.

8-Bromo-1-isopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

[0163] A solution of N-trifluoroacetyl-8-bromo-1-isopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (0.013 g, 0.03 mmol) in methanol (0.5 mL) was treated with 15% aqueous NaOH (0.5 mL), and stirred overnight at 20°C. The product mixture was diluted with brine (5 mL), extracted twice with EtOAc (5 mL), dried with $MgSO_4$, and concentrated to give 0.10 g of a clear oil. ^1H NMR (400 MHz, CD_3OD) δ 7.08 (s, 1 H), 6.84 (s, 1 H), 3.72 (s, 3 H), 3.2-3.10 (m, 3 H), 2.7-2.5 (m, 3 H), 2.3-2.1 (m, 2 H), 0.98 (d, 3 H), 0.83 (d, 3 H). MS calculated for $C_{14}H_{20}BrNO+H$: 298, observed: 298.

Example 22: (R,S) 8-Bromo-7-hydroxy-1-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0164]

*N-Trifluoroacetyl-8-bromo-7-hydroxy-1-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine*

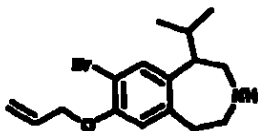
[0165] A solution of N-trifluoroacetyl-8-bromo-1-isopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (0.041 g, 0.10 mmol) in dichloromethane (1 mL) was treated with BBr_3 (0.32 mL, 1.0 M solution in CH_2Cl_2) and stirred overnight at 20°C. The excess BBr_3 is quenched with water and the resulting mixture diluted with ether (50 mL), washed twice with saturated aqueous Na_2CO_3 (20 mL) and concentrated. Flash chromatography (20% EtOAc in hexanes, silica) resulted in 0.037 g clear oil. MS calculated for $C_{15}H_{17}BrF_3NO_2+H$: 380, observed: 380.

8-Bromo-7-hydroxy-1-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0166] A solution of N-trifluoroacetyl-8-bromo-7-hydroxy-1-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.018 g, 0.047 mmol) in methanol (1 mL) was treated with 15% aqueous NaOH (1 mL), and stirred for 3 hours at 50°C. The product mixture was brought to pH 7-8 with 10% aqueous HCl, extracted three times with EtOAc (50 mL), dried with $MgSO_4$, and concentrated to give 0.013 g of a white solid. ^1H NMR (400MHz, CD_3OD) δ 7.10 (s, 1 H), 6.60 (s, 1 H), 3.30 (m, 1H), 3.2-3.0 (m, 2 H), 2.78 (m, 1 H), 2.7-2.5 (m, 2H), 2.3-2.1 (m, 2 H), 1.05 (d, 3 H), 0.73 (d, 3 H). MS calculated for $C_{13}H_{18}BrNO+H$: 284, observed: 284.

Example 23: (R,8) 7-Allyloxy-8-bromo-1-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0167]

***N*-Trifluoroacetyl-7-allyloxy-8-bromo-1-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine**

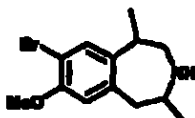
[0168] A solution of *N*-trifluoroacetyl-8-bromo-7-hydroxy-1-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.017 g, 0.045 mmol) in dichloromethane (1 mL) was treated with *N*''-tert-butyl-*N*, *N*, *N*', *N*', *N*'', *N*''-hexamethylphosphorimidic triamide (0.016 g, 0.068 mmol), allyl bromide (0.011 g, 0.09 mmol) and stirred for 3 hours at 20°C. The product mixture was diluted with 10% aqueous HCl, extracted twice with dichloromethane (20 mL), and concentrated. Flash chromatography (10% EtOAc in hexanes, silica) resulted in 0.011 g of a clear oil. MS calculated for C₁₈H₂₁BrF₃NO₂+H: 420, observed: 420.

***7*-Allyloxy-8-bromo-1-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine**

[0169] A solution of *N*-trifluoroacetyl-7-allyloxy-8-bromo-1-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.011 g, 0.026 mmol) in methanol (0.5 mL) was treated with 15% aqueous NaOH (0.5 mL), and stirred for 3 hours at 50°C. The product mixture was diluted with brine (5 mL), extracted twice with EtOAc (5 mL), dried with MgSO₄, and concentrated to give 0.010 g of a clear oil. ¹H NMR (400 MHz, CD₃OD) δ 7.09 (s, 1 H), 6.62 (s, 1 H), 5.94 (m, 1 H), 5.32 (dd, 1 H), 5.12 (dd, 1 H), 4.48 (d, 2 H), 3.19 (m, 1 H), 3.05 (m, 2 H), 2.88 (m, 1 H), 2.5 (bm, 2 H), 2.3-2.1 (m, 2 H), 0.95 (d, 3 H), 0.63 (d, 3 H). MS calculated for C₁₈H₂₂BrNO+H: 324, observed: 324.

Example 24: 8-Bromo-7-methoxy-1,4-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0170]

***N*-Trifluoroacetyl-1-(3-methoxyphenyl)-2-propylamine**

[0171] A solution of 1-(3-methoxyphenyl)-2-propylamine (3.58 g, 21.7 mmol) in dichloromethane (75 mL) at 0°C, was treated with pyridine (2.1 mL, 26.2 mmol), trifluoroacetic anhydride (5.9 g, 26.2 mmol), and then stirred for 3 hours while warming to 20°C. The product mixture was diluted with EtOAc (300 mL), washed sequentially with 10% aqueous HCl (100 mL), water (100 mL), brine (100 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (20% EtOAc in hexanes, silica) resulted in 4.29 g of a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 7.17 (dd, *J*=8, 6 Hz, 1 H), 6.76 (m, 3 H), 4.18 (m, 1 H), 3.77 (s, 3 H), 2.78 (m, 2 H), 1.21 (d, *J*=7 Hz, 2 H).

***N*-Trifluoroacetyl-1-(2-iodo-5-methoxyphenyl)-2-propylamine**

[0172] A solution of *N*-trifluoroacetyl-1-(3-methoxyphenyl)-2-propylamine (4.29 g, 15.7 mmol) in methanol (100 mL) was cooled to -78°C and treated with CaCO₃ (3.17 g, 31.4 mmol), followed by a solution of ICl (6.37 g, 39.3 mmol) in methanol (50 mL). The reaction was allowed to warm to 20°C while stirring overnight. The product mixture was filtered, concentrated, dissolved in EtOAc (200 mL), washed twice with 5% aqueous sodium bisulfite (100 mL), once with brine (100 mL), dried with Na₂SO₄ and concentrated to give 6.72 g of a white solid powder. MS calculated for C₁₂H₁₃F₃INO₂+H: 368, observed: 368.

N-Allyl, N-trifluoroacetyl-1-(2-iodo-5-methoxyphenyl)-2-propylamine

[0173] A solution of *N*-trifluoroacetyl-1-(2-iodo-5-methoxyphenyl)-2-propylamine (8.09 g, 15.7 mmol) in toluene (450 mL) was treated with K_2CO_3 (2.82 g, 20.4 mmol), KOH (2.45 g, 47.1 mmol), *n*-Bu₄NBr (0.506 g, 1.57 mmol) and allyl bromide (2.47 g, 20.4 mmol), and stirred overnight at 80°C. The product mixture was acidified with 10% aqueous HCl, separated, the aqueous phase extracted with ether (500 mL), the combined organic phases were washed with brine (200 mL), dried with Na₂SO₄ and concentrated to give 4.45 g of a brown oil.

N-Trifluoroacetyl-7-methoxy-4-methyl-1-methylene-2,3,4,5-tetrahydro-1H-3-benzazepine

[0174] A solution of *N*-allyl, *N*-trifluoroacetyl-1-(2-iodo-5-methoxyphenyl)-2-propylamine (4.45 g, 10.8 mmol) in dimethylformamide (120 mL) was treated with KOAc (3.17 g, 32.3 mmol), *n*-Bu₄NBr (3.47 g, 10.8 mmol), PPh₃ (0.283 g, 1.08 mmol), Pd(OAc)₂ (0.242 g, 1.08 mmol) and stirred overnight at 80°C. The product mixture was cooled to 20°C, filtered, diluted with water (200 mL), extracted with ether (3 x 200 mL), the combined organic phases washed with water (100 mL), brine (100 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (10% EtOAc in hexane, silica) resulted in 1.39 g of a yellow oil.

N-Trifluoroacetyl-1,4-dimethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

[0175] A solution of *N*-trifluoroacetyl-7-methoxy-4-methyl-1-methylene-2,3,4,5-tetrahydro-1H-3-benzazepine (1.39 g, 4.64 mmol) in ethanol (40 mL) was treated with 10% Pd/C (0.49 g, 0.46 mmol) and stirred overnight under an atmosphere of hydrogen. The product mixture was filtered through a pad of celite and silica and then concentrated. Flash chromatography (20% EtOAc in hexane, silica) resulted in 0.77 g of a clear oil. ¹H NMR (400 MHz, CDCl₃, mixture of rotamers) δ 7.06 (m, 1 H), 6.71 (m, 1 H), 6.63 (m, 1 H), 4.38 (bm, 1 H), 3.8 (s, 3H), 3.8 (m, 1 H), 3.25 (m, 1 H), 3.16 (bm, 2 H), 2.72 (m, 1 H), 1.34 (m, 3 H) 1.22 (m, 3 H).

N-Trifluoroacetyl-8-bromo-1,4-dimethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

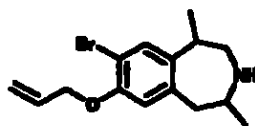
[0176] A solution *N*-trifluoroacetyl-1,4-dimethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (0.452 g, 1.50 mmol) in acetonitrile (20 mL) was treated with *N*-bromosuccinimide (0.294 g, 1.65 mmol) and stirred overnight at 20°C. The product mixture was diluted with EtOAc (100 mL), washed with sodium bisulfite (50 mL) and brine (50 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (20% EtOAc in hexane, silica) resulted in a clear oil. ¹H NMR (400 MHz, CDCl₃, mixture of rotamers) δ 7.32 (s, 1 H), 6.62 (m, 1 H), 4.37 (m, 1 H), 3.87 (s, 3 H), 3.81 (m, 1 H), 3.28-3.10 (m, 3 H), 2.73 (m, 1 H), 1.31 (m, 3 H), 1.25 (m, 3 H).

8-Bromo-1,4-dimethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

[0177] A solution of *N*-trifluoroacetyl-8-bromo-1,4-dimethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (21 mg, 0.055 mmol) in methanol (2 mL) was treated with 15% aqueous NaOH (2 mL), and stirred overnight at 20°C. The product mixture was diluted with water (5 mL), extracted twice with EtOAc (10 mL), the combined organic phases were washed with brine (10 mL), dried with Na₂SO₄ and concentrated to give 11 mg of a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.29 (s, 1 H), 6.64 (s, 1 H), 3.88 (s, 3 H), 3.02 (m, 2 H), 2.88 (dd, J=9, 14 Hz, 1 H), 2.80 (m, 1 H), 2.87 (d, J=14 Hz, 1 H), 2.53 (dd, J=10, 13, 1 H) 1.30 (d, J=7 Hz, 3 H), 1.19 (d, J=6 Hz, 3 H). MS calculated for C₁₃H₁₈BrNO+H: 284, observed: 284.

Example 25: 7-Allyloxy-8-bromo-1,4-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0178]

*N-Trifluoroacetyl-8-bromo-1,4-dimethyl-7-hydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine*

[0179] A solution of *N*-trifluoroacetyl-8-bromo-1,4-dimethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (0.383

g, 1.01 mmol) in dichloromethane (30 mL) was treated with BBr_3 (2.35 mL of a 1.0M solution in CH_2Cl_2 , 2.35 mmol) and stirred overnight while warming to 20°C . The excess BBr_3 is quenched with water, and the resulting mixture was diluted with ether (100 mL), washed with saturated aqueous Na_2CO_3 (50 mL) and brine (50 mL), dried with Na_2SO_4 and concentrated. Flash chromatography (15% EtOAc in hexane, silica) resulted in 0.302 g of a white solid. ^1H NMR (400 MHz, CDCl_3 , mixture of rotamers) δ 7.22 (m, 1 H), 6.77 (m, 1 H), 5.34 (s, 1 H), 4.35 (m, 1 H), 3.82 (m, 1 H), 3.24 (m, 1 H), 3.13 (m, 2 H), 2.69 (m, 1 H), 1.31 (m, 3 H), 1.22 (m, 3 H).

N-Trifluoroacetyl-7-allyloxy-8-bromo-1,4-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine

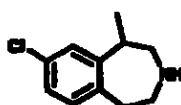
[0180] A solution *N*-trifluoroacetyl-8-bromo-1,4-dimethyl-7-hydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine (0.030 g, 0.082 mmol) in dichloromethane (2 mL) was treated with allyl bromide (0.030 g, 0.246 mmol), DBU (0.037 g, 0.246 mmol) and stirred 2 hours at 20°C . The product mixture was diluted with EtOAc (10 mL), washed with 5% aqueous HCl (2 mL), brine (5 mL), dried with Na_2SO_4 and concentrated. Flash chromatography (15% EtOAc in hexane, silica) resulted in 0.028 g of a clear oil. ^1H NMR (400 MHz, CDCl_3 , mixture of rotamers) δ 7.32 (s, 1 H), 6.62 (m, 1 H), 6.02 (m, 1 H), 5.45 (d, $J=17$ Hz, 1 H), 5.30 (d, $J=11$ Hz, 1 H), 4.58 (s, 2 H), 4.36 (m, 1 H), 3.82 (m, 1 H), 3.23 (m, 1 H), 3.11 (m, 1 H), 2.81 (d, $J=10$ Hz, 1 H), 2.70 (m, 1 H), 1.34 (m, 3 H), 1.21 (m, 3 H).

7-Allyloxy-8-bromo-1,4-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0181] A solution of *N*-trifluoroacetyl-7-allyloxy-8-bromo-1,4-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.028 g, 0.089 mmol) in methanol (2 mL) was treated with 15% aqueous NaOH (2 mL), and stirred for 3 hours at 20°C . The product mixture was diluted with water (10 mL), extracted twice with EtOAc (10 mL), the combined organic phases were washed with brine (10 mL), dried with Na_2SO_4 and concentrated to give 0.020 g of a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 7.30 (s, 1 H), 6.64 (s, 1 H), 6.06 (m, 1 H), 5.47 (d, $J=17$ Hz, 1 H), 5.30 (d, $J=11$ Hz, 1 H), 4.58 (s, 2 H), 3.03 (m, 2 H), 2.90 (dd, $J=9, 14$ Hz, 1 H), 2.80 (m, 1 H), 2.65 (d, $J=14$ Hz, 1 H), 2.55 (dd, $J=10, 14$ Hz, 1 H), 1.77 (bs, 1 H), 1.30 (d, $J=7$ Hz, 3 H), 1.20 (d, $J=6$ Hz, 3 H).

