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SUPERINDUSTRIA Y COMERCIO	
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Trámite	002 PATENTES D 1 REGISTRO/ 329 COMPLEMEN
Dependencia	2020 DIVISION DE NUEVAS CREACIONES

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E S D.

Re P1 -PHARMACIA & UPJOHN COMPANY .-Solicitud de Patente de
Invención para "AMINOALCOXICARBAZOLES PARA EL
TRATAMIENTO DE ENFERMEDADES DEL SNC" -Clase A 61 -
Expediente numero 00-066 777 -

1 Me refiero a mi solicitud arriba nombrada de fecha 5 de Septiembre de 2000

2 Anexas me permito presentar a usted

(1) Copias autenticas (2) de las primeras solicitudes de patente presentadas para el invento arriba nombrado respecto de las cuales reclamo prioridad, a saber

(a) Copia auténtica debidamente certificada de la solicitud estadounidense numero 60/152 638 de 7 de Septiembre de 1999, junto con la traducción Oficial numero LLC-069-2000 correspondiente a las legalizaciones y reivindicaciones de dicho documento,

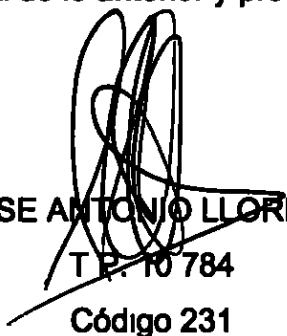
(b) Copia autentica debidamente certificada de la solicitud estadounidense numero 60/203 771 de 12 de Mayo de 2000 junto con la traducción oficial numero LLC-070-2000 correspondiente a las legalizaciones y reivindicaciones de dicho documento,

(2) Copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá de los documentos que acreditan la calidad de Traductor Oficial del Señor Gabriel Rueda Chadid quien elaboró la traducción de las solicitudes estadounidenses numero 60/152 638 y 60/203 771, respecto de las cuales se reivindica prioridad en el presente caso

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3 Ruego a usted tomar nota de lo anterior y proceder de conformidad

Señor Superintendente,



JOSE ANTONIO LLORED A

T.P. 10 784

Código 231

**EL SUSCRITO JEFE DEL AREA DE
LEGALIZACIONES DE MINISTERIO DE
RELACIONES EXTERIORES.**

HACE CONSTAR

Que el señor Gabriel Rueda, se encuentra debidamente registrado ante este Ministerio, como traductor e intérprete oficial para los idiomas INGLES -ESPAÑOL, ESPAÑOL - INGLES.

Para efectos de esta certificación el interesado presenta copia autenticada de la certificación del Ministerio de Justicia acerca de la vigencia de la resolución 1982

Dada en Santafe de Bogota, D C , a los diez y nueve días (19) del mes de diciembre de 1994


Neilson Sánchez Torres
Jefe Area de Legalizaciones

NOTARIO SEX O ENCARGADO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE ESTA COPIA FOTOSTATICA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
21 AGO. 1998
PABLO MENDEZ BARZ JAS
NOTARIO



Ministerio de Justicia y del Derecho

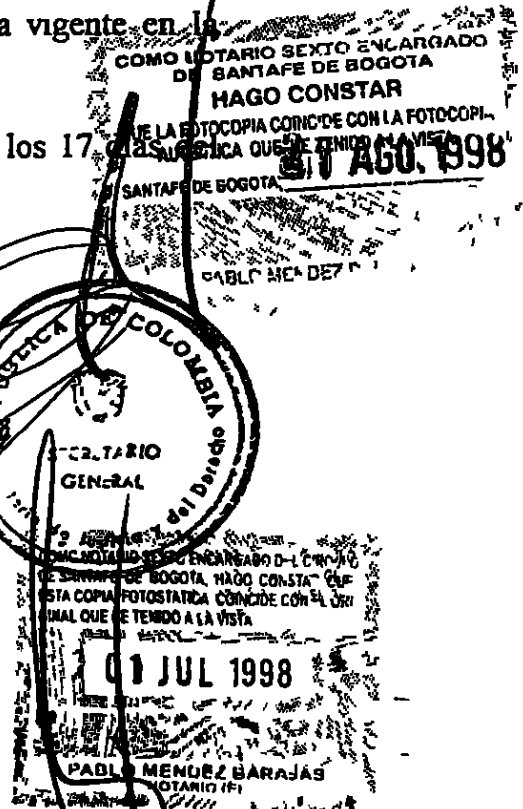
EL SECRETARIO GENERAL DEL MINISTERIO DE
JUSTICIA Y DEL DERECHO

CERTIFICA

Que por Resolución 5996 del 29 de noviembre de 1982, le fue expedida licencia para ejercer funciones de Traductor e Interprete Oficial en los idiomas INGLES-ESPAÑOL, ESPAÑOL-INGLES a GABRIEL RUEDA CHADID, identificado con la cedula de ciudadanía No 17 124 145 expedida en Bogota Que dicha resolucion se encuentra vigente en la fecha

A solicitud del interesado, en Santafe de Bogota D C, a los 17
mes de noviembre de 1994

JORGE LUIS SABOGAL SABOGAL



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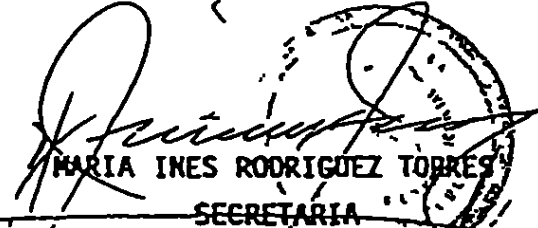
TRIBUNAL SUPERIOR DEL DISTRITO JUDICIAL DE SANTAFE DE BOGOTA
SECRETARIA GENERAL

LA SUSCRITA SECRETARIA DEL H. TRIBUNAL SUPERIOR DEL DISTRITO JUDICIAL
DE SANTAFE DE BOGOTA,

C E R T I F I C A

Que el Acuerdo No. 183 de diciembre 3 de 1982 emanado de esta Corporación, por medio del cual dió posesión al señor GABRIEL RUEDA CHADID, identificado con Cédula de Ciudadanía número 17 124 145 de Bogotá, como TRADUCTOR E INTERPRETE OFICIAL de los idiomas INGLÉS-ESPAÑOL, ESPAÑOL-INGLES, en virtud de la Resolución No. 5996, de 21 AGO. 1998 VIGENTE.

Se expide en Santafé de Bogotá D C , a dieciseis (16) de noviembre de mil novecientos noventa y cuatro (1994)


MARIA INES RODRIGUEZ TORRES
SECRETARIA
COMO NOTARIO ENCARGADO
DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CONCIERDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 16 SET 1998

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CONCIERDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA
01 JUL 1998
JUAN MANUEL BOTERO MEDINA
NOTARIO
PASLO MENDEZ PARRA
COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CONCIERDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA
23 NOV. 1998
JUAN MANUEL BOTERO MEDINA
NOTARIO

CTM /

REF LLC-069-2000 La presente es Traducción Oficial de un documento presentado originalmente en inglés Esta traducción es elaborada por Gabriel Rueda Chadid (Traductor Oficial)

ESTADOS UNIDOS DE AMERICA

A TODOS AQUELLOS QUE LLEGAREN A LEER EL CONTENIDO DEL

PRESENTE DOCUMENTO LES CERTIFICAMOS

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Marcas y Patentes de los Estados Unidos

Junio 13 del 2000

Se certifica que anexo se encuentra fiel copia de los Registros de la Oficina de Marcas y Patentes de los Estados Unidos correspondientes a los documentos de la patente solicitada y cuya identificación aparece más adelante, la cual cumplió con los requerimientos exigidos para que se otorgue una fecha de presentación de acuerdo con lo dispuesto en la Sección 35 USC 111

Número de Solicitud 60/152 638

Fecha de presentación Septiembre 07 de 1999

Por autorización del

COMISIONADO DE MARCAS REGISTRADAS Y PATENTES

P SWAIN

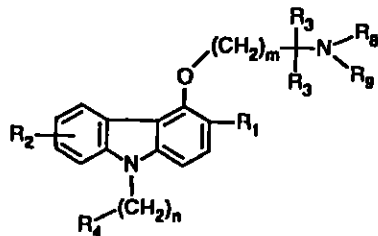
Funcionario Encargado de Certificaciones (Hay firma y sello)

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REIVINDICACIONES

1 Un compuesto de la formula



I

donde

R_1 es

- (a) H,
- (b) halo, o
- (c) alquilo C_{1-6} ,

R_2 es

- (a) H,
- (b) halo,
- (c) -OH,
- (d) -CN,
- (e) -CF₃,
- (f) -O(C_{1-6})alquilo,
- (g) alquilo C_{1-6} ,
- (h) cicloalquilo C_{3-6} ,
- (i) -NR₅R₆,
- (j) -CONR₅R₆,
- (k) -SO₂NR₅R₆,
- (l) -COOR₇,
- (m) fenilo, sustituido opcionalmente por halo, OH,

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alquilo O(C₁₋₄), o alquilo C₁₋₆,

donde cada R₃ es independientemente

- (a) H,
- (b) alquilo C₁₋₆, o
- (c) cicloalquilo C₃₋₆,

R₄ es

- (a) arilo, o
- (b) heteroarilo,

R₅ y R₆ son independientemente

- (a) H,
- (b) alquilo C₁₋₆, o
- (c) cicloalquilo C₃₋₆,

R₇ es

- (a) H,
- (b) alquilo C₁₋₆, o
- (c) fenilo-(alquilo C₁₋₃) donde el fenilo puede sustituirse por R₃,