Example 26: (R,S) 8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0182]



N-Trifluoroacetyl-4-chlorophenethylamine

[0183] A solution of 4-chlorophenethylamine (1.0 g, 6.4 mmol) in dichloromethane (20 mL) was cooled to 0°C , treated with pyridine (1.0 mL, 12.8 mmol), trifluoroacetic anhydride (1.6 g, 7.7 mmol) and then stirred for 1 hour while warming to 20°C . The product mixture was diluted with EtOAc (100 mL), washed sequentially with 10% aqueous HCl (50 mL), water (50 mL), brine (50 mL), dried with Na_2SO_4 and concentrated to give 1.6 g of a white solid.

N-Trifluoroacetyl-2-iodo-4-chlorophenethylamine

[0184] A solution of *N*-trifluoroacetyl-4-chlorophenethylamine (1.6 g, 6.4 mmol) in dichloromethane (20 mL) was treated with bis(pyridine)iodonium(I)tetrafluoroborate (2.6 g, 7.0 mmol), $\text{CF}_3\text{SO}_3\text{H}$ (2.1 g, 14.1 mmol) and stirred overnight at 20°C . The product mixture was concentrated, dissolved in EtOAc (100 mL), washed twice with 5% aqueous sodium bisulfite (50 mL), twice with saturated aqueous NaHCO_3 (50 mL) once with brine (50 mL), dried with Na_2SO_4 and concentrated to give 0.94 g of a clear oil. MS calculated for $\text{C}_{10}\text{H}_9\text{ClF}_3\text{INO}+\text{H}$: 378, observed: 378.

N-Allyl, N-trifluoroacetyl-2-iodo-4-chlorophenethylamine

[0185] A solution of *N*-trifluoroacetyl-2-iodo-4-chlorophenethylamine (0.94 g, 2.4 mmol) in toluene (25 mL) was treated with K_2CO_3 (0.43 g, 3.12 mmol), KOH (0.40 g, 7.2 mmol), $n\text{-Bu}_4\text{NBr}$ (0.077 g, 0.24 mmol) and allyl bromide (0.43 g, 3.6 mmol) sequentially. The mixture was stirred at 60°C for 3.5 hours, cooled to 20°C and acidified with 10% aqueous HCl. The phases were separated, the aqueous phase extracted with ether (100 mL), the combined organic phases were washed with brine (50 mL), dried with Na_2SO_4 and concentrated to give 0.76 g of a clear oil. MS calculated for

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$C_{13}H_{12}ClF_3NO+H$: 418, observed: 418.

N-Trifluoroacetyl-8-chloro-1-methylene-2,3,4,5-tetrahydro-1H-3-benzazepine

[0186] A solution of N-allyl, N-trifluoroacetyl-2-iodo-4-chlorophenethylamine (0.76 g, 1.8 mmol) in dimethylformamide (20 mL) was treated with KOAc (0.53 g, 5.4 mmol), *n*-Bu₄NBr (0.58 g, 1.8 mmol), PPh₃ (0.047 g, 0.18 mmol), Pd(OAc)₂ (0.041 g, 0.18 mmol) and stirred overnight at 105°C. The product mixture was cooled to 20°C, filtered, diluted with water (100 mL), extracted with ether (3 x 100 mL), the combined organic phases washed with water (100 mL), brine (100 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (10% EtOAc in hexane, silica) resulted in 0.228 g of a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.29 (s, 1 H), 7.18 (m, 1 H), 7.04 (m, 1 H), 5.38 (m, 2 H), 5.40 (d, J=18 Hz, 2 H), 3.60 (m, 2 H), 3.00 (m, 2 H). MS calculated for C₁₃H₁₁ClF₃NO+H: 290, observed: 290.

N-Trifluoroacetyl-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

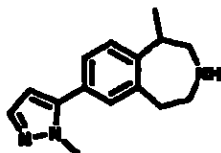
[0187] A solution of N-trifluoroacetyl-8-chloro-1-methylene-2,3,4,5-tetrahydro-1H-3-benzazepine (0.16 g, 0.55 mmol) in methanol (10 mL) was treated with 10% Pd/C (0.02 g) and stirred 30 minutes under an atmosphere of hydrogen. The product mixture was filtered, concentrated and purified by flash chromatography (5% EtOAc in hexane, silica) resulting in 0.057 g of a white solid. MS calculated for C₁₃H₁₃ClF₃NO+H: 292, observed: 292.

8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0188] A solution of N-trifluoroacetyl-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (65 mg, 0.22 mmol) in methanol (2 mL) was treated with 15% aqueous NaOH (2 mL), and stirred for 3.5 hours at 60°C. The product mixture was concentrated, extracted 3 times with CH₂Cl₂ (5 mL), dried with Na₂SO₄ and concentrated to give 35 mg of a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.11 (s, 1 H), 7.05 (d, J=8 Hz, 1 H), 6.98 (d, J=8 Hz, 1 H), 3.1-2.9 (m, 6 H), 2.71 (m, 1 H), 2.68 (bs, 1 H), 1.32 (d, J=8 Hz, 3 H). MS calculated for C₁₁H₁₄ClN+H: 196, observed: 196.

(Comparative) Example 27: (R,8) 7-(2-Methyl-2H-pyrazol-3-yl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0189]



N-Trifluoroacetyl-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0190] A solution of N-trifluoroacetyl-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (0.506 g, 1.76 mmol) in dichloromethane (20 mL) was treated with BBr₃ (4.1 mL of a 1.0M solution in CH₂Cl₂, 4.1 mmol) and stirred overnight while warming to 20°C. The excess BBr₃ was quenched with water, and the resulting mixture was diluted with ether (200 mL), washed with Na₂CO₃ (100 mL) and brine (100 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (15% EtOAc in hexane, silica) resulted in 0.460 g of a white solid foam. MS calculated for C₁₃H₁₄F₃NO₂+H: 274, observed: 274.

N-Trifluoroacetyl-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, O-trifluoromethanesulfonate

[0191] A solution of N-trifluoroacetyl-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (460 mg, 1.76 mmol) in dichloromethane (15 mL) was treated with pyridine (417 mg, 5.27 mmol), trifluoromethanesulfonic anhydride (991 mg, 3.52 mmol) and stirred 1.5 hours at 20°C. The product mixture was diluted with dichloromethane (100 mL), washed with water (50 mL), 5% aqueous HCl (50 mL), saturated aqueous NaHCO₃ (50 mL), brine (50 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (15% EtOAc in hexane, silica) resulted in 658 mg of a clear oil. MS calculated for C₁₄H₁₃F₆NO₄S+H: 406, observed: 406.

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N-Trifluoroacetyl-7-(2-Methyl-2H-pyrazol-3-yl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

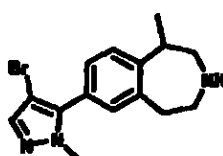
[0192] To a solution of *N*-trifluoroacetyl-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, *O*-trifluoromethanesulfonate (100 mg, 0.25 mmol) in dimethylformamide (2 mL) was treated with (2-methyl-2H-pyrazol-3-yl)-tri-*n*-butyltin (138 mg, 0.37 mmol), LiCl (21 mg, 0.50 mmol), Pd(PPh₃)₂Cl₂ (35 mg, 0.05 mmol) and stirred at 100°C for 4 hours. The product mixture was diluted with EtOAc (20 mL), washed twice with water (10 mL), once with brine (10 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (30% EtOAc in hexane, silica) resulted in 80 mg of a clear oil. MS calculated for C₁₇H₁₈F₃N₃O+H: 338, observed: 338.

7-(2-Methyl-2H-pyrazol-3-yl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0193] A solution of *N*-trifluoroacetyl-7-(2-Methyl-2H-pyrazol-3-yl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (48 mg, 0.14 mmol) in methanol (2 mL) was treated with 15% aqueous NaOH (2 mL), and the solution stirred overnight at 20° C. The product mixture was concentrated, extracted 3 times with CH₂Cl₂ (5 mL), dried with Na₂SO₄ and the solvent evaporated. Flash chromatography (0-15% MeOH in CH₂Cl₂, silica) resulted in 30 mg of a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.48 (s, 1 H), 7.21 (m, 2 H), 7.13 (s, 1 H), 6.27 (s, 1 H), 3.89 (s, 3 H), 3.3-2.9 (m, 9 H), 2.79 (dd, J=7, 14 Hz, 1 H), 1.40 (d, J=8 Hz, 3 H). MS calculated for C₁₅H₁₈N₃+H: 242, observed: 242.

(Comparative) Example 28: (R,S) 7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0194]

*N*-Trifluoroacetyl-7-(4-bromo-2-Methyl-2H-pyrazol-3-yl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0195] To a solution of *N*-trifluoroacetyl-7-(2-Methyl-2H-pyrazol-3-yl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (30 mg, 0.082 mmol) in dichloromethane (1 mL) was treated with *N*-bromosuccinimide (15.3 mg, 0.088 mmol) and stirred overnight at 20°C. The product mixture was absorbed on silica and purified by flash chromatography (2-5% MeOH in CH₂Cl₂, silica) resulting in 37 mg of a white crystalline solid. MS calculated for C₁₇H₁₇BrF₃N₃O+H: 418, observed: 418.

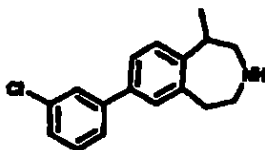
7-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0196] A solution of *N*-trifluoroacetyl-7-(4-bromo-2-Methyl-2H-pyrazol-3-yl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (37 mg, 0.089 mmol) in methanol (2 mL) was treated with 15% aqueous NaOH (2 mL), and stirred overnight at 20° C. The product mixture was concentrated, extracted 3 times with CH₂Cl₂ (5 mL), dried with Na₂SO₄ and the solvent evaporated. Flash chromatography (0-15% MeOH in CH₂Cl₂, silica) resulted in 28 mg of a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.50 (s, 1 H), 7.25 (d, J=8 Hz, 1 H), 7.17 (d, J=8 Hz, 1 H), 7.10 (s, 1 H), 3.83 (s, 3 H), 3.17 (m, 1 H), 3.1-2.9 (m, 8 H), 2.80 (dd, J=7, 13 Hz, 1 H), 2.48 (bs, 1 H), 1.40 (d, J=8 Hz, 3 H). MS calculated for C₁₈H₁₈BrN₃+H: 320, observed: 320.

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(Comparative) Example 29: (R,S) 7-(3-Chlorophenyl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

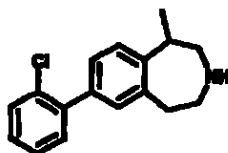
[0197]



[0198] A solution of N-trifluoroacetyl-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, O-trifluoromethanesulfonate (50 mg, 0.123 mmol) in 1,4-dioxane (1.5 mL) was treated with 2-chlorophenylboronic acid (39 mg, 0.243 mmol), CaF (58 mg, 0.37 mmol), water (50 mg, 2.78 mmol), Pd(PPh₃)₄ (29 mg, 0.025 mmol) and stirred overnight at 75°C. The product mixture was diluted with EtOAc (20 mL), washed with water (10 mL), brine (10 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (10-20% EtOAc in hexane, silica) resulted in 45 mg of a clear oil. MS calculated for C₁₉H₁₇ClF₃NO+H: 368, observed: 368. The product (27 mg, 0.073 mmol) was dissolved in methanol (2 mL) treated with 15% aqueous NaOH (2 mL), and stirred overnight at 20°C. The product mixture was concentrated, extracted 3 times with CH₂Cl₂ (5 mL), dried with Na₂SO₄ and the solvent evaporated to give 18 mg of a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.54 (s, 1 H), 7.42 (d, J=8 Hz, 1 H), 7.35-7.21 (m, 5 H), 3.14 (m, 1 H), 3.1-2.9 (m, 8 H), 2.80 (bm, 2 H), 1.38 (d, J=8 Hz, 3 H). MS calculated for C₁₇H₁₈ClN₃+H: 272, observed: 272.

(Comparative) Example 30: (R,S) 7-(2-Chlorophenyl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

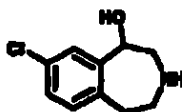
[0199]



[0200] A solution of N-trifluoroacetyl-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, O-trifluoromethanesulfonate (50 mg, 0.123 mmol) in 1,4-dioxane (1.5 mL) was treated with 2-chlorophenylboronic acid (39 mg, 0.243 mmol), CaF (58 mg, 0.37 mmol), water (50 mg, 2.78 mmol), Pd(PPh₃)₄ (29 mg, 0.025 mmol) and stirred overnight at 75°C. The product mixture was diluted with EtOAc (20 mL), washed with water (10 mL), brine (10 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (10-20% EtOAc in hexane, silica) resulted in 38 mg of a clear oil. MS calculated for C₁₉H₁₇ClF₃NO+H: 368, observed: 368. The product (27 mg, 0.073 mmol) was dissolved in methanol (2 mL) treated with 15% aqueous NaOH (2 mL), and stirred overnight at 20°C. The product mixture was concentrated, extracted 3 times with CH₂Cl₂ (5 mL), dried with Na₂SO₄ and the solvent evaporated to give 24 mg of a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.44 (d, J=8 Hz, 1 H), 7.35-7.22 (m, 5 H), 7.15 (s, 1 H), 3.14 (m, 1 H), 3.1-2.9 (m, 8 H), 2.80 (dd, J=13 Hz, 1 H), 2.51 (bs, 1 H), 1.38 (d, J=8 Hz, 3 H). MS calculated for C₁₇H₁₈ClN₃+H: 272, observed: 272.

Example 31: (R,S) 8-Chloro-1-hydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine

[0201]



N-Trifluoroacetyl-8-chloro-1-oxo-3,4,5-trihydro-1*H*-3-benzazepine

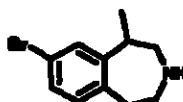
[0202] A solution of *N*-trifluoroacetyl-8-chloro-1-methylene-3,4,5-trihydro-1*H*-3-benzazepine (0.23 g, 0.80 mmol) in 1:1 methanol/dichloromethane (45 mL) was cooled to -78°C, treated with ozone until the solution turned blue (about 20 minutes), PPh₃ (0.21 g, 0.80 mmol) was added and the resulting solution was stirred 90 minutes while warming to 20°C. The product mixture was concentrated and purified by flash chromatography (30% EtOAc in hexane, silica) resulting in 0.215 g of a white solid. MS calculated for C₁₂H₉ClF₃NO₂+H: 292, observed: 292.

8-Chloro-1-hydroxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine

[0203] A solution of *N*-trifluoroacetyl-8-chloro-1-oxo-3,4,5-trihydro-1*H*-3-benzazepine (50 mg, 0.17 mmol) in methanol (2 mL) was treated with NaBH₄ and the resulting mixture was stirred 16 hours at 20°C. The white solid product was collected by filtration, washed with water and dried, resulting in 30 mg of a white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.39 (s, 1 H), 7.12 (d, J=8 Hz, 1 H), 7.06 (d, J=8 Hz, 1 H), 4.74 (d, J=8 Hz, 1 H), 3.1-2.7 (m, 6 H). MS calculated for C₁₀H₁₂ClNO+H: 198, observed: 198.