R₈ y R₉ son independientemente

- (a) H,
- (b) alquilo C₁₋₆, sustituido opcionalmente por arilo, heteroarilo, o cicloalquilo C₃₋₆,
- (c) alqueno C₂₋₆,
- (d) cicloalquilo C₃₋₆,
- (e) alquilo C₂₋₆ sustituido por R₁₀,
- (f) -CHO, con la condición de que tan solo uno de los R₈

y R_8 sea CHO, y el otro sea H,

- (g) arilo,
- (h) heterocíclico, donde el heterocíclico se enlaza por medio del átomo de carbono al nitrógeno al cual se encuentra adherido, o

(1) R_8 y R_9 tomados conjuntamente con el nitrógeno al cual se adhieren forman un anillo heterocíclico donde el anillo heterocíclico puede tener de uno a dos heteroátomos adicionales que se seleccionan a partir del grupo conformado por oxígeno, azufre y N(Y) y donde los átomos de carbono del anillo heterocíclico se sustituyen opcionalmente por uno o dos R_{14} ,

R_{10} es

- (a) -OH,
- (b) -O(alquilo C_{1-4}), alquilo opcionalmente sustituido por OH,
- (c) -O(alquilo C_{1-4})- $NR_{11}R_{12}$,
- (d) heterocíclico, o
- (e) -CO₂R₅,

R_{11} y R_{12} son independientemente,

- (c) H, o
- (d) alquilo C_{1-4} ,

arilo es fenilo o naftilo, sustituido opcionalmente por uno o más R_{13} ,

heteroarilo es un radical de un anillo aromático monocíclico de cinco o seis miembros que tiene uno o dos heteroátomos y cada uno se selecciona a partir del grupo conformado por oxígeno, azufre, y N(X), o un radical de un anillo aromático bicíclico

orto-fusionado de nueve o diez miembros que tiene uno, dos o tres heteroátomos, donde cada uno se selecciona a partir del grupo conformado por oxígeno, azufre, y N(X),

donde los átomos de carbono del heteroarilo pueden estar sustituidos por R₁₃,

el heterocíclico es un radical de un anillo heterocíclico parcialmente saturado o insaturado de cinco, seis o siete miembros que tiene uno, dos o tres heteroátomos que se selecciona a partir del grupo conformado por oxígeno, azufre y N(Y) donde los átomos de carbono del anillo heterocíclico pueden sustituirse por R₁₄,

X está ausente, H o alquilo C₁₋₄,

Y es

- (a) H,
- (b) alquilo C₁₋₆, sustituido opcionalmente por arilo o heteroarilo,
- (c) cicloalquilo C₃₋₆, o
- (d) alquilo C₂₋₆ sustituido por -OH, -O(alquilo C₁₋₄), -O(alquilo C₁₋₄)-NR₁₁R₁₂, -CO₂R₅, o NHCHO, o
- (e) -OH,

R₁₃ es

- (a) halo,
- (b) -OH,
- (c) -CN,
- (d) -CF₃,
- (e) -O(C₁₋₆)alquilo,
- (f) alquilo C₁₋₆,
- (g) cicloalquilo C₃₋₆,

- (h) $-NR_5R_6$,
- (i) $-CONR_5R_6$,
- (j) $-SO_2NR_5R_6$,
- (k) $-COOR_7$,
- (l) $-OCF_3$, o
- (m) fenilo, sustituido opcionalmente por halo, OH, $O(C_{1-4})$ alquilo, o alquilo C_{1-6} ,

R_{14} es

- (a) alquilo C_{1-6} ,
- (b) cicloalquilo C_{3-6} ,
- (c) alquilo C_{2-6} sustituido por $-OH$, $-O(\text{alquilo } C_{1-4})$, $-O(\text{alquilo } C_{1-4})-NR_{11}R_{12}$, o $-CO_2R_5$,
- (d) $-OH$, o
- (e) oxo ($=O$),

m es 2, 3 o 4,

n es 1, 2, 3 o 4,

Cicloalquilo C_{3-6} en cada una de las definiciones dadas anteriormente, pueden sustituirse cada uno y en forma independiente por OH, alquilo C_{1-4} , u oxo ($=O$), con las siguientes condiciones

(a) cuando R_4 es arilo sustituido por fluoro, R_2 no puede ser fluoro ni cloro en la posición C-6 de la formula I,

(b) cuando R_4 es 4-tiazolilo, no se puede sustituir por 4-clorofenilo,

o una sal farmacéuticamente aceptable, racemate, solvato, tautomero, isomero óptico o sus derivados de precursores de drogas,

(c) cuando R₄ es heteroarilo, heteroarilo no es 4-piridilo

2 Un compuesto de la reivindicación 1 donde R₁ es H, halo, o alquilo C₁₋₆

3 Un compuesto de la reivindicación 1 donde R₁ es H, CH₃, fluoro o cloro

4 Un compuesto de la reivindicación 1 donde R₁ es H

5 Un compuesto de la reivindicación 1 donde R₂ es H, halo, -OH, -CN, -CF₃, -O(C₁₋₆)alquilo, alquilo C₁₋₆, cicloalquilo C₃₋₆, -NR₅R₆, -CONR₅R₆, -SO₂NR₅R₆, -COOR₇, o fenilo, sustituido opcionalmente por halo, OH, O(C₁₋₄)alquilo, o alquilo C₁₋₆, donde R₅, R₆ y R₇ corresponden a la definición dada en la reivindicación 1

6 Un compuesto de la reivindicación 1 donde R₂ es H, halo, o alquilo C₁₋₆

7 Un compuesto de la reivindicación 1 donde R₂ es H

8 Un compuesto de la reivindicación 1 donde R₂ es cloro o fluoro

9 Un compuesto de la reivindicación 1 donde R₂ es metilo

10 Un compuesto de la reivindicación 1 donde m es 2

11 Un compuesto de la reivindicación 1 donde R₄ es arilo o heteroarilo

12 Un compuesto de la reivindicación 1 donde R₄ es fenilo

13 Un compuesto de la reivindicación 1 donde R₄ es fenilo sustituido por fluoro o cloro

14 Un compuesto de la reivindicación 1 donde R₄ es piridilo, tiofeno, benzotiofeno, benzofurano, benzimidazola, imidazola o tiazola

15 Un compuesto de la reivindicación 1 donde R₄ es metilo-1,3-tiazol-4-ilo o 5-cloro-1-benzotiofn-3-ilo

16 Un compuesto de la reivindicación 1 donde cada R₃ es independientemente H, alquilo C₁₋₆, o cicloalquilo C₃₋₆

17 Un compuesto de la reivindicación 1 donde cada R₃ es independientemente H

18 Un compuesto de la reivindicación 1 donde R₈ y R₉ son independientemente

- (a) H,
- (b) alquilo C₁₋₆, sustituido opcionalmente por arilo, heteroarilo, o cicloalquilo C₃₋₆,
- (c) alqueno C₂₋₆,
- (d) cicloalquilo C₃₋₆,

- (e) alquilo C_{2-6} sustituido por R_{10} ,
- (f) $-CHO$,
- (g) arilo,
- (h) heterocíclico, donde el heterocíclico se enlaza vía átomo de carbono con el nitrógeno al cual se adhiere, o

(1) R_8 y R_9 tomados conjuntamente con el nitrógeno al cual se adhieren forman un anillo heterocíclico donde dicho anillo heterocíclico puede tener de uno a dos heteroátomos adicionales que se seleccionan a partir del grupo conformado por oxígeno, azufre y $N(Y)$ y donde los átomos de carbono del anillo heterocíclico se sustituyen opcionalmente por uno o dos R_{14} , donde R_{10} y Y son iguales a la definición dada en la reivindicación 1

19 Un compuesto de la reivindicación 1 donde R_8 es H, R_9 es H

20 Un compuesto de la reivindicación 1 donde R_8 es H, R_9 es alquilo C_{1-6} , alqueno C_{2-4} , o $-CHO$

21 Un compuesto de la reivindicación 1 donde R_8 es H, R_9 es metilo

22 Un compuesto de la reivindicación 1 donde R_8 es H, R_9 es alquilo C_{1-6} sustituido por cicloalquilo C_{3-6} , donde el cicloalquilo es sustituido opcionalmente por $-OH$, alquilo C_{1-4} , u oxo

23 Un compuesto de la reivindicación 22 donde el cicloalquilo es ciclopropilo, ciclobutilo, ciclopentilo, o ciclohexilo

24 Un compuesto de la reivindicación 1 donde R₈ es H, R₉ es alquilo C₂₋₆ sustituido por -OH, -O(alquilo C₁₋₄), -O(alquilo C₁₋₄-OH), o -CO₂alquilo C₁₋₄

25 Un compuesto de la reivindicación 1 donde R₈ es H, R₉ es ciclopropilo, ciclobutilo, ciclopentilo, o ciclohexilo, sustituido opcionalmente por -OH, alquilo C₁₋₄ u oxo

26 Un compuesto de la reivindicación 1 donde R₈ es H, R₉ es alquilo C₁₋₆ sustituido por

- (a) fenilo, sustituido opcionalmente por fluoro o cloro,
- (b) piridilo, tiofeno, benzotiofeno, benzofurano, benzimidazola, imidazola o tiazola, o
- (c) heterocíclico, que se enlaza por medio del átomo de carbono al nitrógeno al que se le adhiere

27 Un compuesto de la reivindicación 21 donde R₈ es H, R₉ es alquilo C₁₋₄ sustituido por fluorofenilo, clorofenilo, piridilo, benzimidazola, o 1-benzil-piperidinilo

28 Un compuesto de la reivindicación 1 donde R₈ es H, R₉ es alquilo C₂₋₆ sustituido por acetidilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, 1-benzil-piperidinilo, 1-metil-piperidinilo, dioxolano, imidazolidina, oxazolidinilo, oxatolano, 4-hidroxi-1-piperidinilo, 4-etanol-1-piperazinilo-, 4-etilformamida-1-

piperazinilo-, o 4-metil-1-piperazinilo

29 Un compuesto de la reivindicación 1 donde R₈ y R₉ tomados conjuntamente con el nitrógeno al que se le adhieren forman un anillo heterocíclico, donde dicho anillo heterocíclico puede tener de uno a dos heteroátomos adicionales que se seleccionan a partir del grupo conformado por oxígeno, azufre y N(Y), donde Y corresponde a la definición dada en la reivindicación 1

30 Un compuesto de la reivindicación 1 donde R₈ y R₉ tomados conjuntamente con el nitrógeno al que se le adhieren forman 4-morfolinilo, 1-pirrolidinilo, 1-piperidinilo, 1-piperazinilo, 4-hidroxil-1-piperidinilo, 4-etanol-1-piperazinilo-, 4-etilformamida-1-piperazinilo-, o 4-metil-1-piperazinilo

31 Un compuesto de la reivindicación 1 donde R₈ y R₉ son independientemente H, metilo, etilo, propilo, 1-propanol, 2-propen, 1-pentanol, 2-metil-1-propanol, 2-butanol, 1-etanol, etoxi-1-etanol, -CH₂CH₂CO₂etilo, 2-metoxietilo, 4-clorofenetilo, o 4-fluorofenetilo

32 Un compuesto de la reivindicación 1 donde R₈ y R₉ tomados conjuntamente con el nitrógeno al que se le adhieren forman el 4-metil-1-piperazinilo

33 Un compuesto de la reivindicación que es
a) N-(2-[(9-benzil-9H-carbazol-4-il)oxi]etil)-N,N-dietilamina,

- b) N-{2-[(9-benzil-8-cloro-9H-carbazol-4-il)oxi]etil}-N,N-dietilamina,
- c) N-(2-{[8-cloro-9-(4-fluorobenzil)-9H-carbazol-4-il]oxi}etil)-N,N-dietilamina,
- d) N-{2-[(9-benzil-8-metil-9H-carbazol-4-il)oxi]etil}-N,N-dietilamina,
- e) N,N-dietil-N-{2-{[9-(4-fluorobenzil)-8-metil-9H-carbazol-4-il]oxi}etil)amina,
- f) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-N-(2-piridinilmetil)amina,
- g) N-{2-[(9-benzil-8-fluoro-9H-carbazol-4-il)oxi]etil}-N,N-dietilamina,
- h) 9-benzil-4-[2-(4-morfolinil)etoxi]-9H-carbazola,
- i) 2-(4-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-1-piperazinil)-1-etanol,
- j) 3-({2-[(9-benzil-9H-carbazol-4-il)oxi]etil}amino)-1-propanol,
- k) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-2-propen-1-amina,
- l) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-3-(4-morfolinil)-1-propanamina,
- m) 5-({2-[(9-benzil-9H-carbazol-4-il)oxi]etil}amino)-1-pentanol,
- n) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-1-propanamina,
- o) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-N-propil-1-propanamina,
- p) 1-benzil-N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-4-piperidinamina,
- q) 2-({2-[(9-benzil-9H-carbazol-4-il)oxi]etil}amino)-2-metil-1-propanol,

- r) 2-[(9-benzil-9H-carbazol-4-il)oxi]-N-(4-clorofenetil)-1-etanamina,
- s) 2-[(9-benzil-9H-carbazol-4-il)oxi]-N-(ciclohexilmetil)-1-etanamina,
- t) 2-[(9-benzil-9H-carbazol-4-il)oxi]-N-[2-(4-morfolinil)etil]-1-etanamina,
- u) 1-({2-[(9-benzil-9H-carbazol-4-il)oxi]etil}amino)-2-butanol,
- v) 2-[(9-benzil-9H-carbazol-4-il)oxi]-N-(4-fluorofenetil)-1-etanamina,
- w) 2-[2-({2-[(9-benzil-9H-carbazol-4-il)oxi]etil}amino)etoxi]-1-etanol,
- x) (1S,2S)-2-({2-[(9-benzil-9H-carbazol-4-il)oxi]etil}amino)ciclohexanol,
- y) etil 3-({2-[(9-benzil-9H-carbazol-4-il)oxi]etil}amino)propanoato,
- z) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}ciclobutanamina,
- aa) 2-{4-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-1-piperazinil}etilformamida,
- bb) N-(1H-benzimidazol-2-ilmetil)-2-[(9-benzil-9H-carbazol-4-il)oxi]-1-etanamina,
- cc) 1-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-4-piperidinol,
- dd) 9-benzil-4-[2-(4-metil-1-piperazinil)etoxi]-9H-carbazola,
- ee) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-N-ciclopropilamina,
- ff) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-N,N-dimetilamina,
- gg) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}formamida,

- hh) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-N-metilamina, o su sal de ácido maleico,
- ii) 2-[(9-benzil-9H-carbazol-4-il)oxi]etilamina,
- jj) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-N-(2-metoxietil)amina,
- kk) N-etil-N-[(1-fenil-1,2-dihidro[1,4]oxazino[2,3,4-jk]carbazol-7-il)oxi]etil)amina, o su sal de ácido maleico,
- ll) 9-benzil-4-[2-(1-pirrolidinil)etoxi]-9H-carbazola,
- mm) 9-benzil-4-[2-(1-piperidinil)etoxi]-9H-carbazola,
- nn) 9-benzil-4-[2-(1-piperazinil)etoxi]-9H-carbazola,
- oo) 2-[(9-benzil-fluoro-9H-carbazol-4-il)oxi]etilamina,
- pp) N,N-di-etil-N-(2-[(8-fluoro-9-(4-fluorobenzil)-9H-carbazol-4-il)oxi]etil)amina,
- qq) N-{2-[(9-benzil-6-cloro-9H-carbazol-4-il)oxi]etil}-N,N-di-etilamina,
- rr) N-{2-[(9-benzil-6-fluoro-9H-carbazol-4-il)oxi]etil}-N,N-di-etilamina,
- ss) N-{2-[(9-benzil-6-metil-9H-carbazol-4-il)oxi]etil}-N,N-di-etilamina,
- tt) 2-[(9-benzil-6-metil-9H-carbazol-4-il)oxi]etilamina,
- uu) N-{2-[(9-benzil-6-metil-9H-carbazol-4-il)oxi]etil}-N-metilamina,
- vv) N,N-di-etil-N-{2-[(9-(4-fluorobenzil)-6-metil-9H-carbazol-4-il)oxi]etil)amina,
- ww) 2-[(2-[(9-benzil-9H-carbazol-4-il)oxi]etil)amino]-1-etanol o su sal de ácido maleico,
- xx) 2-[(9-[(5-cloro-1-benzotiofen-3-il)metil]-9H-carbazol-4-il)oxi]etilamina o su sal de sulfonato de metano, o

yy) 2-({9-[(2-Metil-1,3-tiazol-4-il)metil]-9H-carbazol-4-il}oxi)etilamina o su sal de sulfonato de metano

34 Un compuesto de la reivindicación 1 que es

- a) 2-[(9-benzil-8-fluoro-9H-carbazol-4-il)oxi]etilamina, o
- b) 2-[(9-benzil-8-fluoro-9H-carbazol-4-il)oxi]etilamina

35 Un compuesto de la reivindicación 1 el cual es

- a) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-N-metilamina o su sal de ácido maleico,
- b) 9-benzil-4-[2-(4-metil-1-piperazinil)etoxi]-9H-carbazol, o
- c) N-{2-[(9-benzil-6-metil-9H-carbazol-4-il)oxi]etil}-N-metilamina

36 Un método para el tratamiento de enfermedad o condición en un mamífero donde el receptor 5-HT está implicado y la modulación de la función 5-HT es deseable y comprende la administración de una cantidad terapéuticamente eficaz de un compuesto de uno de los productos descritos en la reivindicación 1 al mamífero

37 El método de la reivindicación 36 donde el receptor es receptor 5-HT₆

38 El método de la reivindicación 36 donde la enfermedad o condición es ansiedad, depresión, esquisofrenia, enfermedad relacionada con el estrés, trastorno de pánico, fobia, trastorno obsesivo compulsivo, síndrome de estrés post-

traumático, depresión del sistema inmune, psicosis, parafrenia, manía, trastornos convulsivos, desordenes de la personalidad, cefalea de migraña, drogadicción, alcoholismo, obesidad, trastornos de la alimentación, o trastornos del sueño

39 El método de la reivindicación 36 donde la enfermedad o condición es síntoma psicótico, afectivo, vegetativo y psicomotor de esquizofrenia y efectos colaterales motores extrapiramidales de otros medicamentos antipsicóticos

40 El método de la reivindicación 36 donde la enfermedad es ansiedad, obesidad, depresión o enfermedad relacionada con el estrés