Example 32: (R,S) 8-Bromo-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine

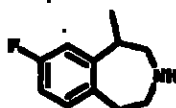
[0204]



[0205] By the same general procedure as in example 26, (R,S) 8-bromo-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine was obtained from 4-bromophenethylamine as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.27 (s, 1 H), 7.22 (d, J=8 Hz, 1 H), 6.94 (d, J=8 Hz, 1 H), 3.1-2.85 (m, 6 H), 2.72 (m, 1 H), 2.25 (bs, 1 H), 1.33 (d, J=7 Hz, 3 H). MS calculated for C₁₁H₁₄BrN+H: 240, observed: 240.

Example 33: (R,S) 8-Fluoro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine

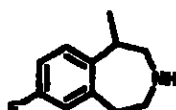
[0206]



[0207] By the same general procedure as in example 26, (R,S) 8-fluoro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine was obtained from 4-fluorophenethylamine as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.00 (dd, J=8, 10 Hz, 1 H), 6.88 (d, J=10 Hz, 1 H), 6.76 (d, J=8 Hz, 1 H), 3.08-2.56 (m, 7 H), 1.85 (bs, 1 H), 1.31 (d, J=7 Hz, 3 H). MS calculated for C₁₁H₁₄FN+H: 180, observed: 180.

(Comparative) Example 34: (R,S) 7-Fluoro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine

[0208]



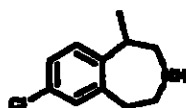
[0209] By the same general procedure as in example 26, (R,S) 7-fluoro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine was obtained from 3-fluorophenethylamine as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.09 (dd, J=6, 8

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Hz, 1 H), 6.85-6.78 (m, 2 H), 3.10-2.89 (m, 6 H), 2.71 (dd, J=7, 13 Hz, 1 H), 1.91 (bs, 1 H), 1.33 (d, J=7 Hz, 3 H). MS calculated for $C_{11}H_{14}FN+H$: 180, observed: 180.

(Comparative) Example 35: (R,S) 7-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

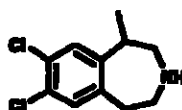
[0210]



[0211] By the same general procedure as in example 26, (R,S) 7-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine was obtained from 3-chlorophenethylamine as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J=8 Hz, 1 H), 7.06 (m, 2 H), 3.1-2.9 (m, 6 H), 2.70 (dd, J=13, 7 Hz, 1 H), 1.89 (bs, 1 H), 1.31 (d, J=7 Hz, 3 H). MS calculated for $C_{11}H_{14}ClN+H$: 196, observed: 196.

Example 36: (R,S) 7,8-Dichloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

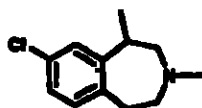
[0212]



[0213] By the same general procedure as in example 26, (R,S) 7,8-dichloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine was obtained from 3,4-dichlorophenethylamine as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 1 H), 7.16 (s, 1 H), 3.05-2.88 (m, 6 H), 2.71 (dd, J=7, 13 Hz, 1 H), 1.83 (bs, 1 H), 1.33 (d, J=7 Hz, 3 H). MS calculated for $C_{11}H_{13}Cl_2N+H$: 230, observed: 230.

Example 37: (R,S) N-Methyl-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

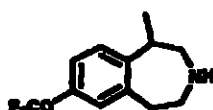
[0214]



[0215] By the same general procedure as in example 9, (R,S) N-methyl-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine was obtained from (R,S) 8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine as a colorless oil. MS calculated for $C_{12}H_{16}ClN+H$: 210, observed: 210.

(Comparative) Example 38: (R,S) 1-Methyl-7-trifluoromethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

[0216]



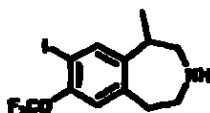
[0217] By the same general procedure as in example 26, (R,S) 1-methyl-7-trifluoromethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine was obtained from 3-trifluoromethoxyphenethylamine as a colorless oil. ^1H NMR (400 MHz, CD_3OD)

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7.39 (d, J=8 Hz, 1 H), 7.19 (m, 1 H), 3.46 (m, 2 H), 3.38 (d, J=13 Hz, 1 H), 3.29 (m, 1 H), 3.16 (m, 2 H), 3.05 (dd, J=13, 9 Hz, 1 H), 1.50 (d, J=6 Hz, 3 H). MS calculated for $C_{12}H_{14}F_3NO+H$: 246, observed: 246.

Example 38: (R,S) 8-Iodo-1-methyl-7-trifluoromethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

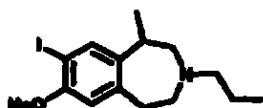
[0218]



[0218] By the same general procedure as in example 3, (R,S) 8-Iodo-1-methyl-7-trifluoromethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine was obtained from N-trifluoroacetyl-1-methyl-7-trifluoromethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine as a colorless oil. ^1H NMR (400 MHz, CD_3OD) δ 7.79 (s, 1 H), 7.25 (s, 1 H), 3.46-3.40 (m, 3 H), 3.28-3.12 (m, 3 H), 3.07 (dd, J=13, 9 Hz, 1 H), 1.47 (d, J=7 Hz, 3 H). MS calculated for $C_{12}H_{14}F_3INO+H$: 372, observed: 372.

Example 40: (R,S) N-Propyl-8-Iodo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

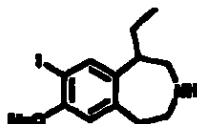
[0220]



[0221] By the same general procedure as in example 10, (R,S) N-Propyl-8-Iodo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine was obtained from (R,S) 8-Iodo-7-methoxy-1-methyl-1,2,4,5-tetrahydro-3H-3-benzazepine as a colorless oil. MS calculated for $C_{18}H_{22}INO+H$: 360, observed: 360.

Example 41: (R,S) 1-Ethyl-8-Iodo-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

[0222]

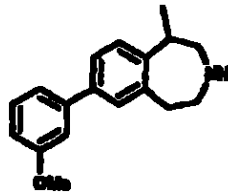


[0223] By the same general procedure as in example 19, (R,S) 1-ethyl-8-Iodo-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine was obtained from N-trifluoroacetyl-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1 H), 6.54 (s, 1 H), 3.86 (s, 3 H), 3.20-2.87 (m, 4 H), 2.93-2.75 (m, 3 H), 2.64 (m, 1 H), 1.76 (m, 2 H), 0.85 (dd, J=8, 6 Hz, 3 H). MS calculated for $C_{13}H_{16}INO+H$: 332, observed: 332.

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(Comparative) Example 42: (R,S) 7-(3-Methoxyphenyl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

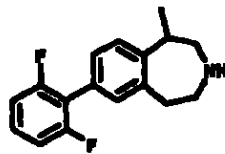
[0224]



[0225] By the same general procedure as in example 29, (R,S) 7-(3-Methoxyphenyl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine was obtained from N-trifluoroacetyl-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, O-trifluoromethanesulfonate as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.37 (dd, J=7, 7 Hz, 1 H), 7.30 (m, 2 H), 7.21 (d, J=7 Hz, 1 H), 7.14 (d, J=7 Hz, 1 H), 7.09 (s, 1 H), 6.86 (d, J=8 Hz, 1 H), 3.85 (s, 3 H), 3.2-2.9 (m, 6 H), 2.80 (m, 1 H), 2.64 (bs, 1 H), 1.36 (d, J=7 Hz, 3 H). MS calculated for C₁₈H₂₁NO+H: 266, observed: 266.

(Comparative) Example 43: (R,S) 7-(2,6-difluorophenyl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

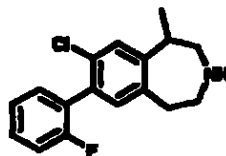
[0226]



[0227] By the same general procedure as in example 29, (R,S) 7-(2,6-difluorophenyl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine was obtained from N-trifluoroacetyl-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, O-trifluoromethanesulfonate as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.10 (m, 5 H), 6.95 (dd, J=7, 8 Hz, 1 H), 3.2-2.9 (m, 6 H), 2.79 (dd, J=8, 13 Hz, 1 H), 2.70 (bs, 1 H), 1.36 (d, J=8 Hz, 3 H). MS calculated for C₁₇H₁₇F₂N+H: 274, observed: 274.

Example 44: (R,S) 7-(2-fluorophenyl)-6-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

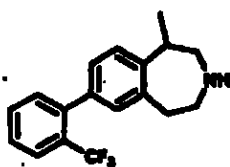
[0228]



[0229] By the same general procedure as in example 29, (R,S) 7-(2-fluorophenyl)-6-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine was obtained from N-trifluoroacetyl-6-chloro-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.23 (m, 3 H), 7.18-7.09 (m, 2 H), 7.03 (s, 1 H), 3.15-2.85 (m, 7 H), 2.76 (dd, J=8, 13 Hz, 1 H), 1.36 (d, J=8 Hz, 3 H). MS calculated for C₁₇H₁₇ClFN+H: 290, observed: 290.

(Comparative) Example 45: (R,S) 7-(2-Trifluoromethylphenyl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

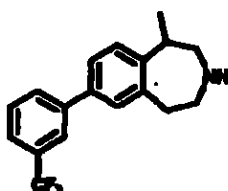
[0230]



[0231] By the same general procedure as in example 29, (R,S) 7-(2-trifluoromethylphenyl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine was obtained from N-trifluoroacetyl-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, O-trifluoromethanesulfonate as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, J=8 Hz, 1 H), 7.52 (dd, J=7, 8 Hz, 1 H), 7.42 (dd, J= 7, 8 Hz, 1 H), 7.31 (d, J=7 Hz, 1 H), 7.17 (d, J=8 Hz, 1 H), 7.11 (d, J=8 Hz, 1 H), 3.15 (m, 1 H), 3.1-2.9 (m, 5 H), 2.76 (dd, J=8, 13 Hz, 1 H), 2.37 (bs, 1 H), 1.38 (d, J=8 Hz, 3 H). MS calculated for C₁₈H₁₈F₃N+H: 306, observed: 306.

(Comparative) Example 46: (R,S) 7-(3-Trifluoromethylphenyl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

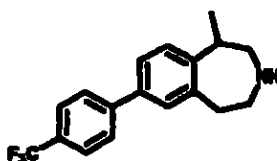
[0232]



[0233] By the same general procedure as in example 29, (R,S) 7-(3-trifluoromethylphenyl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine was obtained from N-trifluoroacetyl-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, O-trifluoromethanesulfonate as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.80 (s, 1 H), 7.73 (d, J=8 Hz, 1 H), 7.57-7.48 (m, 2 H), 7.38 (d, J=8 Hz, 1 H), 7.30 (s, 1 H), 7.24 (d, J=7 Hz, 1 H), 3.16 (m, 1 H), 3.1-2.9 (m, 6 H), 2.79 (dd, J=8, 13 Hz, 1 H), 1.38 (d, J=8 Hz, 3 H). MS calculated for C₁₉H₁₉F₃N+H: 306, observed: 306.

(Comparative) Example 47: (R,S) 7-(4-Trifluoromethylphenyl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

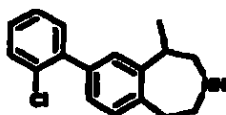
[0234]



[0235] By the same general procedure as in example 29, (R,S) 7-(4-trifluoromethylphenyl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine was obtained from N-trifluoroacetyl-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, O-trifluoromethanesulfonate as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.65 (s, 4 H), 7.38 (d, J=8 Hz, 1 H), 7.31 (s, 1 H), 7.24 (d, J=8 Hz, 1 H), 3.15 (m, 1 H), 3.1-2.9 (m, 5 H), 2.80 (dd, J=8, 13 Hz, 1 H), 2.48 (bs, 1 H), 1.38 (d, J=8 Hz, 3 H). MS calculated for C₁₉H₁₉F₃N+H: 306, observed: 306.

(Comparative) Example 48: (R,S) 8-(2-Chlorophenyl)-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

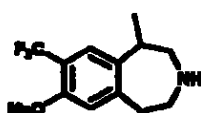
[0236]



[0237] A solution of N-trifluoroacetyl-8-bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (84 mg, 0.229 mmol) in dimethylformamide (2.5 mL) was treated with 2-chlorophenylboronic acid (43 mg, 0.275 mmol), CsF (52 mg, 0.34 mmol), water (70 mg, 3.9 mmol), Pd(PPh₃)₄ (27 mg, 0.023 mmol) and stirred overnight at 75°C. The product mixture was diluted with EtOAc (20 mL), washed with water (10 mL), brine (10 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (10-20% EtOAc in hexane, silica) resulted in 36 mg of a clear oil. MS calculated for C₁₈H₁₇ClF₃NO+H: 368, observed: 368. The product (39 mg, 0.106 mmol) was dissolved in methanol (2 mL) treated with 15% aqueous NaOH (2 mL), and stirred overnight at 20°C. The product mixture was concentrated, extracted 3 times with CH₂Cl₂ (5 mL), dried with Na₂SO₄ and the solvent evaporated to give 18 mg of a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.44 (d, J=8 Hz, 1 H), 7.35-7.17 (m, 5 H), 7.12 (d, J=8 Hz, 1 H), 3.14 (m, 1 H), 3.1-2.8 (m, 5 H), 2.79 (dd, J=7, 13 Hz, 1 H), 2.36 (bs, 1H), 1.36 (d, J=7 Hz, 3 H). MS calculated for C₁₇H₁₈ClN₃+H: 272, observed: 272.

Example 49: (R,S) 7-Methoxy-1-methyl-8-trifluoromethyl-2,3,4,5-tetrahydro-1H-3-benzazepine

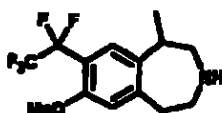
[0238]



[0239] A solution of N-trifluoromethylacetyl-8-iodo-7-methoxy-1-methyl-1,2,4,5-tetrahydro-3H-3-benzazepine (135 mg, 0.327 mmol) in dimethylformamide (3 mL) and toluene (0.5 mL) was treated with sodium trifluoroacetate (133 mg, 0.981 mmol), copper (I) iodide (124 mg, 0.654 mmol) and the toluene distilled off to remove any residual water. The reaction mixture was stirred at 155°C for 3.5 hours, diluted with EtOAc, filtered, absorbed on silica and purified by flash chromatography (10% EtOAc in hexane, silica) resulting in 28 mg of a colorless oil. MS calculated for C₁₆H₁₈F₃NO₂+H: 356, observed: 356. The intermediate (26 mg, 0.073 mmol) in methanol (2 mL) was treated with 15% aqueous NaOH (2 mL), and stirred 0.5 hours at 50°C. The product mixture was diluted with water (5 mL), extracted twice with EtOAc (5 mL), the combined organic phases were washed with brine (5 mL), dried with Na₂SO₄ and concentrated to give 14 mg of a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.32 (s, 1H), 6.73 (s, 1 H), 3.89 (s, 3 H), 3.1-2.9 (bm, 6 H), 2.75 (bm, 1 H), 2.23 (bs, 1 H), 1.36 (d, J=8 Hz, 3 H). MS calculated for C₁₅H₁₈F₃NO+H: 280, observed: 280.