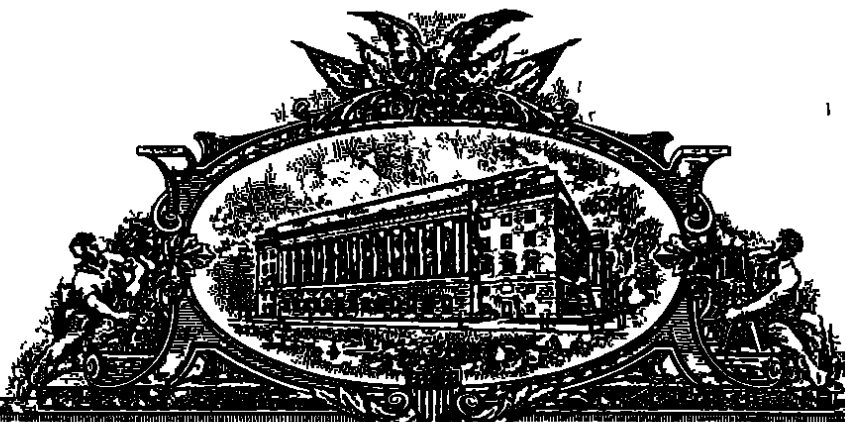
41 Un método para la modulación de la función del receptor 5-HT, que comprende la puesta en contacto del receptor con una cantidad inhibitoria eficaz de un compuesto de la reivindicación 1

42 El método de la reivindicación 41 donde el receptor es receptor 5-HT₆

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Santafé de Bogotá D C , Agosto 28 del 2000

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APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A
FILING DATE UNDER 35 USC 111

APPLICATION NUMBER 60/152,638

FILING DATE September 07, 1999



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PROVISIONAL APPLICATION COVER SHEET

CERTIFICATE OF MAILING (37 CFR 1.10)

"Express Mail" No EM177638830 US Date of Deposit September 3, 1999

I hereby certify that this transmittal together with the patent application referred to below is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, DC 20231

Julie K. Lyons, Legal Assistant

Name of Person Mailing Paper

Signature Julie K. Lyons

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner of Patents and Trademarks
Washington DC 20231

TRANSMITTAL OF A PROVISIONAL APPLICATION
UNDER 37 CFR 1.53(c)

Sir

This is a request for filing a provisional application under 37 CFR 1.53(c). The application is entitled *Aminoalkoxy Carbazoles for the Treatment of CNS Diseases* our Docket No 6219 and consists of

- [71] page(s) of Specification
- [10] page(s) of Claims
- [0] page(s) of Drawings
- [0] page(s) of Sequence Listings
- [1] page(s) of Abstract

- [] A disk containing nucleotide and/or amino acid sequences in a computer readable format is attached. The contents of the sequence listing in the application is the same as the document on the disk. (37 CFR 1.821(f) and MPEP 2422.06)
- [X] The name(s) and residence address(es) of the inventor(s) are set forth on the attached Inventor Information Sheet.
- [] As provided in 37 CFR 1.41(a)(3) instead of providing the names of the inventors at this time, the applicant identifier is PNU

This application is being sent by Express Mail under 37 CFR 1.10 and the required certificate appears above

Respectfully submitted,

Date. 9-3-99

Enclosures

- ☒ Patent Application
☐ Disk containing Nucleotide and/or Amino Acid Sequence Listing
☒ Inventor Information Sheet

INVENTOR INFORMATION SHEET

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6015538-000709

AMINOALKOXY CARBAZOLES FOR THE TREATMENT OF CNS DISEASES

FIELD OF THE INVENTION

5 The present invention provides aminoalkoxy carbazole derivatives, and more specifically provides compounds of formula (I) described herein below. These compounds are 5-HT ligands, and are useful for treating diseases wherein modulation of 5-HT activity is desired.

BACKGROUND OF THE INVENTION

10 Many diseases of the central nervous system are influenced by the adrenergic, the dopaminergic, and the serotonergic neurotransmitter systems. For example, serotonin has been implicated in a number of diseases and conditions which originate in the central nervous system. These include diseases and conditions related to sleeping, eating, - -
15 perceiving pain, controlling body temperature, controlling blood pressure, depression, anxiety, schizophrenia, and other bodily states. R. W. Fuller, *Biology of Serotonergic Transmission*, 221 (1982), D. J. Boullin, *Serotonin in Mental Abnormalities* 1316 (1978), J. Barchas, et al. *Serotonin and Behavior*, (1973). Serotonin also plays an important role in peripheral systems, such as the gastrointestinal system, where it has been found to mediate a
20 variety of contractile, secretory, and electrophysiologic effects.

 As a result of the broad distribution of serotonin within the body, there is a tremendous interest in drugs that affect serotonergic systems. In particular, receptor-specific agonists and antagonists are of interest for the treatment of a wide range of disorders, including anxiety, depression, hypertension, migraine, obesity, compulsive
25 disorders, schizophrenia, autism, neurodegenerative disorders (e.g., Alzheimer's disease, Parkinsonism, and Huntington's chorea), and chemotherapy-induced vomiting. M. D. Gershon, et al. *The Peripheral Actions of 5-Hydroxytryptamine*, 246 (1989), P. R. Saxena, et al. *Journal of Cardiovascular Pharmacology*, 15 Supplement 7 (1990).

 The major classes of serotonin receptors (5-HT₁₋₇) contain fourteen to eighteen
30 separate receptors that have been formally classified. See Glennon, et al., *Neuroscience and Behavioral Reviews*, 1990, 14, 35, and D. Hoyer, et al. *Pharmacol. Rev.* 1994, 46, 157-203. Recently discovered information regarding subtype identity, distribution, structure,

and function suggests that it is possible to identify novel subtype specific agents having improved therapeutic profiles (e.g. fewer side effects)

For example, The 5-HT₆ receptor was identified in 1993 (Monsma et al. *Mol. Pharmacol.* 1993, 43: 320-327 and Ruat, M. et al. *Biochem. Biophys. Res. Com.* 1993, 193, 269-276). Several antidepressants and atypical antipsychotics bind to the 5-HT₆ receptor with high affinity and this binding may be a factor in their profile of activities (Roth et al. *J. Pharm. Exp. Therapeut.* 1994, 268: 1403-1410, Sleight et al. *Exp. Opin. Ther. Patents* 1998, 8: 1217-1224, Bourson et al. *Brit. J. Pharm.* 1998, 125, 1562-1566, Boess et al. *Mol. Pharmacol.* 1998, 54, 577-583, Sleight et al. *Brit. J. Pharmacol.* 1998, 124, 556-562). In addition, the 5-HT₆ receptor has been linked to generalized stress and anxiety states (Yoshioka et al. *Life Sciences* 1998, 17/18: 1473-1477). Together these studies and observations suggest that compounds that antagonize the 5-HT₆ receptor will be useful in treating disorders of the central nervous system. Compounds of the present invention are

5-HT ligands (e.g. receptor-specific agonists or antagonists). Thus they are useful for treating diseases wherein modulation of 5-HT activity is desired. Specifically, the compounds of this invention are useful in the treatment of psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, anxiety, migraine headache, drug addiction, convulsive disorders, personality disorders, post-traumatic stress syndrome, alcoholism, panic attacks, obsessive-compulsive disorders, and sleep disorders. The compounds of this invention are also useful to treat psychotic, affective, vegetative, and psychomotor symptoms of schizophrenia and the extrapyramidal motor side effects of other antipsychotic drugs. This last action will allow higher doses of antipsychotics to be used and thus greater antipsychotic efficacy to be obtained as a result of a reduction in side effects. The compounds of this invention are also useful in the modulation of eating behavior and thus are useful in treating excess weight and associated morbidity and mortality.

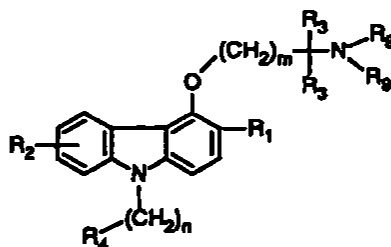
INFORMATION DISCLOSURE

International Publication No. WO95/03296 discloses carbazole and dibenzofuran hapten compounds.

Abstract of International Publication No. WO/9747601 discloses new heterocyclic compounds useful for treating schizophrenia.

Abstract of French Patent No 2516512 discloses pyrido-indole derivatives useful for treating cardiac rhythm diseases.

20 The present invention provides a compound of formula I



I

R₁ 15

- R₂ is**

- (a) H_1

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10

15

- R₄ is**

- 20

25

(a) H,
(b) C₁₋₆ alkyl, or
(c) (C₁₋₃ alkyl)-phenyl wherein phenyl may be substituted with R₃

30

- (a) H,
(b) C₁₋₆ alkyl, optionally substituted with aryl, heteroaryl, or C₃₋₆ cycloalkyl,
(c) C₂₋₆ alkene,
(d) C₃₋₆ cycloalkyl,

הנהגתו היתה נכונה

- (e) C₂₋₆ alkyl substituted with R₁₀,
(f) -CHO, provided that only one of the R₈ and R₉ is CHO the other one is H,
(g) aryl,
(h) heterocyclic, which is bonded via carbon atom to the nitrogen to which it is
5 attached or
(i) R₈ and R₉ taken together with the nitrogen to which they are attached form a
heterocyclic ring wherein the heterocyclic ring may have one to two additional heteroatoms
selected from the group consisting of oxygen, sulfur and N(Y) and wherein the carbon
atoms of the heterocyclic ring is optionally substituted with one or two R₁₄,
10 R₁₀ is
(a) -OH,
(b) -O(C₁₋₄ alkyl), optionally alkyl is substituted with OH,
(c) -O(C₁₋₄ alkyl)-NR₁₁R₁₂
(d) heterocyclic, or
15 (e) -CO₂R₅,
R₁₁ and R₁₂ are independently,
(a) H, or
(b) C₁₋₄ alkyl,
aryl is phenyl or naphthyl, optionally substituted with one or more R₁₃
20 heteroaryl is a radical of a five- or six-membered monocyclic aromatic ring having one or
two heteroatoms each selected from the group consisting of oxygen, sulfur, and N(X), or a
radical of a nine- or ten-membered ortho-fused bicyclic aromatic ring having one, two or
three heteroatoms each selected from the group consisting of oxygen, sulfur, and N(X),
wherein carbon atoms of heteroaryl may be substituted with R₁₃,
25 heterocyclic is a radical of a five- six-, or seven-membered partially-saturated or
unsaturated heterocyclic ring having one, two or three heteroatoms selected from the group
consisting of oxygen sulfur and N(Y) wherein the carbon atoms of the heterocyclic ring
may be substituted with R₁₄,
X is absent, H or C₁₋₄ alkyl,
30 Y is
(a) H,
(b) C₁₋₆ alkyl, optionally substituted with aryl or heteroaryl,
(c) C₃₋₆ cycloalkyl, or

(d) C₂₋₆ alkyl substituted with -OH, -O(C₁₋₄ alkyl), -O(C₁₋₄ alkyl)-NR₁₁R₁₂,
-CO₂R₅, or NHCHO or

(e) -OH,

R₁₃ is

- 5 (a) halo
- (b) -OH
- (c) -CN,
- (d) -CF₃,
- (e) -O(C₁₋₆)alkyl, —
- 10 (f) C₁₋₆ alkyl,
- (g) C₃₋₆ cycloalkyl
- (h) -NR₅R₆
- (i) -CONR₅R₆
- (j) -SO₂NR₅R₆,
- 15 (k) -COOR₇
- (l) -OCF₃ or
- (m) phenyl, optionally substituted with halo, OH, O(C₁₋₄) alkyl or C₁₋₆ alkyl

R₁₄ is

- (a) C₁₋₆ alkyl,
- 20 (b) C₃₋₆ cycloalkyl
- (c) C₂₋₆ alkyl substituted with -OH, -O(C₁₋₄ alkyl), -O(C₁₋₄ alkyl)-NR₁₁R₁₂, or
-CO₂R₅,
- (d) -OH, or
- (e) oxo (=O),

25 m is 2, 3 or 4

n is 1, 2, 3 or 4,

C₃₋₆ cycloalkyl in each of the above definitions, may be each and independently substituted with -OH, C₁₋₄ alkyl, or oxo (=O) and with the following provisos

- (a) when R₄ is aryl substituted with fluoro, R₂ cannot be fluoro or chloro at the C-6
30 position of formula I,
- (b) when R₄ is 4-thiazolyl, it cannot be substituted with 4-chlorophenyl,
or a pharmaceutically acceptable salt, racemate, solvate, tautomer, optical isomer or prodrug
derivative thereof,

(c) when R₄ is heteroaryl heteroaryl is not 4-pyridyl

In another aspect, the present invention also provides

a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient (the composition preferably comprises a therapeutically effective amount of the compound or salt),

a method for treating a disease or condition in a mammal (e.g. a human) wherein a 5-HT receptor is implicated and modulation of a 5-HT function is desired comprising administering a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof to the mammal

a method for treating or preventing anxiety obesity, depression, schizophrenia, a stress related disease (e.g. general anxiety disorder) panic disorder, a phobia, obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, a stress induced problem with the gastrointestinal or cardiovascular system, eating disorders or sexual dysfunction in a mammal (e.g. a human) comprising administering a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof to the mammal,

a method of treating or preventing anxiety obesity, depression, or a stress related disease, comprising administering to a mammal (e.g. a human) in need of such treatment, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof

a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in medical diagnosis or therapy (e.g. the treatment or prevention of 5-HT related disease such as anxiety, obesity, depression, or a stress related disease),

the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof to prepare a medicament for treating or preventing anxiety, obesity, depression, schizophrenia, a stress related disease (e.g. general anxiety disorder) panic disorder, a phobia, obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, a stress induced problem with the gastrointestinal or cardiovascular system, or sexual dysfunction in a mammal (e.g. a human),

the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof to prepare a medicament for treating or preventing anxiety, obesity, depression, or a stress related disease in a mammal (e.g. a human) and

a method for modulating 5-HT (e.g. 5-HT₆) receptor function comprising contacting (*in vitro* or *in vivo*) the receptor with an effective inhibitory amount of a compound of formula I, or a pharmaceutically acceptable salt thereof

The invention also provides novel intermediates and processes disclosed herein that
5 are useful for preparing compounds of formula I.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are generally named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of
10 ordinary skill in the art may be used (e.g. "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "h" for hour or hours and "rt" for room temperature)

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} indicates a moiety of the integer 'i' to the integer 'j' carbon atoms,
15 inclusive. Thus, for example, C₁₋₇alkyl refers to alkyl of one to seven carbon atoms, inclusive.

Specific and preferred values listed below for radicals, substituents and ranges, are for illustration only, they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

20 The following definitions are used, unless otherwise described.

Halo is fluoro, chloro, bromo, or iodo

Alkyl denotes both straight and branched groups but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. Specifically, C₁₋₇ alkyl can be methyl,
25 ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, or hexyl.

Alkene denotes both straight and branched groups —

C₃₋₆ cycloalkyl denotes a cycloalkyl having three to six carbon atoms. Specifically, C₃₋₆ cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

Aryl denotes a phenyl or a naphthyl radical. Optionally, aryl is substituted with one
30 or more halo, OH, CN, CF₃, O(C₁₋₆)alkyl, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, NR₅R₆, CONR₅R₆, SO₂NR₅R₆, COOR₇, OCF₃, or phenyl which in turn may be substituted with halo, OH, O(C₁₋₄) alkyl, or C₁₋₆ alkyl. R₅ and R₆ are the same as summarized above.

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A specific value for R₂ is H, halo, -OH, -CN, -CF₃, -O(C₁₋₆)alkyl, C₁₋₆ alkyl,

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140/52

A specific value for R_2 is H, halo or C_{1-6} alkyl

A specific value for R_2 is H, chloro fluoro, or methyl

A specific value for R_2 is H

A specific value for R_2 is fluoro or methyl

5 A specific value for each R_3 is independently-H, C_{1-6} alkyl, or C_{3-6} cycloalkyl-

A specific value for each R_3 is independently H.

A specific value is wherein R_8 and R_9 are independently H, C_{1-6} alkyl (optionally substituted with aryl, heteroaryl or C_{3-6} cycloalkyl) C_{2-6} alkene C_{3-6} cycloalkyl C_{2-6} alkyl substituted with R_{10} , -CHO (provided that only one of the R_8 and R_9 is -CHO, the other one is hydrogen), aryl, heterocyclic wherein heterocyclic is bonded via carbon atom to the nitrogen to which it is attached, or R_8 and R_9 taken together with the nitrogen to which they are attached form a heterocyclic ring wherein the heterocyclic ring may have one to two additional heteroatoms selected from the group consisting of oxygen sulfur and N(Y) and wherein the carbon atoms of the heterocyclic ring is optionally substituted with one or two

10 R_{13} wherein R_{10} , and Y are as defined above, wherein each C_{3-6} cycloalkyl is optionally substituted with -OH, C_{1-4} alkyl, or oxo

A specific value is wherein R_8 is H, and R_9 is H C_{1-6} alkyl C_{2-4} alkene C_{1-6} alkyl substituted with phenyl, wherein phenyl is optionally substituted with fluoro or chloro

A specific value is wherein R_8 is H and R_9 is C_{1-6} alkyl substituted with

20 C_{3-6} cycloalkyl, wherein cycloalkyl is optionally substituted with -OH, C_{1-4} alkyl or oxo

A specific value is wherein R_8 is H, and R_9 is C_{2-6} alkyl substituted with -OH, -O(C_{1-4} alkyl), -O(C_{1-4} alkyl-OH) or -CO₂ C_{1-4} alkyl

A specific value is wherein R_8 is H, and R_9 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, all of which may be substituted with -OH, C_{1-4} alkyl, oxo, or -CHO

25 A specific value is wherein R_8 is H, and R_9 is C_{1-6} alkyl substituted with phenyl pyridyl thiophene, benzothiophene, benzofuran, benzimidazole, imidazole or thiazole.

A specific value is wherein R_8 is H, and R_9 is heterocyclic wherein heterocyclic is bonded via carbon atom to the nitrogen to which it is attached

A specific value is wherein R_8 is H, and R_9 is pyridyl methyl, benzimidazole methyl, or 1-benzyl-piperidinyl.

30

A specific value is wherein R_8 is H, and R_9 is C_{2-6} alkyl substituted with azetidyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1-benzyl-piperidinyl, 1-methyl-piperidinyl, dioxolane, imidazolidine, oxazolidinyl,

oxathiolane, 4-hydroxyl-1-piperidinyl, 4-ethanol-1-piperazinyl-, 4-ethylformamide-1-piperazinyl-, or 4-methyl-1-piperazinyl

A specific value is wherein R_8 and R_9 taken together with the nitrogen to which they are attached form a heterocyclic ring wherein the heterocyclic ring may have one to two additional heteroatoms selected from the group consisting of oxygen sulfur and N(Y) wherein Y is the same as defined in claim 1

A specific value is wherein R_8 and R_9 taken together with the nitrogen to which they are attached form 4-morpholinyl, 1-pyrrolidinyl 1-piperidinyl, 1-piperazinyl, 4-hydroxyl-1-piperidinyl 4-ethanol-1-piperazinyl-, 4-ethylformamide-1-piperazinyl-, or 4-methyl-1-piperazinyl

A specific value for R_8 and R_9 are independently H methyl ethyl propyl, 1-propanol 2-propen, 1-pentanol, 2-methyl-1-propanol 2-butanol, 1-ethanol, ethoxyl-1-ethanol, $-\text{CH}_2\text{CH}_2\text{CO}_2\text{ethyl}$, 2-methoxyethyl, 4-chlorophenethyl or 4-fluorophenethyl