Example 50: (R,S) 7-Methoxy-1-methyl-8-pentafluoroethyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0240]

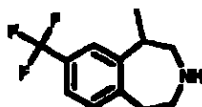


[0241] A solution of N-trifluoromethylacetyl-8-iodo-7-methoxy-1-methyl-1,2,4,5-tetrahydro-3H-3-benzazepine (100 mg, 0.242 mmol) in dimethylformamide (3 mL) and toluene (1 mL) was treated with sodium pentafluoroethylate (84 mg, 0.344 mmol), copper (I) iodide (82 mg, 0.484 mmol) and the toluene distilled off to remove any residual water. The reaction mixture was stirred at 160°C for 3.5 hours, diluted with EtOAc, filtered, absorbed on silica and purified by flash chromatography (10% EtOAc in hexane, silica) resulting in 22 mg of a colorless oil. MS calculated for C₁₈H₁₅F₈NO₂+H:

406, observed: 406. The intermediate (22 mg, 0.054 mmol) in methanol (2 mL) was treated with 15% aqueous NaOH (2 mL), and stirred 0.5 hours at 50°C. The product mixture was diluted with water (5 mL), extracted twice with EtOAc (5 mL), the combined organic phases were washed with brine (5 mL), dried with Na₂SO₄ and concentrated to give 14 mg of a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.25 (s, 1 H), 6.74 (s, 1 H), 3.85 (s, 3 H), 3.1-2.9 (bm, 6 H), 2.76 (bm, 1 H), 2.37 (bs, 1 H), 1.35 (d, J=8 Hz, 3 H). MS calculated for C₁₄H₁₈F₃NO+H: 310, observed: 310.

Example 51: (R,S) 8-Trifluoromethyl-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

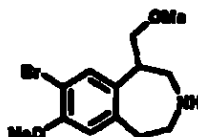
[0242]



[0243] By the same general procedure as in example 26, (R,S) 8-trifluoromethyl-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine was obtained from 4-trifluoromethylphenethylamine as a colorless oil. ¹H NMR (400 MHz, DMSO) δ 7.55 (d, J=8 Hz, 1 H), 7.49 (s, 1 H), 7.43 (d, J=8 Hz, 1 H), 3.55-3.50 (m, 1H) 3.43-3.23 (m, 7 H), 3.13 (dd, J=16, 7 Hz, 1H), 3.0-2.91 (m, 2H), 1.36 (d, J=7 Hz, 3 H). MS calculated for C₁₂H₁₄F₃N+H: 230.19, observed: 230.4

Example 52: (R,S) 8-bromo-1-methoxymethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

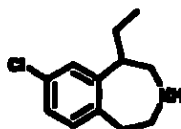
[0244]



[0245] A solution of 8-bromo-1-hydroxymethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (0.075 g, 0.28 mmol) in dichloromethane (2 mL) was treated with BOC₂O (0.062 g, 0.29 mmol), and stirred overnight at 20°C. The product was absorbed on silica and purified by flash chromatography (33% EtOAc in hexane, silica) resulting in 0.034 g of a clear oil. MS calculated for C₁₇H₂₄BrNO₄+H: 386, observed: 386. The BOC-protected intermediate was dissolved in dimethylformamide (1 mL), treated with excess NaH and excess iodomethane sequentially, and then stirred for 1 hour at 20°C. The reaction mixture was quenched with water (5 mL), extracted twice with EtOAc (5 mL), the combined organic phases were washed with brine (5 mL), dried with Na₂SO₄ and concentrated to give 0.019 g of a clear oil. MS calculated for C₁₈H₂₆BrNO₄+H: 400, observed: 400. The N-BOC protected methylether was then treated with 4M HCl in dioxane (1 mL) and stirred 2 hours at 20°C. Evaporation resulted in 0.009 g of the desired product as a clear oil. ¹H NMR (400 MHz, CD₃OD) δ 7.30 (s, 1 H), 6.92 (s, 1 H), 3.87 (s, 3H), 3.65 (s, 3H) 3.5-3.1 (m, 9 H). MS calculated for C₁₃H₁₈BrNO₂+H: 300, observed: 300.

Example 53: (R,S) 8-Chloro-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine

[0246]



N-Crotyl, N-trifluoroacetyl-2-iodo-4-chlorophenethylamine

[0247] A solution of N-trifluoroacetyl-2-iodo-4-chlorophenethylamine (6.2 g, 15.8 mmol) in dimethylformamide (350 mL) was treated with K₂CO₃ (15.8 g, 114 mmol) and crotyl bromide (8.0 g, 44 mmol) sequentially, the mixture was

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stirred at 60°C for 16 hours and then cooled to 20°C. The mixture was diluted with EtOAc (350 mL), washed with water (3 x 300 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (5-15% EtOAc in hexane) resulted in 2.5 g of a clear oil. MS calculated for C₁₄H₁₄ClF₃INO+H: 432, observed: 432.

5 ***N*-Trifluoroacetyl-8-chloro-1-ethyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine**

[0248] A solution of *N*-crotyl, *N*-trifluoroacetyl-2-iodo-4-chlorophenethylamine (2.5 g, 5.8 mmol) in dimethylformamide (250 mL) was treated with KOAc (1.07 g, 10.9 mmol), *n*-Bu₂Et₂NBr (1.33 g, 5.84 mmol), Pd(OAc)₂ (0.063 g, 0.28 mmol) and stirred overnight at 77°C. The product mixture was cooled to 20°C, filtered, diluted with water (100 mL),
 10 extracted with EtOAc (3 x 100 mL), the combined organic phases washed with water (100 mL), brine (100 mL), dried with Na₂SO₄ and concentrated. Flash chromatography (2-20% EtOAc in hexane, silica) resulted in 0.339 g of a clear oil. The product, which was assumed to be a mixture of double-bond isomers, was dissolved in methanol (50 mL) treated with Et₃N (0.2 mL), 10% Pd/C (0.10 g) and stirred 16 hours under 100 psi (0.69 MPa) of hydrogen. The product mixture was filtered, concentrated and purified by flash chromatography (5% EtOAc in hexane, silica) resulting in 0.20
 15 g of a white solid. MS calculated for C₁₄H₁₅ClF₃NO+H: 306, observed: 306.

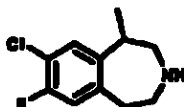
***8*-Chloro-1-ethyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine**

[0249] A solution of *N*-trifluoroacetyl-8-chloro-1-ethyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (63 mg, 0.207 mmol) in methanol (2 mL) was treated with 15% aqueous NaOH (2 mL), and stirred for 3.5 hours at 60°C. The product mixture was concentrated, extracted 3 times with CH₂Cl₂ (5 mL), dried with Na₂SO₄ and concentrated to give 35 mg of a clear oil. 1H NMR (400 MHz, DMSO-*d*₆) δ 7.2 (m, 3 H), 3.3-3.0 (m, 7 H), 1.9-1.8 (m, 2 H), 0.91 (t, *J*=7 Hz, 3 H). MS calculated for C₁₂H₁₆ClN+H: 210, observed: 210.

25 **Example 54: (R,S) 8-Chloro-7-fluoro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine**

[0250]

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35 ***N*-Trifluoroacetyl-8-chloro-7-fluoro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine**

[0251] A solution of *N*-trifluoroacetyl-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (2.5 g, 8.5 mmol) in 1,2-dichloroethane (15 mL) was treated with Selectfluor (3.9 g, 11 mmol), trifluoromethanesulfonic acid (8 mL, 90 mmol) and stirred 80 hours at 75°C. The product mixture was poured into water (200 mL), extracted with EtOAc (200 mL),
 40 the organic phase washed with saturated aqueous NaHCO₃ (2 x 100 mL), brine (100 mL), dried with Na₂SO₄ and concentrated. The crude product was purified by flash chromatography (6 % EtOAc in hexane, silica) resulting in 1.8 g of a white solid. MS calculated for C₁₃H₁₂ClF₄NO+H: 310, observed: 310.

***8*-Chloro-7-fluoro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine**

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[0252] A solution of *N*-trifluoroacetyl-8-chloro-7-fluoro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (160 mg, 0.22 mmol) in methanol (3 mL) was treated with 15% aqueous NaOH (2 mL), and stirred for 3.5 hours at 25°C. The product mixture was concentrated, extracted 3 times with CH₂Cl₂ (5 mL), dried with Na₂SO₄ and concentrated to give 83 mg of a clear oil. 1H NMR (400 MHz, CDCl₃) δ 7.11 (m, 1 H), 6.85 (m, 1 H), 3.05-2.95 (m, 3 H), 2.95-2.80 (m, 3H), 2.68
 50 (m, 1 H), 2.38 (bm, 1 H), 1.31 (m, 3 H). MS calculated for C₁₁H₁₃ClFN+H: 214, observed: 214.

Example 55 Separation of enantiomers for selected compounds of the invention

[0253] The following compounds were separated into their respective enantiomers using a Varian ProStar HPLC system with a 20 mm x 250 mm Chiralcel OD chiral column, eluting with 0.2 % diethylamine in various concentrations of isopropanol (IPA) in hexanes, see Table 1 below. In some cases, the separations were performed on the intermediate trifluoroacetamide protected amines.

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Table 1

Example	Enantiomer	Retention time for the free amine (mins)	Retention time for the trifluoroacetamide	Conditions
1	1	21.9		5% IPA in hexane
	2	24.5		10 mL/min
2	1	42		5% IPA in hexane
	2	47		9 mL/min
3	1	20.8		5% IPA in hexane
	2	24.2		10 mL/min
19	1	34.9		1 % IPA in hexane
	2	39.5		9 mL/min
26	1		23.8 ¹	5% IPA in hexane
	2		29.2 ²	7 mL/min
37	1		23.8 ³	5% IPA in hexane
	2		29.2 ⁴	7 mL/min
51	1		18.6 ⁵	1% IPA in hexane
	2		21.4 ⁶	9 mL/min
53	1		13.7 ⁷	5% IPA in hexane
	2		20.2 ⁸	10 mL/min

¹ The separated trifluoroacetamide enantiomer was hydrolyzed to give Enantiomer 1 of Compound 26.
² The separated trifluoroacetamide enantiomer was hydrolyzed to give Enantiomer 2 of Compound 26.
³ The separated trifluoroacetamide enantiomer was hydrolyzed and subsequently N-methylated to give Enantiomer 1 of Compound 37.
⁴ The separated trifluoroacetamide enantiomer was hydrolyzed and subsequently N-methylated to give Enantiomer 2 of Compound 37.
⁵ The separated trifluoroacetamide enantiomer was hydrolyzed to give Enantiomer 1 of Compound 51.
⁶ The separated trifluoroacetamide enantiomer was hydrolyzed to give Enantiomer 2 of Compound 51.
⁷ The separated trifluoroacetamide enantiomer was hydrolyzed to give Enantiomer 1 of Compound 53.
⁸ The separated trifluoroacetamide enantiomer was hydrolyzed to give Enantiomer 2 of Compound 53.

Example 56

Intracellular IP₃ Accumulation Assay

[0254] HEK293 cells were transfected in 15cm sterile dishes with or without (control) 16ug of human 5-HT_{2C} receptor cDNA using 25ul of lipofectamine. Cells were then incubated for 3-4 hours at 37°C/5%CO₂ and then transfection media was removed and replaced with 100ul of DMEM. Cells were then plated onto 100cm sterile dishes. The next day cells were plated into 96 well PDL microtiter plates at a density of 55K/0.2ml. Six hours latter, media was exchanged with [3H]inositol (0.25 uCi/well) in inositol free DMEM and plates were incubated at 37°C/5%CO₂ overnight. The next day, wells were aspirated and 200ul of DMEM containing test compound, 10uM pargyline, and 10mM LiCl was added to appropriate wells. Plates were then incubated at 37°C/5%CO₂ for three hours followed aspiration and by addition of fresh ice cold stop solution (1M KOH, 19mM Na-borate, 3.8 mM EDTA) to each well. Plates were kept on ice for 5-10 min and the wells were neutralized by addition of 200ul of fresh ice cold neutralization solution (7.5% HCl). Plates were then frozen until further processing is desired. The lysate was then transferred into 1.5 ml Eppendorf tubes and 1 ml of chloroform/methanol (1:2) was added/tube. The solution was vortexed for 15 seconds and the upper phase was applied to a Biorad AG1-X8™ anion exchange resin (100-200 mesh). First, the resin was washed with water at 1:1.25 W/V and 0.9 ml of upper phase was loaded onto the column. The column was then washed with 10 ml of 5 mM myo-Inositol and 10 ml of 5 mM Na-borate/80mM Na-formate. The inositol tris phosphates were eluted into scintillation vials containing 10 ml of scintillation cocktail with 2 ml of 0.1 M formic acid/ 1 M ammonium formate. The columns were regenerated by washing with 10 ml of 0.1 M formic acid/3M ammonium formate and rinsed twice with dd H₂O and stored at 4°C in water.

[0255] The biological activities in the IP Accumulation Assay for several representative compounds are shown in Table 2 below:

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Compound (Example Number)	5-HT _{2C} (IC ₅₀)* IP Accumulation Assay (nM)
1	4.2
2	4.5
3	1.4
4	2.1
5	12.1
12	6.3
19	18
26	5.8
32	2.1

* Reported values are averages of at least two trials.

[0256] The majority of the other compounds of the Examples were tested at least once, and they showed activities in the IP Accumulation Assay in the range between ~1.4 nM and ~ 5 μ M.

Example 57

Inhibition of food intake in food-deprived rats

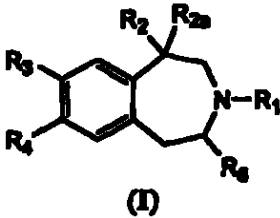
[0257] Male Sprague-Dawley rats (250-350g) were deprived of food overnight prior to testing. Prior to food deprivation, the animals were weighed and separated into treatment groups in order to balance groups according to body weight. On the test day, animals were placed into individual cages (no bedding) at 9:00am with free access to water. At 10:00am, animals were injected with test compound (p.o., i.p., or s.c.) and then presented with a pre-weighed amount of food in a dish either 60min (p.o.) or 30min (i.p. and s.c.) after drug administration. Food consumption over different time points was then determined by weighing the food cup at 1, 2, 4, and 6hr after the food was presented. Thus, food consumption was measured at 2, 3, 5, and 7hr post-injection in p.o. studies, and at 1.5, 2.5, 4.5, and 6.5hr post-injection in i.p. and s.c. studies.

[0258] Figures 1A-G illustrate the effects of seven different compounds on food intake in food-deprived rats. All compounds inhibited food intake dose-dependently. This effect was consistently most pronounced over the first 1hr after food presentation. Some compounds (Figures 1A, 1C, and 1E) maintained an inhibitory effect on food intake relative to vehicle-treated controls at 6hr after food presentation. Compounds were also shown to be effective via all routes of administration including p.o.

[0259] Each of the patents, applications, printed publications, and other published documents mentioned or referred to in this specification are cited in order to more fully describe the state of the art to which the invention pertains.

Claims

1. A compound of Formula (I):



wherein:

R_1 is: -H or
C₁₋₈alkyl;

R_2 is: C₁₋₈alkyl,
-CH₂-O-C₁₋₈alkyl,
-C(=O)-O-C₁₋₈alkyl,
-C(=O)-NH-C₁₋₈alkyl,
-OH, or
-CH₂OH;

R_{2a} is: -H;

or R_2 and R_{2a} together form -CH₂-CH₂;

R_3 is: halogen;
perhaloalkyl; or
a 5-membered heteroaryl ring having up to two heteroatoms selected from O, N and S;

R_4 is -H, halogen, perhaloalkyl, -CN, -OR₆, -SR₅, -NHR₅, -N(R₅)₂, -OH, aryl, or heteroaryl, wherein said aryl can be optionally substituted with up to two substituents selected from C₁₋₈alkyl, halogen, perhaloalkyl, and alkoxy, and said heteroaryl can be optionally substituted with up to two substituents selected from halogen and C₁₋₈alkyl;
or:

R_3 and R_4 together with the atoms to which they are attached form a 5- or 6-member heterocyclic ring having one O atom;

each R_5 is independently C₁₋₈alkyl, C₁₋₈alkenyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl or perhaloalkyl, or allyl; and

R_6 is -H or C₁₋₈alkyl;

or a pharmaceutically acceptable salt, solvate or hydrate thereof;
provided that:

If R_6 is other than -H, then R_4 cannot be -H; and

If R_1 and R_2 are methyl, and R_4 is -H, then R_3 cannot be imidazole, substituted imidazole, or an imidazole derivative;

and wherein:

aryl denotes a monocyclic or polycyclic aromatic group having from 3 to 14 carbon atoms;

heteroaryl denotes a monocyclic or polycyclic aromatic group having from 3 to 14 carbon atoms, and from 1 to 4 ring heteroatoms selected from O, N, and S; alkoxy denotes -O-alkyl;

C₁₋₈alkyl denotes a straight chain, branched, or cyclic hydrocarbon group having from 1 to 8 carbon atoms;

C₁₋₈alkenyl denotes a straight chain, branched, or cyclic hydrocarbon group having from 1 to 8 carbon atoms and at least one double bond;

alkyl, other than C₁₋₈alkyl, denotes methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, sec-butyl, tert-butyl, cyclobutyl, cyclopropylmethyl, n-pentyl, isopentyl, tert-pentyl, cyclopentyl, cyclopentylmethyl, n-hexyl, or cyclohexyl.

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2. A compound according to claim 1 wherein R_1 is -H.
3. A compound according to claim 1 wherein R_1 is C_{1-8} alkyl.
- 5 4. A compound according to claim 1 wherein R_1 is methyl.
5. A compound according to claim 1 wherein R_1 is n-propyl.
6. A compound according to any one of claims 1 to 5 wherein R_2 is C_{1-8} alkyl.
- 10 7. A compound according to any one of claims 1 to 5 wherein R_2 is methyl.
8. A compound according to any one of claims 1 to 5 wherein R_2 is ethyl.
- 15 9. A compound according to any one of claims 1 to 5 wherein R_2 is isopropyl.
10. A compound according to any one of claims 1 to 5 wherein R_2 and R_{2a} together form $-CH_2-CH_2-$.
11. A compound according to any one of claims 1 to 10 wherein R_3 is halogen.
- 20 12. A compound according to any one of claims 1 to 10 wherein R_3 is chlorine.
13. A compound according to any one of claims 1 to 10 wherein R_3 is bromine.
- 25 14. A compound according to any one of claims 1 to 10 wherein R_3 is iodine.
15. A compound according to any one of claims 1 to 10 wherein R_3 is perhaloalkyl.
16. A compound according to any one of claims 1 to 10 wherein R_3 is $-CF_3$.
- 30 17. A compound according to any one of claims 1 to 10 wherein R_3 is a 5-membered heteroaryl ring having up to two heteroatoms selected from O, N and S.
18. A compound according to any one of claims 1 to 10 wherein R_3 is selected from: thiophenyl, furanyl, pyrrolyl, pyrazolyl and imidazolyl.
- 35 19. A compound according to any one of claims 1 to 18 wherein R_4 is $-OR_5$.
20. A compound according to any one of claims 1 to 18 wherein R_4 is methoxy, ethoxy, n-propoxy, isopropoxy or allyloxy.
- 40 21. A compound according to any one of claims 1 to 18 wherein R_4 is perhaloalkyl.
22. A compound according to any one of claims 1 to 18 wherein R_4 is $-CF_3$.
- 45 23. A compound according to any one of claims 1 to 18 wherein R_4 is a 5-membered heteroaryl ring having up to two heteroatoms selected from O, N and S, and up to two substituents selected from halogen and C_{1-8} alkyl.
24. A compound according to claim 1 wherein R_4 is selected from thiophenyl, furanyl, pyrrolyl, pyrazolyl and imidazolyl optionally substituted with one or two substituents selected from halogen and methyl.
- 50 25. A compound according to any one of claims 1 to 18 wherein R_4 is phenyl optionally substituted with up to two substituents selected from C_{1-8} alkyl, halogen, and alkoxy.
26. A compound according to any one of claims 1 to 10 wherein R_3 and R_4 taken together form $-O-CH=C(CH_3)-$.
- 55 27. A compound according to any one of claims 1 to 10 wherein:
 R_3 is halogen; and

R_4 is $-OR_5$ wherein R_5 is C_{1-6} alkyl.

28. A compound according to any one of claims 1 to 10 wherein:

5 R_3 is halogen; and
 R_4 is methoxy.

29. A compound according to any one of claims 1 to 10 wherein:

10 R_3 is chlorine or bromine; and
 R_4 is methoxy.

30. A compound according to any one of claims 1 to 10 wherein:

15 R_3 is halogen; and
 R_4 is allyloxy.

31. A compound according to claim 1 wherein:

20 R_2 is methyl, ethyl, isopropyl, or $-CH_2OH$; or
 R_2 and R_{2a} taken together form $-CH_2-CH_2-$;
 R_3 is halogen or a 5-membered heteroaryl ring having up to two heteroatoms selected from O, N and S, and
up to two substituents selected from halogen and C_{1-6} alkyl;
 R_4 is $-H$, alkoxy, a 5-membered heteroaryl ring having up to two heteroatoms selected from O, N and S and
25 up to two substituents selected from halogen and C_{1-6} alkyl, or phenyl optionally substituted with up to two
substituents selected from C_{1-6} alkyl, halogen, and alkoxy;
or R_3 and R_4 taken together form $-O-CH=C(CH_3)-$; and
 R_5 is $-H$ or methyl.

30 32. A compound according to claim 1 wherein:

R_2 is methyl, ethyl, isopropyl, or $-CH_2OH$; or
 R_2 and R_{2a} taken together form $-CH_2-CH_2-$;
 R_3 is chlorine, bromine, or iodine;
35 R_4 is alkoxy; and
 R_5 is $-H$ or methyl.

33. A compound according to claim 1 wherein:

40 R_1 is $-H$;
 R_2 is methyl;
 R_3 is chlorine, bromine, or thiophene;
 R_4 is alkoxy, pyrazol-3-yl or phenyl wherein said pyrazole optionally has up to two substituents selected from
halogen and C_{1-6} alkyl, and said phenyl optionally has a single halogen substituent; and
45 R_5 is $-H$.

34. A compound of claim 1 selected from:

50 8-bromo-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
7-allyloxy-8-bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
7-benzyloxy-8-bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
8-bromo-7-ethoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
8-bromo-7-isopropoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
N-propyl-8-bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
55 7-hydroxy-8-iodo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
7-allyloxy-8-iodo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
7-allyloxy-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
7-methoxy-1-methyl-8-(2-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine;

8-bromo-1-cyclopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine;
 8-bromo-1-hydroxymethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine;
 8-bromo-1-isopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine;
 8-bromo-7-hydroxy-1-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
 7-allyloxy-8-bromo-1-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
 8-bromo-7-methoxy-1,4-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
 7-allyloxy-8-bromo-1,4-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
 8-chloro-1-hydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine;
 8-bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
 8-fluoro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
 7,8-dichloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
 N-methyl-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
 8-iodo-1-methyl-7-trifluoromethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine;
 N-propyl-8-iodo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
 1-ethyl-8-iodo-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine;
 7-(2-fluorophenyl)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine; and
 8-bromo-1-methoxymethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine;

and pharmaceutically acceptable salts, solvates and hydrates thereof.

35. A compound according to claim 1 selected from:

8-bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
 8-chloro-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
 8-iodo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
 N-methyl-8-bromo-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
 8-bromo-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine;
 8-chloro-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine;
 8-iodo-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine;
 7-methoxy-1-methyl-8-trifluoromethyl-2,3,4,5-tetrahydro-1H-3-benzazepine; and
 7-methoxy-1-methyl-8-pentafluoroethyl-2,3,4,5-tetrahydro-1H-3-benzazepine;

and pharmaceutically acceptable salts, solvates and hydrates thereof.

36. A compound according to any one of claims 1 to 35, which is an R enantiomer.

37. A compound according to any one of claims 1 to 35, which is an S enantiomer.

38. A compound according to claim 1 selected from the following compound, and pharmaceutically acceptable salts, solvates and hydrates thereof:

8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

39. A compound according to claim 38, which is an R enantiomer.

40. A compound according to claim 38, which is an S enantiomer.

41. A compound according to claim 1 selected from the following compound, and pharmaceutically acceptable salts, solvates and hydrates thereof:

8-bromo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

42. A compound according to claim 1 selected from the following compound, and pharmaceutically acceptable salts, solvates and hydrates thereof:

8-iodo-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

43. A compound according to claim 1 selected from the following compound, and pharmaceutically acceptable salts,

solvates and hydrates thereof:

8-trifluoromethyl-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine.

44. A compound according to claim 43, which is an *R* enantiomer.

45. A compound according to claim 43, which is an *S* enantiomer.

46. A compound according to claim 1 selected from the following compound, and pharmaceutically acceptable salts, solvates and hydrates thereof:

8-trifluoromethyl-1-ethyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine.

47. A compound according to claim 1 selected from the following compound, and pharmaceutically acceptable salts, solvates and hydrates thereof:

8-chloro-1-ethyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine.

48. A compound according to claim 47, which is an *R* enantiomer.

49. A compound according to claim 47, which is an *S* enantiomer.

50. A compound according to claim 1 selected from the following compound, and pharmaceutically acceptable salts, solvates and hydrates thereof:

8-bromo-1-ethyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine.

51. A compound according to claim 1 selected from the following compound, and pharmaceutically acceptable salts, solvates and hydrates thereof:

8-iodo-1-ethyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine.

52. A compound according to claim 1 selected from the following compound, and pharmaceutically acceptable salts, solvates and hydrates thereof:

7,8-dichloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine.

53. A compound according to claim 1 selected from the following compound, and pharmaceutically acceptable salts, solvates and hydrates thereof:

7,8-dichloro-1-ethyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine.

54. A compound according to claim 1 selected from the following compound, and pharmaceutically acceptable salts, solvates and hydrates thereof:

8-chloro-7-fluoro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine.

55. A compound according to claim 1 selected from the following compound, and pharmaceutically acceptable salts, solvates and hydrates thereof:

8-chloro-7-fluoro-1-ethyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine.

56. A pharmaceutical composition comprising a compound according to any one of claims 1 to 55 and a pharmaceutically acceptable carrier or excipient.

57. A pharmaceutical composition comprising a compound according to any one of claims 1 to 55 and its enantiomer, and a pharmaceutically acceptable carrier or excipient.

58. A pharmaceutical composition comprising a racemate of a compound according to any one of claims 1 to 55 and its enantiomer, and a pharmaceutically acceptable carrier or excipient.
- 5 59. A compound according to any one of claims 1 to 55 for use in a method of treatment of the human or animal body by therapy.
60. A compound according to any one of claims 1 to 55 for use in a method of prophylaxis or treatment of obesity of a mammal.
- 10 61. A compound according to any one of claims 1 to 55 for use in a method of decreasing food intake of a mammal.
62. A compound according to any one of claims 1 to 55 for use in a method of inducing satiety in a mammal.
63. A compound according to any one of claims 1 to 55 for use in a method of controlling weight gain of a mammal.
- 15 64. Use of a compound according to any one of claims 1 to 55 for the manufacture of a medicament for use in the prophylaxis or treatment of obesity of a mammal.
65. Use of a compound according to any one of claims 1 to 55 for the manufacture of a medicament for use in a method of decreasing food intake of a mammal.
- 20 66. Use of a compound according to any one of claims 1 to 55 for the manufacture of a medicament for use in a method of inducing satiety in a mammal.
- 25 67. Use of a compound according to any one of claims 1 to 55 for the manufacture of a medicament for use in a method of controlling weight gain of a mammal.

30 Patentansprüche

1. Verbindung der Formel (I):



worin:

45 R_1 -H oder
 C_{1-8} -Alkyl ist;

R_2 C_{1-8} -Alkyl,
-CH₂-O- C_{1-8} -Alkyl,
50 -C(=O)-O- C_{1-8} -Alkyl,
-C(=O)-NH- C_{1-8} -Alkyl,
-OH oder
-CH₂OH ist;

55 R_{2a} -H ist;

oder R_2 und R_{2a} zusammen -CH₂-CH₂- bilden;

R_3 Halogen,
Perhalogenalkyl oder
ein 5-gliedriger Heteroaryling mit bis zu zwei Heteroatomen, ausgewählt aus O, N und S, ist;

R_4 -H, Halogen, Perhalogenalkyl, -CN, -OR₆, SR₆, -NHR₆, -N(R₆)₂, -OH, Aryl oder Heteroaryl ist, worin das Aryl gegebenenfalls mit bis zu zwei Substituenten, ausgewählt aus C₁₋₈-Alkyl, Halogen, Perhalogenalkyl und Alkoxy, substituiert ist und das Heteroaryl gegebenenfalls mit bis zu zwei Substituenten, ausgewählt aus Halogen und C₁₋₈-Alkyl, substituiert ist;
oder:

R_3 und R_4 zusammen mit den Atomen, an die sie gebunden sind, einen 5- oder 6-gliedrigen heterozyklischen Ring mit einem O-Atom bilden;

die R_5 jeweils unabhängig voneinander C₁₋₈-Alkyl, C₁₋₈-Alkenyl, Aryl, Heteroaryl, Arylalkyl, Heteroarylalkyl oder Perhalogenalkyl oder Allyl sind; und

R_6 -H oder C₁₋₈-Alkyl;

oder ein pharmazeutisch annehmbares Salz, Solvat oder Hydrat davon;
mit der Maßgabe, dass:

wenn R_6 nicht -H ist, R_4 nicht -H sein kann; und

wenn R_1 und R_2 Methyl sind und R_4 -H ist, R_3 nicht Imidazol, substituiertes Imidazol oder ein Imidazolderivat sein kann;

und worin:

Aryl eine monozyklische oder polyzyklische aromatische Gruppe mit 3 bis 14 Kohlenstoffatomen bezeichnet;

Heteroaryl eine monozyklische oder polyzyklische aromatische Gruppe mit 3 bis 14 Kohlenstoffatomen und 1 bis 4 Ring-Heteroatomen, ausgewählt aus O, N und S, bezeichnet;

Alkoxy -O-Alkyl bezeichnet;

C₁₋₈-Alkyl eine unverzweigte, verzweigte oder zyklische Kohlenwasserstoffgruppe mit 1 bis 8 Kohlenstoffatomen bezeichnet;

C₁₋₈-Alkenyl eine unverzweigte, verzweigte oder zyklische Kohlenwasserstoffgruppe mit 1 bis 8 Kohlenstoffatomen und zumindest einer Doppelbindung bezeichnet;

Alkyl, das nicht C₁₋₈-Alkyl ist, Methyl, Ethyl, n-Propyl, Isopropyl, Cyclopropyl, n-Butyl, sec-Butyl, tert-Butyl, Cyclobutyl, Cyclopropylmethyl, n-Pentyl, Isopentyl, tert-Pentyl, Cyclopentyl, Cyclopentylmethyl, n-Hexyl oder Cyclohexyl bezeichnet.