A specific value is wherein R_8 and R_9 are both hydrogen atoms

A specific value is wherein R_8 is H, and R_9 is methyl

A specific value is wherein R_8 and R_9 taken together with the nitrogen to which they are attached form 4-methyl-1-piperazinyl

A specific value for R_4 is aryl, or heteroaryl, wherein aryl or heteroaryl are as defined as herein above

A specific value for R_4 is phenyl

A specific value for R_4 is pyridyl thiophene benzothiophene, benzofuran, benzimidazole imidazole, thiazole pyridyl, thiophene, benzothiophene, benzofuran, benzimidazole, imidazole or thiazole

A specific value for R_4 is 2-methyl-1,3-thiazol-4-yl, or 5-chloro-1-benzothiophen-3-yl

Examples of the present invention includes

- a) N-(2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)-N,N-diethylamine,
- b) N-(2-[(9-benzyl-8-chloro-9H-carbazol-4-yl)oxy]ethyl)-N,N-diethylamine,
- c) N-(2-[(8-chloro-9-(4-fluorobenzyl)-9H-carbazol-4-yl)oxy]ethyl)-N,N-diethylamine,
- d) N-(2-[(9-benzyl-8-methyl-9H-carbazol-4-yl)oxy]ethyl)-N,N-diethylamine,
- e) N,N-diethyl-N-(2-[(9-(4-fluorobenzyl)-8-methyl-9H-carbazol-4-yl)oxy]ethyl)amine,
- f) N-(2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)-N-(2-pyridinylmethyl)amine,

הַיְּהוּדִים הָיוּ מְשֻׁלָּלִים בְּמִשְׁכַּנְהֶם

- ll) 9-benzyl-4-[2-(1-pyrrolidinyl)ethoxy]-9H-carbazole
 mm) 9-benzyl-4-[2-(1-piperidinyl)ethoxy]-9H-carbazole
 nn) 9-benzyl-4-[2-(1-piperazinyl)ethoxy]-9H-carbazole,
 oo) 2-[(9-benzyl-8-fluoro-9H-carbazol-4-yl)oxy]ethylamine
 5 pp) N,N-diethyl-N-(2-[[8-fluoro-9-(4-fluorobenzyl)-9H-carbazol-4-yl]oxy]ethyl)amine,
 qq) N-(2-[(9-benzyl-6-chloro-9H-carbazol-4-yl)oxy]ethyl)-N,N-diethylamine,
 rr) N-(2-[(9-benzyl-6-fluoro-9H-carbazol-4-yl)oxy]ethyl)-N,N-diethylamine,
 ss) N-(2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethyl)-N,N-diethylamine,
 tt) 2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethylamine
 10 uu) N-(2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethyl)-N-methylamine,
 vv) N,N-diethyl-N-(2-[[9-(4-fluorobenzyl)-6-methyl-9H-carbazol-4-yl]oxy]ethyl)amine,
 ww) 2-((2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)amino)-1-ethanol or its maleic acid salt,
 15 xx) 2-((2-[(5-Chloro-1-benzothiophen-3-yl)methyl]-9H-carbazol-4-yl)oxy)ethylamine or its methane sulfonate salt, or
 yy) 2-((2-[(2-Methyl-1,3-thiazol-4-yl)methyl]-9H-carbazol-4-yl)oxy)ethylamine or its methane sulfonate salt

It will be appreciated by those skilled in the art that compounds of the invention
 20 may contain a chiral center, therefore they may be isolated in optically active or racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically active, polymorphic, tautomeric, or stereoisomeric form, or mixture thereof, of a compound of the invention which possesses the useful properties described herein. It is well known in the art to prepare optically active
 25 forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation (using a chiral stationary phase, for example) and to determine 5-HT₆ activity using the standard tests described herein, or using other similar tests which are well known in the art.

30 The following Schemes describe the preparation of compounds of the present invention. All of the starting materials are commercially available or prepared by procedures described in these schemes or by procedures that would be well known to one of

ordinary skill in organic chemistry The variables used in the Schemes are as defined above or as in the claims

As shown in Chart A hydrazines 3 can be prepared from commercially available anilines 1 Aniline 1 is stirred in an acidic medium such as TFA, acetic acid, or aq sulfuric acid A nitrite such as sodium nitrite, isoamyl nitrite, or n-butyl nitrite is added to give nitroso aniline 2 Nitroso aniline 2 is reduced with lithium aluminum hydride in ether or THF to give hydrazine 3 For a discussion of additional methods of preparing 3, see Sandler, S R. Karo W *Organic Functional Group Preparations* Academic Press New York, 1983, Vol I, 2nd Ed., pp 434-465 Hydrazone 4 is prepared from hydrazine 3 and cyclohexane-1,3-dione in solvents such as water alcohols, or dichloromethane Hydrazone 4 is then treated under the conditions of the Fischer indole synthesis using an acid and a solvent such as acetic acid, toluene, ethanol or others to give tetrahydrocarbazole 5 Alternatively hydrazine 3 and cyclohexane-1,3-dione may be reacted under Fischer indole conditions to directly give tetrahydrocarbazole 5 Many additional methods for the Fischer indole synthesis are given in Sundberg R.J *Indoles* Academic Press London 1996 and in Hughes D L. Progress in the Fischer Indole Reaction A Review *Org Prep Proceed Int* 1993, 25, 609-632 The nitrogen of tetrahydrocarbazole 5 is alkylated by methods well known to those versed in the art. For example, treatment of tetrahydrocarbazole 5 with a base such as sodium hydride, followed by an alkyl halide such as benzyl chloride or benzyl bromide gives benzyl tetrahydrocarbazole 6

Treatment of compound 6 in a single step using Raney nickel on Pd/carbon in solvents such as cumene, mesitylene 1,2,3-trimethylbenzene, 1,2,4-trimethylbenzene, decalin, carbitol, or diphenyl ether at temperatures between 130-270 °C provides phenol 9 directly Alternatively, benzyl tetrahydrocarbazole 6 is first treated with a copper (II) halide, preferably CuCl₂ or CuBr₂, in solvents such as DMF, acetonitrile, EtOAc chloroform, acetic acid, or acetic acid/water at temperatures between 50 and 120 °C to give halo tetrahydrocarbazoles 7 and 8 For a reference to this reaction see Matsumoto, M, Ishida, Y Watanabe, N *Heterocycles* 1985, 23, 165-170 A third useful method is treatment of benzyl tetrahydrocarbazole 6 with pyridinium bromide perbromide or phenyltrimethylammonium tribromide in solvents such as DMF acetonitrile, or THF to give halo tetrahydrocarbazoles 7 and 8 Halo tetrahydrocarbazoles 7 and 8 may be separated and carried on individually in the next steps, or they may be carried forward as a mixture to phenols 9 and 10 and separated at that time Halo tetrahydrocarbazoles 7 and 8

(separately or together) are then treated with lithium chloride or lithium bromide (anhydrous LiCl or LiBr is preferred, but hydrated forms also may be used) in the presence of lithium carbonate in a solvent such as DMF at 110-130 °C to give phenols 9 and 10

Charts B and D disclose some of the ways phenols 9 and 10 may be alkylated with various alkylating agents, and Chart C discloses further transformations of carbazole amine 13 to give alkyl amines 15, 16, and 17 directly or after several steps. Which method is used will depend on the type of amine that is desired and on the availability of alkylating agents. For clarity, only 13 is depicted in Chart C, but the reaction scheme applies equally well to 14. In chart D, only phenol 9 is depicted, but the reaction scheme applies equally well to phenol 10.

In Chart B, X refers to a halogen atom. Phenols 9 and 10 are alkylated with chloro or bromoethyl amine in the presence of bases such as sodium hydride, potassium carbonate, cesium carbonate, or sodium carbonate in solvents such as DMF, acetonitrile, or acetone at room temperature to 120 °C to give carbazole amines 13 and 14 directly. Alternatively, phenols 9 and 10 are alkylated with chloro or bromoacetonitrile in the presence of bases such as sodium hydride, potassium carbonate, cesium carbonate or sodium carbonate in solvents such as DMF, acetonitrile, or acetone at room temperature to 120 °C to give nitriles 11 and 12. Reduction of nitriles 11 and 12 with borane in THF or borane-methyl sulfide complex in THF at room temperature to 80 °C gives carbazole amines 13 and 14 (R8 and R9 are hydrogen atoms). Other methods for the reduction of the nitrile group to an amine may be found in March, J. *Advanced Organic Chemistry*, 3rd ed. John Wiley and Sons, New York, 1985.

Chart C discloses further functionalization of carbazole amine 14 by several methods. In Chart C, Q refers to hydrogen, alkyl, or aryl. Z refers to hydrogen or alkyl. One method is acylation with acylating agents such as ethyl formate, acetic anhydride, and the like to give acyl carbazole 15. The carbonyl function of acyl carbazole 15 is reduced to an alkyl group using reagents such as borane in THF or borane-methyl sulfide complex in THF at room temperature to 80 °C to give monoalkylamino carbazole 16, or using lithium aluminum hydride in ethereal solvents to effect the reduction to monoalkylamino carbazole 16. A second method is reductive amination of 14 with an equivalent amount of an aldehyde or ketone in the presence of reducing agents such as sodium cyanoborohydride or sodium triacetoxyborohydride in solvents such as dichloromethane, dichloroethane, and THF at 0 to 80 °C, or Pd/C under a hydrogen atmosphere in solvents such as methanol.

ethanol or ethyl acetate to give monoalkylamino carbazole 16. A third method is alkylation of carbazole amine 14 with alkyl halides or mesylates or tosylates in the presence of base in solvents such as THF, acetonitrile, dichloromethane, DMF and the like using methods well known to those versed in the art to give monoalkylamino carbazole 16.

5 When dialkylamino carbazole 17 is desired, a second equivalent of the same or a different aldehyde, ketone, or alkylating agent depending on the method used, is added to monoalkylamino carbazole 16 using the conditions described above. Alternatively, dialkylaminocarbazole 17 may be prepared directly from 14 using two equivalents of the aldehyde, ketone, or alkylating agent.

10 Chart D describes another method of preparing mono or dialkylamino carbazole 21 wherein phenol 9 is alkylated by methods well-known to those versed in the art to give carbazole halide 18 or carbazole alcohol 19. In Chart D, L refers to a leaving group such as halo atom or a sulfonate group. The alcohol group of carbazole alcohol 19 is converted to a leaving group with methane sulfonyl halide or toluene sulfonyl halide to give carbazole
15 sulfonate 20. The mesyl or tosyl group of carbazole sulfonate 20 or carbazole halide 18 is then displaced by amines to give amino carbazole 21.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by mixing a compound of the present invention with a suitable acid.

20 Compounds of the present invention can conveniently be administered in a pharmaceutical composition containing the compound in combination with a suitable excipient. Such pharmaceutical compositions can be prepared by methods and contain excipients which are well known in the art. A generally recognized compendium of such methods and ingredients is Remington's Pharmaceutical Sciences by E.W. Martin (Mark Publ. Co., 15th
25 Ed., 1975). The compounds and compositions of the present invention can be administered parenterally (for example, by intravenous, intraperitoneal or intramuscular injection), topically, orally, or rectally.

For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches,
30 capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active

compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets troches, pills capsules, and the like may also contain the following binders such as gum tragacanth, acacia, corn starch or gelatin excipients such as dicalcium phosphate a disintegrating agent such as corn starch, potato starch alginic acid and the like, a lubricant such as magnesium stearate and a sweetening agent such as sucrose, fructose lactose or aspartame or a flavoring agent such as peppermint oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain in addition to materials of the above type, a liquid carrier such as a vegetable oil or a polyethylene glycol Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives a dye and flavoring such as cherry or orange flavor Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed In addition, the active compound may be incorporated into sustained-release preparations and devices.

The compounds or compositions can also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms

Pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions optionally encapsulated in liposomes In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol liquid polyethylene glycols and the like) vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by

the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents for example, parabens, chlorobutanol phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions the preferred methods of preparation are vacuum drying and the freeze drying techniques which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e. when they are liquids. However it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads used to impregnate bandages and other dressings or sprayed onto the affected area using pump-type or aerosol sprayers. Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art, for example, see U.S. Pat. No. 4,938,949.

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The compound is conveniently administered in unit dosage form for example, containing about 0.05 mg to about 500 mg, conveniently about 0.1 mg to about 250 mg, most conveniently, about 1 mg to about 150 mg of active ingredient per unit dosage form. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g. into a number of discrete loosely spaced administrations.

The compositions can conveniently be administered orally, sublingually, transdermally or parenterally at dose levels of about 0.01 to about 150 mg/kg, preferably about 0.1 to about 50 mg/kg, and more preferably about 0.1 to about 30 mg/kg of mammal body weight.

For parenteral administration the compounds are presented in aqueous solution in a concentration of from about 0.1 to about 10%, more preferably about 0.1 to about 7%. The solution may contain other ingredients such as emulsifiers, antioxidants or buffers.

The exact regimen for administration of the compounds and compositions disclosed herein will necessarily be dependent upon the needs of the individual subject being treated, the type of treatment and, of course, the judgment of the attending practitioner.

Generally, compounds of the invention are 5-HT ligands. The ability of a compound of the invention to bind or act at a 5-HT receptor, or to bind or act selectively at a specific 5-HT receptor subtype can be determined using *in vitro* and *in vivo* assays that are known in the art. As used herein, the term "bind selectively" means a compound binds at least 2 times, preferably at least 10 times, and more preferably at least 50 times more readily to a given 5-HT subtype than to one or more other subtypes. Preferred compounds of the invention bind selectively to one or more 5-HT receptor subtypes.

The ability of a compound of the invention to act as a 5-HT receptor agonist or antagonist can also be determined using *in vitro* and *in vivo* assays that are known in the art. The invention provides compounds of formula I that act as either agonists or as antagonists of one or more 5-HT receptor subtypes.

5-HT₆ RECEPTOR BINDING ASSAY

Growth of Cells and Membrane Preparation

Hela cells containing the cloned human 5-HT₆ receptor were acquired from Dr. David R. Sibley's laboratory in National Institute of Health (see Sibley D.R. I

Neurochemistry 66, 47-56, 1996) Cells were grown in high glucose Dulbecco's modified Eagle's medium, supplemented with L-glutamine 0.5% sodium pyruvate, 0.3% penicillin-streptomycin 0.025% G-418 and 5% Gibco fetal bovine serum and then were harvested, when confluent, in cold phosphate buffered saline

5 Harvested intact cells were washed once in cold phosphate-buffered saline. The cells were pelleted and resuspended in 100 ml of cold 50 mM Tris 5 mM EDTA and 5 mM EGTA, pH 7.4. Homogenization was with a Vir Tishear generator, 4 cycles for 30 seconds each at setting 50. The homogenized cells were centrifuged at 700 RPM (1000 X g) for 10 minutes and the supernatant was removed. The pellet was resuspended in 100 ml of the
10 above buffer and rehomogenized for 2 cycles. The rehomogenized cells were then centrifuged at 700 RPM (1000 X g) for 10 minutes and the supernatant was removed. The combined supernatant (200ml) was centrifuged at 23,000 RPM (80,000 X g) for 1 hour in a Beckman Rotor (42.1 Ti). The membrane pellet was resuspended in 50-80 ml of assay buffer containing HEPES 20 mM, MgCl₂ 10 mM, NaCl 150 mM, EDTA 1 mM, pH 7.4 and stored
15 frozen in aliquots at -70°C

5-HT₆ Receptor Binding Assay

The radioligand binding assay used [³H]-lysergic acid diethylamide (LSD). The assay was carried out in Wallac 96-well sample plates by the addition of 11 µl of the test sample at the appropriate dilution (the assay employed 11 serial concentrations of samples
20 run in duplicate). 11 µl of radioligand, and 178 µl of a washed mixture of WGA-coated SPA beads and membranes in binding buffer. The plates were shaken for about 5 minutes and then incubated at room temperature for 1 hour. The plates were then loaded into counting cassettes and counted in a Wallac MicroBeta Trilux scintillation counter.

Binding Constant (K_i) Determination

25 Eleven serial dilutions of test compounds were distributed to assay plates using the PE/Cetus Pro/Pette pipettor. These dilutions were, followed by radioligand and the bead-membrane mixture prepared as described above. The specifically bound cpm obtained were fit to a one-site binding model using GraphPad Prism ver 2.0. Estimated IC₅₀ values were converted to K_i values using the Cheng-Prusoff equation (Cheng Y. C. et al, Biochem,
30 Pharmacol, 22, 3099-108, 1973). The K_i values obtained from the assay are shown in Table 1.

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TABLE I
5-HT₆ receptor Binding Assay Data

EXAMPLE NO	K _i (nM)
1	24
2	6
3	22
4	18
5	38
6	69
7	26
8	398
9	62
10	20
11	23
12	184
13	43
14	40
15	394
16	148
17	164
18	356
19	311
20	37
21	72
22	81
23	32
24	85
25	40
26	47
27	138
28	72

50452538.000709

150 x 64

29	11
30	12
31	21
32	-
33	211
34	57
35	23
36	16
37	11
38	69
39	12
40	88
41	24
42	20
43	182
44	180
45	66
46	61
47	22
48	123
49	45
50	138
51	113

The compounds and their preparations of the present invention will be better understood in connection with the following examples, which are intended as an illustration
5 of and not a limitation upon the scope of the invention.

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EXAMPLES OF PREFERRED EMBODIMENTS

Preparation 1 1,2,3,9-Tetrahydro-4H-carbazol-4-one

To a solution of 1,3-cyclohexane dione (1.99 g, 17.7 mmol) in water (55 mL) is added phenylhydrazine (1.92 g, 17.7 mmol) in 10 mL of water. A gummy solid quickly formed, which after completion of the addition is scrapped with a spatula to give a solid. The solid is collected, washed with water, and dried in a vacuum oven to give 3.0 g of a tan solid. After drying, the tan solid is stirred at reflux in TFA (25 mL) overnight. Upon cooling, TFA is removed in vacuo and water is added to the residue. The resulting solid is collected, washed with water, and dried to give 1.82 g (55%) of the title compound, mp 218-220 °C, IR (drift) 3150, 3130, 3104, 3093, 3056, 2976, 2954, 2944, 1607, 1577, 1466, 1413, 1251, 1178, 755 cm⁻¹. ¹H NMR (CDCl₃) δ 2.26, 2.64, 3.00, 7.26, 7.35, 8.21, 8.74. Anal. Calcd for C₁₂H₁₁NO: C, 77.81, H, 5.99, N, 7.56. Found: C, 77.82, H, 6.15, N, 7.54.