2. Verbindung nach Anspruch 1, worin R_1 -H ist.

3. Verbindung nach Anspruch 1, worin R_1 C₁₋₈-Alkyl ist.

4. Verbindung nach Anspruch 1, worin R_1 Methyl ist.

5. Verbindung nach Anspruch 1, worin R_1 n-Propyl ist.

6. Verbindung nach einem der Ansprüche 1 bis 5, worin R_2 C₁₋₈-Alkyl ist.

7. Verbindung nach einem der Ansprüche 1 bis 5, worin R_2 Methyl ist.

8. Verbindung nach einem der Ansprüche 1 bis 5, worin R_2 Ethyl ist.

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9. Verbindung nach einem der Ansprüche 1 bis 5, worin R_2 Isopropyl ist.
10. Verbindung nach einem der Ansprüche 1 bis 5, worin R_2 und R_{2a} zusammen $-\text{CH}_2\text{-CH}_2$ bilden.
- 5 11. Verbindung nach einem der Ansprüche 1 bis 10, worin R_3 Halogen ist.
12. Verbindung nach einem der Ansprüche 1 bis 10, worin R_3 Chlor ist.
13. Verbindung nach einem der Ansprüche 1 bis 10, worin R_3 Brom ist.
- 10 14. Verbindung nach einem der Ansprüche 1 bis 10, worin R_3 Iod ist.
15. Verbindung nach einem der Ansprüche 1 bis 10, worin R_3 Perhalogenalkyl ist.
- 15 16. Verbindung nach einem der Ansprüche 1 bis 10, worin R_3 $-\text{CF}_3$ ist.
17. Verbindung nach einem der Ansprüche 1 bis 10, worin R_3 ein 5-gliedriger Heterocyclusring mit bis zu zwei Heteroatomen, ausgewählt aus O, N und S, ist.
- 20 18. Verbindung nach einem der Ansprüche 1 bis 10, worin R_3 aus der aus Thiophenyl, Furanyl, Pyrrolyl, Pyrazolyl und Imidazolyl bestehenden Gruppe ausgewählt ist.
19. Verbindung nach einem der Ansprüche 1 bis 18, worin R_4 $-\text{OR}_5$ ist.
- 25 20. Verbindung nach einem der Ansprüche 1 bis 18, worin R_4 Methoxy, Ethoxy, n-Propoxy, Isopropoxy oder Allyloxy ist.
21. Verbindung nach einem der Ansprüche 1 bis 18, worin R_4 Perhalogenalkyl ist.
22. Verbindung nach einem der Ansprüche 1 bis 18, worin R_4 $-\text{CF}_3$ ist.
- 30 23. Verbindung nach einem der Ansprüche 1 bis 18, worin R_4 ein 5-gliedriger Heterocyclusring mit bis zu zwei Heteroatomen, ausgewählt aus O, N und S, und mit bis zu zwei Substituenten, ausgewählt aus Halogen und C_{1-8} -Alkyl, ist.
- 35 24. Verbindung nach einem der Ansprüche 1 bis 18, worin R_4 aus Thiophenyl, Furanyl, Pyrrolyl, Pyrazolyl und Imidazolyl, gegebenenfalls substituiert mit einem oder zwei Substituenten, ausgewählt aus Halogen und Methyl, ausgewählt ist.
- 40 25. Verbindung nach einem der Ansprüche 1 bis 18, worin R_4 Phenyl, gegebenenfalls substituiert mit bis zu zwei Substituenten, ausgewählt aus C_{1-8} -Alkyl, Halogen und Alkoxy, ist.
26. Verbindung nach einem der Ansprüche 1 bis 10, worin R_3 und R_4 zusammen $-\text{O-CH=C(CH}_3\text{)-}$ bilden.
27. Verbindung nach einem der Ansprüche 1 bis 10, worin:
- 45 R_3 Halogen ist; und
 R_4 $-\text{OR}_5$ ist, worin R_5 C_{1-8} -Alkyl ist.
28. Verbindung nach einem der Ansprüche 1 bis 10, worin:
- 50 R_3 Halogen ist; und
 R_4 Methoxy ist.
29. Verbindung nach einem der Ansprüche 1 bis 10, worin:
- 55 R_3 Chlor oder Brom ist; und
 R_4 Methoxy ist.

30. Verbindung nach einem der Ansprüche 1 bis 10, worin:

R_3 Halogen ist; und
 R_4 Allyloxy ist.

31. Verbindung nach Anspruch 1, worin:

R_2 Methyl, Ethyl, Isopropyl oder $-\text{CH}_2\text{OH}$ ist; oder
 R_2 und R_{2a} zusammen $-\text{CH}_2-\text{CH}_2-$ bilden;
 R_3 Halogen oder ein 5-gliedriger Heteroaroring mit bis zu zwei Heteroatomen, ausgewählt aus O, N und S, und mit bis zu zwei Substituenten, ausgewählt aus Halogen und C_{1-3} -Alkyl, ist;
 R_4 -H, Alkoxy, ein 5-gliedriger Heteroaroring mit bis zu zwei Heteroatomen, ausgewählt aus O, N und S, und mit bis zu zwei Substituenten, ausgewählt aus Halogen und C_{1-3} -Alkyl, oder Phenyl, gegebenenfalls substituiert mit bis zu zwei Substituenten, ausgewählt aus C_{1-3} -Alkyl, Halogen und Alkoxy, ist; oder
 R_3 und R_4 zusammen $-\text{O}-\text{CH}=\text{C}(\text{CH}_3)-$ bilden; und
 R_5 -H oder Methyl ist.

32. Verbindung nach Anspruch 1, worin:

R_2 Methyl, Ethyl, Isopropyl oder $-\text{CH}_2\text{OH}$ ist; oder
 R_2 und R_{2a} zusammen $-\text{CH}_2-\text{CH}_2-$ bilden;
 R_3 Chlor, Brom oder Iod ist;
 R_4 Alkoxy ist; und
 R_5 -H oder Methyl ist.

33. Verbindung nach Anspruch 1, worin:

R_1 -H ist;
 R_2 Methyl ist;
 R_3 Chlor, Brom oder Thiophen ist;
 R_4 Alkoxy, Pyrazol-3-yl oder Phenyl ist, worin das Pyrazol gegebenenfalls bis zu zwei Substituenten, ausgewählt aus Halogen und C_{1-3} -Alkyl, aufweist und das Phenyl gegebenenfalls einen einzelnen Halogensubstituenten aufweist; und
 R_5 -H ist.

34. Verbindung nach Anspruch 1, ausgewählt aus:

8-Brom-7-hydroxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
7-Allyloxy-8-brom-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
7-Benzoyloxy-8-brom-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
8-Brom-7-ethoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
8-Brom-7-isopropoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
N-Propyl-8-brom-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
7-Hydroxy-8-Iod-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
7-Allyloxy-8-Iod-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
7-Allyloxy-8-chlor-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
7-Methoxy-1-methyl-8-(2-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepin;
8-Brom-1-cyclopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepin;
8-Brom-1-hydroxymethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepin;
8-Brom-1-isopropyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepin;
8-Brom-7-hydroxy-1-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
7-Allyloxy-8-brom-1-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
8-Brom-7-methoxy-1,4-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
7-Allyloxy-8-brom-1,4-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
8-Chlor-1-hydroxy-2,3,4,5-tetrahydro-1H-3-benzazepin;
8-Brom-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
8-Fluor-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
7,8-Dichlor-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin;

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N-Methyl-8-chlor-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
 8-Iod-1-methyl-7-trifluomethoxy-2,3,4,5-tetrahydro-1H-3-benzazepin;
 N-Propyl-8-Iod-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
 1-Ethyl-8-Iod-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepin;
 7-(2-Fluorphenyl)-8-chlor-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin; und
 8-Brom-1-methoxymethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepin;

sowie pharmazeutisch annehmbaren Salzen, Solvaten und Hydraten davon.

35. Verbindung nach Anspruch 1, ausgewählt aus:

8-Brom-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
 8-Chlor-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
 8-Iod-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
 N-Methyl-8-brom-7-methoxy-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin;
 8-Brom-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepin;
 8-Chlor-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepin;
 8-Iod-1-ethyl-7-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepin;
 7-Methoxy-1-methyl-8-trifluomethyl-2,3,4,5-tetrahydro-1H-3-benzazepin; und
 7-Methoxy-1-methyl-8-pentafluorethyl-2,3,4,5-tetrahydro-1H-3-benzazepin;

sowie pharmazeutisch annehmbaren Salzen, Solvaten und Hydraten davon.

36. Verbindung nach einem der Ansprüche 1 bis 35, die ein R-Enantiomer ist.

37. Verbindung nach einem der Ansprüche 1 bis 35, die ein S-Enantiomer ist.

38. Verbindung nach Anspruch 1, ausgewählt aus der folgenden Verbindung und pharmazeutisch annehmbaren Salzen, Solvaten und Hydraten davon:

8-Chlor-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin.

39. Verbindung nach Anspruch 38, die ein R-Enantiomer ist.

40. Verbindung nach Anspruch 38, die ein S-Enantiomer ist.

41. Verbindung nach Anspruch 1, ausgewählt aus der folgenden Verbindung sowie pharmazeutisch annehmbaren Salzen, Solvaten und Hydraten davon:

8-Brom-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin.

42. Verbindung nach Anspruch 1, ausgewählt aus der folgenden Verbindung sowie pharmazeutisch annehmbaren Salzen, Solvaten und Hydraten davon:

8-Iod-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin.

43. Verbindung nach Anspruch 1, ausgewählt aus der folgenden Verbindung sowie pharmazeutisch annehmbaren Salzen, Solvaten und Hydraten davon:

8-Trifluormethyl-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin.

44. Verbindung nach Anspruch 43, die ein R-Enantiomer ist.

45. Verbindung nach Anspruch 43, die ein S-Enantiomer ist.

46. Verbindung nach Anspruch 1, ausgewählt aus der folgenden Verbindung sowie pharmazeutisch annehmbaren Salzen, Solvaten und Hydraten davon:

8-Trifluormethyl-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepin.

47. Verbindung nach Anspruch 1, ausgewählt aus der folgenden Verbindung sowie pharmazeutisch annehmbaren Salzen, Solvaten und Hydraten davon:

8-Chlor-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepin.

48. Verbindung nach Anspruch 47, die ein R-Enantiomer ist.

49. Verbindung nach Anspruch 47, die ein S-Enantiomer ist.

50. Verbindung nach Anspruch 1, ausgewählt aus der folgenden Verbindung sowie pharmazeutisch annehmbaren Salzen, Solvaten und Hydraten davon:

8-Brom-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepin.

51. Verbindung nach Anspruch 1, ausgewählt aus der folgenden Verbindung sowie pharmazeutisch annehmbaren Salzen, Solvaten und Hydraten davon:

8-Iod-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepin.

52. Verbindung nach Anspruch 1, ausgewählt aus der folgenden Verbindung sowie pharmazeutisch annehmbaren Salzen, Solvaten und Hydraten davon:

7,8-dichlor-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin.

53. Verbindung nach Anspruch 1, ausgewählt aus der folgenden Verbindung sowie pharmazeutisch annehmbaren Salzen, Solvaten und Hydraten davon:

7,8-Dichlor-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepin.

54. Verbindung nach Anspruch 1, ausgewählt aus der folgenden Verbindung sowie pharmazeutisch annehmbaren Salzen, Solvaten und Hydraten davon:

8-Chlor-7-fluor-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin.

55. Verbindung nach Anspruch 1, ausgewählt aus der folgenden Verbindung sowie pharmazeutisch annehmbaren Salzen, Solvaten und Hydraten davon:

8-Chlor-7-fluor-1-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepin.

56. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach einem der Ansprüche 1 bis 55 und einen pharmazeutisch annehmbaren Träger oder Arzneimittelträger.

57. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach einem der Ansprüche 1 bis 55 und ihr Enantiomer sowie einen pharmazeutisch annehmbaren Träger oder Arzneimittelträger.

58. Pharmazeutische Zusammensetzung, umfassend ein Racemat einer Verbindung nach einem der Ansprüche 1 bis 55 und ihres Enantiomers sowie einen pharmazeutisch annehmbaren Träger oder Arzneimittelträger.

59. Verbindung nach einem der Ansprüche 1 bis 55 zur Verwendung in einem Verfahren zur Behandlung des menschlichen Körpers oder des Tierkörpers mittels Therapie.

60. Verbindung nach einem der Ansprüche 1 bis 55 zur Verwendung in einem Verfahren zur Prophylaxe gegen oder Behandlung von Obesität eines Säugetiers.

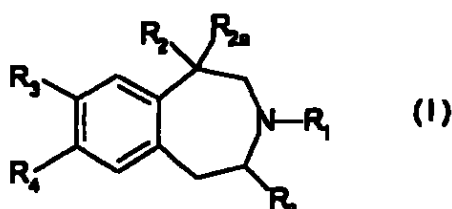
61. Verbindung nach einem der Ansprüche 1 bis 55 zur Verwendung in einem Verfahren zur Reduktion der Nahrungsaufnahme eines Säugetiers.

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62. Verbindung nach einem der Ansprüche 1 bis 55 zur Verwendung in einem Verfahren zur Vermittlung des Sättigungsgefühls bei einem Säugetier.
63. Verbindung nach einem der Ansprüche 1 bis 55 zur Verwendung in einem Verfahren zur Steuerung der Gewichtszunahme bei einem Säugetier.
64. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 55 zur Herstellung eines Medikaments zur Verwendung zur Prophylaxe gegen oder Behandlung von Obesität eines Säugetiers.
65. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 55 zur Herstellung eines Medikaments zur Verwendung in einem Verfahren zur Reduktion der Nahrungsaufnahme eines Säugetiers.
66. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 55 zur Herstellung eines Medikaments zur Verwendung in einem Verfahren zur Vermittlung des Sättigungsgefühls bei einem Säugetier.
67. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 55 zur Herstellung eines Medikaments zur Verwendung in einem Verfahren zur Steuerung der Gewichtszunahme bei einem Säugetier.

Revendications

1. Composé de la formule (I):



où:

R_1 est: -H ou
alkyle C_{1-8} ;

R_2 est: alkyle C_{1-8} ,
-CH₂-O-alkyle C_{1-8} ,
-C(=O)-O-alkyle C_{1-8} ,
-C(=O)-NH-alkyle C_{1-8} ,
-OH, ou
-CH₂OH;

R_{2a} est -H;

ou bien R_2 et R_{2a} forment ensemble -CH₂-CH₂;

R_3 est: halogène;
perhaloalkyle; ou
un cycle hétéroaryle à 5 membres ayant jusqu'à deux hétéroatomes sélectionnés parmi O, N et S;

R_4 est -H, halogène, perhaloalkyle, -CN, -OR₆, -SR₆, -NHR₆, -N(R₆)₂, -OH, aryle, ou hétéroaryle, où ledit aryle peut être facultativement substitué par jusqu'à deux substituants sélectionnés parmi alkyle C_{1-8} , halogène perhaloalkyle, et alcoxy, et ledit hétéroaryle peut être facultativement substitué par jusqu'à deux substituants sélectionnés parmi halogène et alkyle C_{1-8} ;
ou:

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R_3 et R_4 avec les atomes auxquels ils sont attachés forment un cycle hétérocyclique à 5 ou 6 membres ayant un atome de O;

chaque R^5 est indépendamment alkyle C_{1-8} , alcényle C_{1-8} , aryle, hétéroaryle, arylalkyle, hétéroarylalkyle ou perhaloalkyle, ou allyle; et

R_6 est -H ou alkyle C_{1-8} ;

ou un sel, solvate ou hydrate pharmaceutiquement acceptable;
à condition que:

si R_6 est autre que -H, alors R_4 ne puisse être -H; et
si R_1 et R_2 sont méthyle, et R_4 est -H, alors R_3 ne puisse être imidazole, imidazole substitué, ou dérivé d'imidazole;

et où:

aryle désigne un groupe aromatique monocyclique ou polycyclique ayant de 3 à 14 atomes de carbone;

hétéroaryle désigne un groupe aromatique monocyclique ou polycyclique ayant 3 à 14 atomes de carbone, et de 1 à 4 hétéroatomes dans le cycle, sélectionnés parmi O, N, et S;

alcoxy désigne -O-alkyle;

alkyle C_{1-8} désigne un groupe hydrocarbure à chaîne droite, ramifiée ou cyclique ayant de 1 à 8 atomes de carbone;

alcényle C_{1-8} désigne un groupe hydrocarbure à chaîne droite, ramifiée ou cyclique ayant de 1 à 8 atomes de carbone et au moins une double liaison;

alkyle, autre que alkyle C_{1-8} , désigne méthyle, éthyle, n-propyle, isopropyle, cyclopropyle, n-butyle, sec-butyle, tert-butyle, cyclobutyle, cyclopropylméthyle, n-pentyle, isopentyle, tert-pentyle, cyclopentyle, cyclopentylméthyle, n-hexyle, ou cyclohexyle.

2. Composé selon la revendication 1 où R_1 est -H.
3. Composé selon la revendication 1 où R_1 est alkyle C_{1-8} .
4. Composé selon la revendication 1 où R_1 est méthyle.
5. Composé selon la revendication 1 où R_1 est n-propyle.
6. Composé selon l'une quelconque des revendications 1 à 5, où R_2 est alkyle C_{1-8} .
7. Composé selon l'une quelconque des revendications 1 à 5, où R_2 est méthyle.
8. Composé selon l'une quelconque des revendications 1 à 5, où R_2 est éthyle.
9. Composé selon l'une quelconque des revendications 1 à 5, où R_2 est isopropyle.
10. Composé selon l'une quelconque des revendications 1 à 5, où R_2 et R_{2a} forment ensemble $-CH_2-CH_2-$.
11. Composé selon l'une quelconque des revendications 1 à 10, où R_3 est halogène.
12. Composé selon l'une quelconque des revendications 1 à 10, où R_3 est chlore.
13. Composé selon l'une quelconque des revendications 1 à 10, où R_3 est brome.

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14. Composé selon l'une quelconque des revendications 1 à 10, où R_3 est iode.
15. Composé selon l'une quelconque des revendications 1 à 10, où R_3 est perhaloalkyle.
- 5 16. Composé selon l'une quelconque des revendications 1 à 10, où R_3 est $-CF_3$.
17. Composé selon l'une quelconque des revendications 1 à 10, où R_3 est un cycle hétéroaryle à 5 membres ayant jusqu'à deux hétéroatomes sélectionnés parmi O, N et S.
- 10 18. Composé selon l'une quelconque des revendications 1 à 10, où R_3 est sélectionné parmi: thiophényle, furanyle, pyrrolyle, pyrazolylo et imidazolylo.
19. Composé selon l'une quelconque des revendications 1 à 18 où R_4 est $-OR_5$.
- 15 20. Composé selon l'une quelconque des revendications 1 à 18 où R_4 est méthoxy, éthoxy, n-propoxy, isopropoxy ou allyloxy.
21. Composé selon l'une quelconque des revendications 1 à 18 où R_4 est perhaloalkyle.
- 20 22. Composé selon l'une quelconque des revendications 1 à 18 où R_4 est $-CF_3$.
23. Composé selon l'une quelconque des revendications 1 à 18 où R_4 est un cycle hétéroaryle à 5 membres ayant jusqu'à deux hétéroatomes sélectionnés parmi O, N et S, et jusqu'à deux substituants sélectionnés parmi halogène et alkyle C_{1-8} .
- 25 24. Composé selon la revendication 1 où R_4 est sélectionné parmi thiophényle, furanyle, pyrrolyle, pyrazolylo et imidazolylo, facultativement substitué par un ou deux substituants sélectionnés parmi halogène et méthyle.
- 30 25. Composé selon l'une quelconque des revendications 1 à 18, où R_4 est phényle facultativement substitué par jusqu'à deux substituants sélectionnés parmi alkyle C_{1-8} , halogène, et alcoxy.
26. Composé selon l'une quelconque des revendications 1 à 10 où R_3 et R_4 pris ensemble forment $-O-CH=C(CH_3)-$.
- 35 27. Composé selon l'une quelconque des revendications 1 à 10 où:
 R_3 est halogène; et
 R_4 est $-OR_5$ où R_5 est alkyle C_{1-8} .
- 40 28. Composé selon l'une quelconque des revendications 1 à 10, où:
 R_3 est halogène; et
 R_4 est méthoxy.
- 45 29. Composé selon l'une quelconque des revendications 1 à 10 où:
 R_3 est chlore ou brome; et
 R_4 est méthoxy.
- 50 30. Composé selon l'une quelconque des revendications 1 à 10 où:
 R_3 est halogène; et
 R_4 est allyloxy.
- 55 31. Composé selon la revendication 1 où:
 R_2 est méthyle, éthyle, isopropyle, ou $-CH_2OH$; ou
 R_2 et R_{2a} , pris ensemble, forment $-CH_2-CH_2-$;
 R_3 est halogène ou un cycle hétéroaryle à 5 membres ayant jusqu'à deux hétéroatomes sélectionnés parmi

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O, N et S, et jusqu'à deux substituants sélectionnés parmi halogène et alkyle_{C₁₋₈};

R₄ est -H, alcoxy, un cycle hétéroaryle à 5-membres ayant jusqu'à deux hétéroatomes sélectionnés parmi O, N et S et jusqu'à deux substituants sélectionnés parmi halogène et alkyle_{C₁₋₈} ou phényle facultativement substitué par jusqu'à deux substituants sélectionnés parmi alkyle_{C₁₋₈}, halogène et alcoxy;

ou bien R₃ et R₄, pris ensemble, forment -O-CH=C(CH₃)-; et

R₅ est -H ou méthyle.

32. Composé selon la revendication 1 où:

R₂ est méthyle, éthyle, isopropyle, ou -CH₂OH; ou

R₂ et R_{2a}, pris ensemble, forment -CH₂-CH₂-;

R₃ est chlore, brome, ou iode;

R₄ est alcoxy; et

R₅ est -H ou méthyle.

33. Composé selon la revendication 1 où:

R₁ est -H;

R₂ est méthyle;

R₃ est chlore, brome, ou thiophène;

R₄ est alcoxy, pyrazoly-3-yle ou phényle où ledit pyrazole a facultativement jusqu'à deux substituants sélectionnés parmi halogène et alkyle_{C₁₋₈}, et ledit phényle a facultativement un seul substituant halogène; et

R₅ est -H.

34. Composé de la revendication 1, sélectionné parmi:

8-bromo-7-hydroxy-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

7-allyloxy-8-bromo-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

7-benzoyloxy-8-bromo-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

8-bromo-7-éthoxy-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

8-bromo-7-isopropoxy-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

N-propyl-8-bromo-7-méthoxy-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

7-hydroxy-8-iodo-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

7-allyloxy-8-iodo-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

7-allyloxy-8-chloro-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

7-méthoxy-1-méthyl-8-(2-thiényl)-2,3,4,5-tétrahydro-1H-3-benzazépine;

8-bromo-1-cyclopropyl-7-méthoxy-2,3,4,5-tétrahydro-1H-3-benzazépine;

8-bromo-1-hydroxyméthyl-7-méthoxy-2,3,4,5-tétrahydro-1H-3-benzazépine;

8-bromo-1-isopropyl-7-méthoxy-2,3,4,5-tétrahydro-1H-3-benzazépine;

8-bromo-7-hydroxy-1-isopropyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

7-allyloxy-8-bromo-1-isopropyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

8-bromo-7-méthoxy-1,4-diméthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

7-allyloxy-8-bromo-1,4-diméthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

8-chloro-1-hydroxy-2,3,4,5-tétrahydro-1H-3-benzazépine;

8-bromo-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

8-fluoro-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

7,8-dichloro-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

N-méthyl-8-chloro-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

8-iodo-1-méthyl-7-trifluorométhoxy-2,3,4,5-tétrahydro-1H-3-benzazépine;

N-propyl-8-iodo-7-méthoxy-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

1-éthyl-8-iodo-7-méthoxy-2,3,4,5-tétrahydro-1H-3-benzazépine;

7-(2-fluorophényl)-8-chloro-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine; et

8-bromo-1-méthoxyméthyl-7-méthoxy-2,3,4,5-tétrahydro-1H-3-benzazépine;

et leurs sels, solvates et hydrates pharmaceutiquement acceptables.

35. Composé selon la revendication 1, sélectionné parmi:

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8-bromo-7-méthoxy-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;
 8-chloro-7-méthoxy-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;
 8-iodo-7-méthoxy-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;
 N-méthyl-8-bromo-7-méthoxy-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;
 5 8-bromo-1-éthyl-7-méthoxy-2,3,4,5-tétrahydro-1H-3-benzazépine;
 8-chloro-1-éthyl-7-méthoxy-2,3,4,5-tétrahydro-1H-3-benzazépine;
 8-iodo-1-éthyl-7-méthoxy-2,3,4,5-tétrahydro-1H-3-benzazépine;
 7-méthoxy-1-méthyl-8-trifluorométhyl-2,3,4,5-tétrahydro-1H-3-benzazépine;
 et
 10 7-méthoxy-1-méthyl-8-pentafluoroéthyl-2,3,4,5-tétrahydro-1H-3-benzazépine;

et leurs sels, solvates et hydrates pharmaceutiquement acceptables.

36. Composé selon l'une quelconque des revendications 1 à 35, qui est un énantiomère R.

37. Composé selon l'une quelconque des revendications 1 à 35, qui est un énantiomère S.

38. Composé selon la revendication 1, sélectionné parmi le composé qui suit et ses sels, solvates et hydrates pharmaceutiquement acceptables:

8-chloro-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine.

39. Composé selon la revendication 38, qui est un énantiomère R.

40. Composé selon la revendication 38, qui est un énantiomère S.

41. Composé selon la revendication 1 sélectionné parmi le composé suivant, et ses sels, solvates et hydrates pharmaceutiquement acceptables:

8-bromo-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine.

42. Composé selon la revendication 1, sélectionné parmi le composé suivant, et ses sels, solvates et hydrates pharmaceutiquement acceptables:

8-iodo-1-méthyl-2,3,4,5-1H-3-benzazépine.

43. Composé selon la revendication 1, sélectionné parmi le composé suivant, et ses sels, solvates et hydrates pharmaceutiquement acceptables:

8-trifluorométhyl-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine.

44. Composé selon la revendication 43, qui est un énantiomère R.

45. Composé selon la revendication 43, qui est un énantiomère S.

46. Composé selon la revendication 1, sélectionné parmi le composé suivant et ses sels, solvates et hydrates pharmaceutiquement acceptables:

8-trifluorométhyl-1-éthyl-2,3,4,5-tétrahydro-1H-3-benzazépine.

47. Composé selon la revendication 1, sélectionné parmi le composé suivant et ses sels, solvates et hydrates pharmaceutiquement acceptables:

8-chloro-1-éthyl-2,3,4,5-1H-3-benzazépine.

48. Composé selon la revendication 47, qui est un énantiomère R.

49. Composé selon la revendication 47, qui est un énantiomère S.

50. Composé selon la revendication 1, sélectionné parmi le composé suivant et ses sels, solvates et hydrates pharmaceutiquement acceptables:

8-bromo-1-éthyl-2,3,4,5-tétrahydro-1H-3-benzazépine.

51. Composé selon la revendication 1, sélectionné parmi le composé suivant et ses sels, solvates et hydrates pharmaceutiquement acceptables:

8-iodo-1-éthyl-2,3,4,5-tétrahydro-1H-3-benzazépine.

52. Composé selon la revendication 1, sélectionné parmi le composé suivant et ses sels, solvates et hydrates pharmaceutiquement acceptables:

7,8-dichloro-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine.

53. Composé selon la revendication 1, sélectionné parmi le composé suivant et ses sels, solvates et hydrates pharmaceutiquement acceptables:

7,8-dichloro-1-éthyl-2,3,4,5-tétrahydro-1H-3-benzazépine.

54. Composé selon la revendication 1, sélectionné parmi le composé suivant et ses sels, solvates et hydrates pharmaceutiquement acceptables:

8-chloro-7-fluoro-1-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine.

55. Composé selon la revendication 1, sélectionné parmi le composé suivant et ses sels, solvates et hydrates pharmaceutiquement acceptables:

8-chloro-7-fluoro-1-éthyl-2,3,4,5-tétrahydro-1H-3-benzazépine.

56. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 55 et un support ou excipient pharmaceutiquement acceptable.

57. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 55 et son énantiomère, et un support ou excipient pharmaceutiquement acceptable.

58. Composition pharmaceutique comprenant un racémate d'un composé selon l'une quelconque des revendications 1 à 55 et son énantiomère et un support ou excipient pharmaceutiquement acceptable.

59. Composé selon l'une quelconque des revendications 1 à 55 à utiliser dans une méthode de traitement du corps humain ou animal par thérapie.

60. Composé selon l'une quelconque des revendications 1 à 55 à utiliser dans une méthode de prophylaxie ou de traitement de l'obésité d'un mammifère.

61. Composé selon l'une quelconque des revendications 1 à 55 à utiliser dans une méthode pour diminuer l'absorption de nourriture chez un mammifère.

62. Composé selon l'une quelconque des revendications 1 à 55 à utiliser dans une méthode pour induire la satiété chez un mammifère.

63. Composé selon l'une quelconque des revendications 1 à 55 à utiliser dans une méthode pour contrôler le gain de poids d'un mammifère.

64. Utilisation d'un composé selon l'une quelconque des revendications 1 à 55 pour la fabrication d'un médicament à utiliser dans la prophylaxie ou le traitement de l'obésité chez un mammifère.

65. Utilisation d'un composé selon l'une quelconque des revendications 1 à 55 pour la fabrication d'un médicament à

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utiliser dans une méthode pour diminuer l'absorption de nourriture par un mammifère.

66. Utilisation d'un composé selon l'une quelconque des revendications 1 à 55 pour la fabrication d'un médicament à utiliser dans une méthode pour induire la satiété chez un mammifère.
67. Utilisation d'un composé selon l'une quelconque des revendications 1 à 55 pour la fabrication d'un médicament à utiliser dans une méthode pour contrôler le gain de poids d'un mammifère.

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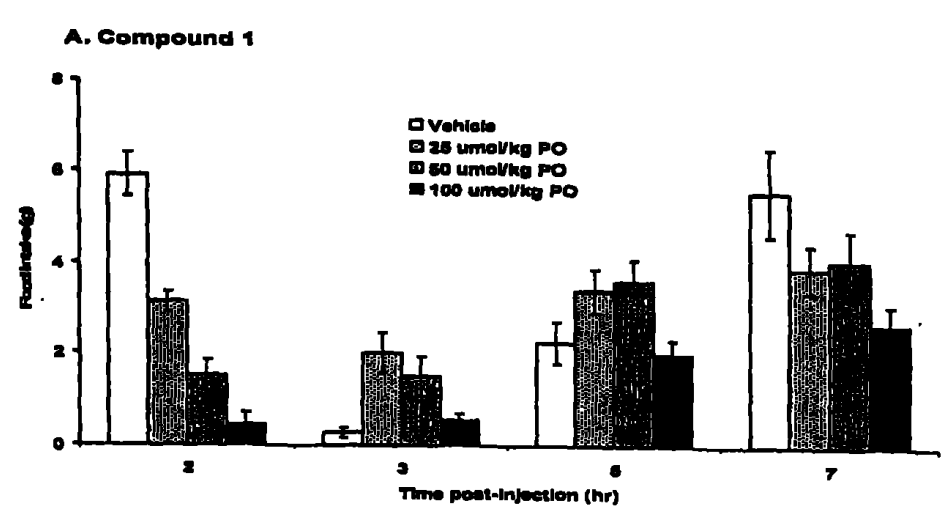
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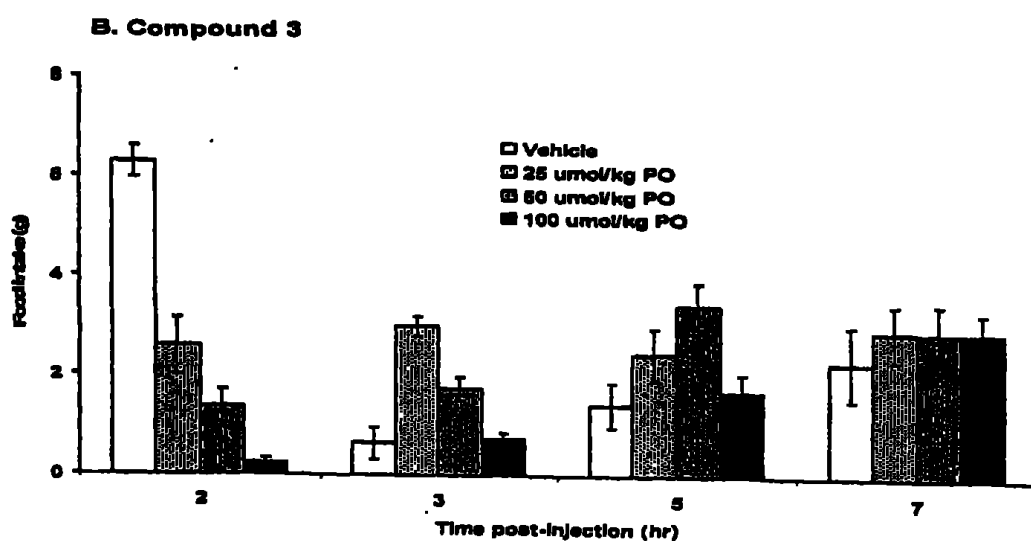
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Fig. 1A



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Fig. 1B



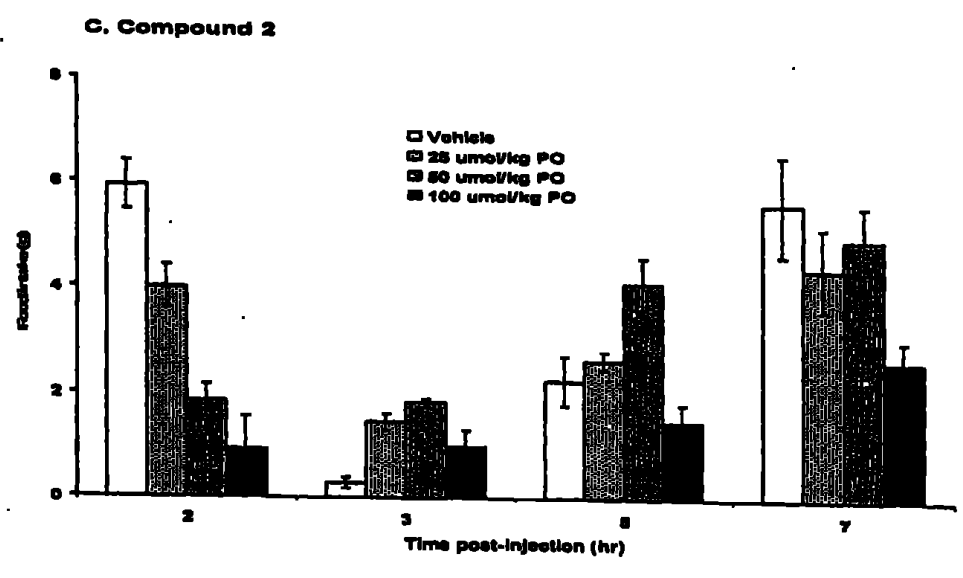


Fig. 1C

Fig. 1D

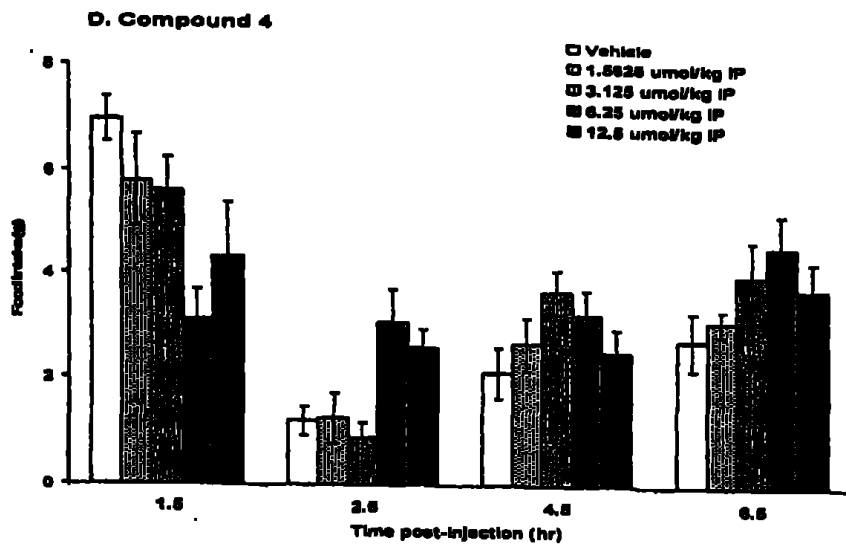
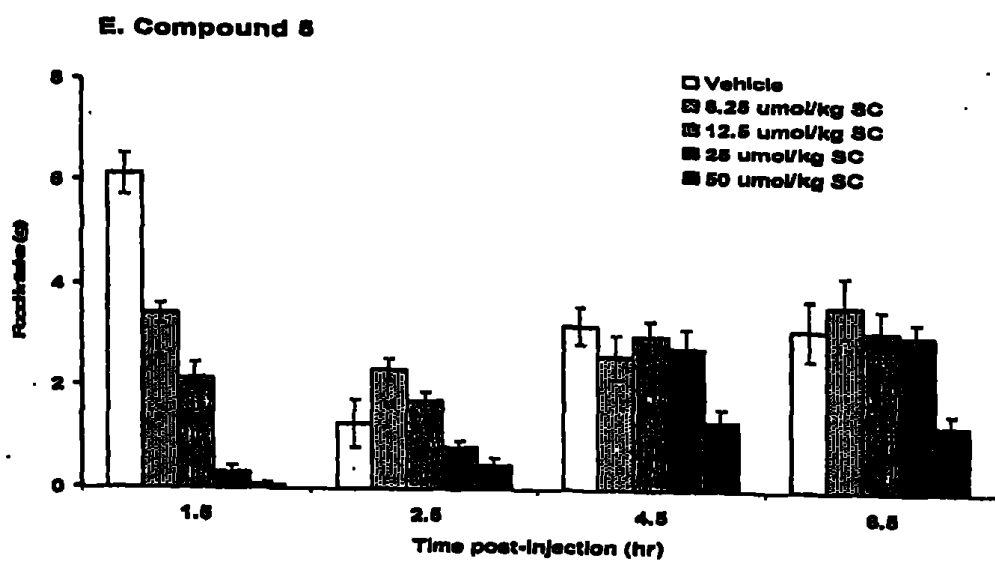


Fig. 1E



F. Compound 12

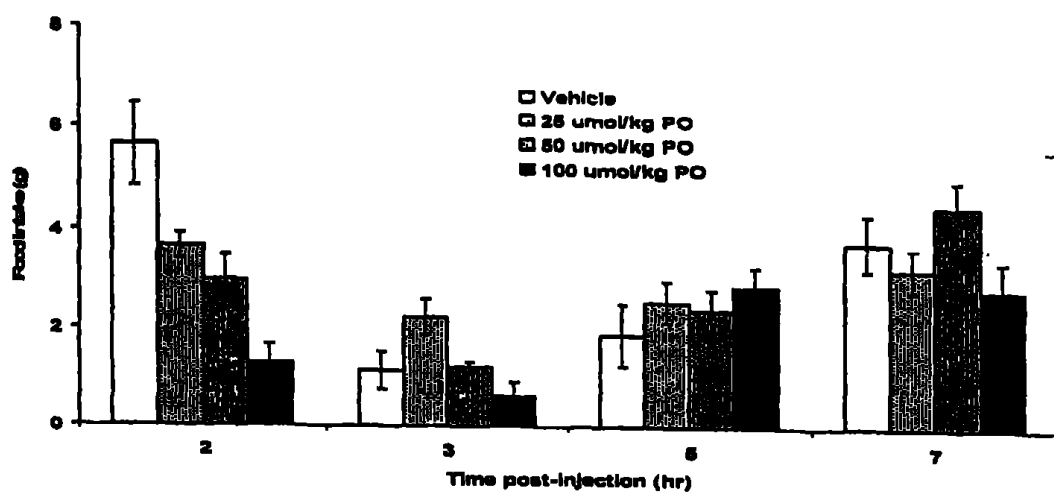
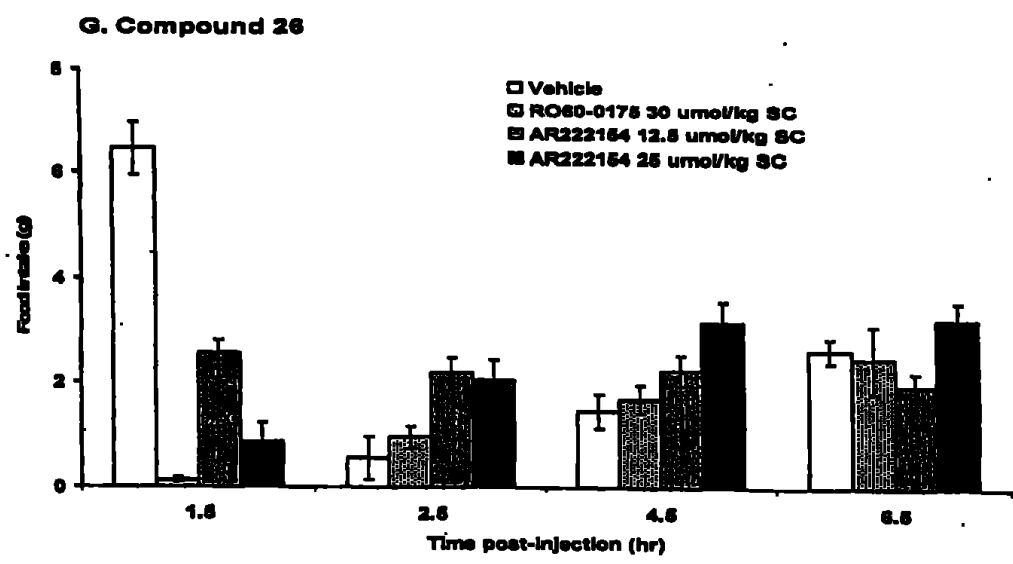


Fig. 1F

Fig. 1G



2020
Bogotá D C

Doctor(a)
ALICIA LLOREDA RICAURTE
Apoderado(a)

REFERENCIA:	Radicación N°	04-100885
	Solicitud internacional	PCT/US03/11076
	Fecha límite de inicio en fase nacional	12/11/2004
	Trámite	011
	Evento	379
	Actuación	416
	Oficio N°	1413
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en el asunto, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486, de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y comercio, se envía el extracto de la solicitud a la oficina de comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo dispone el artículo 40 de la referida Decisión 486.

Cúmplase
Dado en Bogotá D C., 02 Dic. 2003


ALIX CARMENZA CESPEDES DE VERGEL
Jefe División de Nuevas Creaciones.

202028

Al contestar favor indique el número de radicación consignado en el sticker

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