Preparation 2 9-Benzyl-1,2,3,9-tetrahydro-4H-carbazol-4-one

Sodium hydride (60% in oil, 0.207 g, 5.18 mmol) is washed three times with hexane. DMF (3 mL) is added, followed by 36B added in portions. A moderate exotherm ensued. THF (3 mL) is added. After ten minutes benzyl bromide (1.047 g, 6.12 mmol) is added. After stirring for 4 h, an additional 0.1 g of benzyl bromide is added. The mixture is stirred overnight and then the solvents are removed, the residue is partitioned between CH₂Cl₂ and aq. sodium bicarbonate. The organic layers are dried over sodium sulfate. Chromatography on silica gel (150 mL) using CH₃OH-CH₂Cl₂ (1/99) as eluent, followed by re-chromatography of mixed fractions using EtOAc-hexane (30/70), gave 1.023 g (79%) of the title compound, mp 157.0-157.5 °C, IR (drift) 2940, 1636, 1610, 1530, 1484, 1464, 1445, 1399, 1357, 1187, 1133, 749, 742, 731, 698 cm⁻¹. ¹H NMR (CDCl₃) δ 2.23, 2.60, 2.88, 5.34, 7.03, 7.2-7.3, 8.30. Anal. Calcd for C₁₉H₁₇NO: C, 82.88, H, 6.22, N, 5.09. Found: C, 82.51, H, 6.21, N, 5.13.

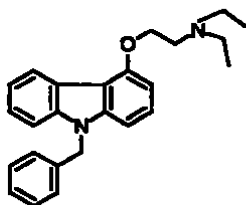
Preparation 3 9-Benzyl-9H-carbazol-4-ol

To a mixture of 9-Benzyl-1,2,3,9-tetrahydro-4H-carbazol-4-one (3.89 g, 14.13 mmol) in THF (20 mL) and DMF (15 mL) is added pyridinium hydrobromide perbromide (5.42 g, 16.96 mmol) as a solution in DMF (5 mL). After stirring for 5 h at room temperature, TLC (EtOAc-hexane 20/80) showed little or no reaction had occurred, so the mixture is stirred at 70 °C for 4 h and then allowed to cool.

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(and stir the remainder of the night) The solvents then are removed and the residue is partitioned between Et₂O and brine, dil Na₂S₂O₃, and brine. The aqueous layer is removed and CH₂Cl₂ is added to the organic layer (from which solids had begun to precipitate). The organic layers are dried over MgSO₄ and taken to dryness. Without further purification, the crude product is stirred with LiBr (2.67 g, 31 mmol) and Li₂CO₃ (2.07 g, 28 mmol) in DMF (50 mL) at 100 °C for 45 min, and then at reflux for 3 h. After cooling, the solvent is removed and the residue is partitioned between CH₂Cl₂ and water. The organic layers are dried over sodium sulfate and concentrated to dryness. The residue is chromatographed on silica gel (250 mL) using EtOAc-heptane (15/85)/CH₂Cl₂ (6/1) as eluent to give 2.78 g of solid mp 119-121.5 °C IR (drift) 3353, 1602, 1485, 1458, 1337, 1328, 1279, 1230, 1138, 1104, 780, 748, 735, 714, 700 cm⁻¹. ¹H NMR (CDCl₃) δ 5.32, 5.50, 6.60, 6.97, 7.14, 7.26, 7.3-7.4, 8.33. Anal. Calcd for C₁₉H₁₅NO: C, 83.49, H 5.53, N 5.12. Found: C, 82.35, H 5.51, N, 5.06.

15 Example 1 N-{2-[(9-Benzyl-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine



A mixture of 9-benzyl-9H-carbazol-4-ol (0.0305 g, 0.1116 mmol), potassium carbonate (0.0308 g, 0.2232 mmol), and DMF (1.0 mL) is stirred at 100 °C. Diethylaminoethyl chloride hydrochloride (0.0230 g, 0.1339 mmol) is added in aliquots over 40 min. After 2.3 h, an additional 0.032 g of potassium carbonate and 0.023 g of diethylaminoethyl chloride hydrochloride are added. The mixture is stirred overnight and then the solvent is removed and the residue partitioned between CH₂Cl₂ and aq. sodium bicarbonate. The organic layers are dried over sodium sulfate. Chromatography on silica gel (15 mL) using acetone-hexane (20/80) gave 0.0382 g of the title compound as a solid mp 79-80.5 °C IR (drift) 2965, 1581, 1457, 1439, 1356, 1342, 1333, 1268, 1147, 1112, 1053, 782, 750, 729, 713 cm⁻¹. ¹H NMR (CDCl₃) δ 1.14, 2.75, 3.13, 4.36, 5.50, 6.71, 6.98, 7.12, 7.2-7.4, 8.38. Anal. Calcd for C₂₅H₂₂N₂O: C 80.61, H 7.58, N 7.52. Found: C, 79.90, H, 7.52, N, 7.43.

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Preparation 4 8-Chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one

2-Chlorophenylhydrazine hydrochloride (1.6885 g, 0.0094 mol) is added portion-wise to a solution of 1,3-cyclohexanedione (1.0316 g, 0.0092 mol) in water (17.4 mL). The mixture is allowed to stir for three days at room temperature. The solids are collected by filtration, washed with water and vacuum dried at 50 °C for 30 min and then overnight at room temperature to give the hydrazone. The hydrazone is then heated at reflux in trifluoroacetic acid (9 mL). After stirring overnight the mixture is cooled and then partitioned between ice water and dichloromethane. The organic layer is washed with aqueous sodium bicarbonate and the aqueous layer is backwashed with dichloromethane. The combined organic layers are then dried over sodium sulfate and concentrated to a foam. Product is precipitated from the foam by adding dichloromethane, methanol and acetone. After filtering the solids, the filtrate is concentrated to a foam and again more product is precipitated using acetone/dichloromethane (2/98). The solids are collected by filtration and the filtrate is chromatographed on silica gel (150 mL) using acetone/dichloromethane (2/98 and 4/96) to give product. All of the solids are combined and recrystallized from dichloromethane/methanol/hexane to give 0.3724 g (18%) of a first crop and 0.1092 g (5%) of a second crop of the title compound, mp > 247 °C. MS (ESI-) for $C_{12}H_{10}ClNO$ m/z 217.9 (M-H). IR (drift) 3155, 3142, 3105, 3080, 2943, 1633, 1613, 1473, 1174, 1139, 1071, 1015, 858, 791, 744 cm^{-1} . ^1H NMR ($CDCl_3$) δ 2.28, 2.61, 3.03, 7.22, 8.11, 8.60. Anal. Calcd for $C_{12}H_{10}ClNO$: C, 65.61, H, 4.59, N, 6.38. Found: C, 65.48, H, 4.62, N, 6.38.

Preparation 5 9-Benzyl-8-chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one

8-Chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.2019 g, 0.92 mmol) is added to a slurry of pentane-washed NaH (0.0275 g, 0.68 mmol) in DMF (1 mL) and after stirring 22 min benzyl bromide (0.13 mL, 0.0011 mol) is added. Starting material remained after 30 min so additional NaH (0.0140 g, 0.35 mmol) and DMF (1 mL) are added and the mixture is allowed to stir overnight. The mixture is then partitioned between aqueous sodium bicarbonate and ethyl acetate and the organic layer is dried over sodium sulfate and concentrated to dryness. The resulting solids are recrystallized from 30% ethyl acetate/hexane and dichloromethane to give 0.1942 g (68%) of the title compound, mp 161-162 °C. MS (ESI+) for $C_{19}H_{16}ClNO$ m/z 310.1 (M+H)⁺, IR (drift) 1644, 1605, 1538, 1484, 1462, 1447, 1425, 1357, 1188, 1106, 793, 784, 737, 725, 699 cm^{-1} , ^1H NMR ($CDCl_3$) δ

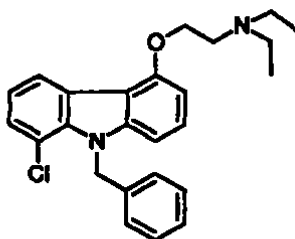
✓ 168
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2 22 2 59 2 85 5 82 6 95, 7 18 7 28 8 28 Anal Calcd for $C_{19}H_{16}ClNO$ C 73 66 H, 5 20 N 4 52 Found C 73 41, H 5 17 N, 4 57

Preparation 6 9-Benzyl-8-chloro-9H-carbazol-4-ol

5 Pyridinium bromide perbromide (0 1856 g 0 58 mmol) is added to a solution of 9-benzyl-8-chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one in THF (0 7 mL) and DMF (0 5 mL) and the mixture is heated to 75 °C After stirring for 5 5 h, THF is removed under reduced pressure and the residue is partitioned between dichloromethane and brine The combined organic layers are washed with dilute sodium sulfate/brine and the aqueous layer is
10 backwashed with dichloromethane The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to give a residue A mixture of the resulting residue lithium bromide (0 0940 g, 0 0011 mol), lithium carbonate (0 0772 g, 0 0010 mol) and DMF (2 mL) is heated at 120 °C for two hours The DMF is then removed under high vacuum and the residue is partitioned between dichloromethane and water The
15 combined organic layers are dried over sodium sulfate and concentrated to an oil The oil is chromatographed on silica gel (80 mL) using 15% ethyl acetate in heptane/dichloromethane (6 1) to give 0 1060 g (72%) of the title compound mp 163-165 5 °C, MS (ESI-) for $C_{19}H_{14}ClNO$ m/z 306 1 (M-H), IR (drift) 3537 1632, 1587 1452, 1417 1351 1339, 1311 1268, 1208, 1112 1073 789 734, 729 cm^{-1} ^1H NMR ($CDCl_3$) δ 5 42, 5 98, 6 59, 6 93,
20 7 09 7 15-7 28 7 36 8 29 Anal Calcd for $C_{19}H_{14}ClNO$ C 74 15 H, 4 59, N 4 55 Found C, 73 22, H, 4 53, N, 4 62

Example 2 N-(2-[(9-Benzyl-8-chloro-9H-carbazol-4-yl)oxy]ethyl)-N,N-diethylamine



25 9-Benzyl-8-chloro-9H-carbazol-4-ol (0 0826 g, 0 27 mmol), 2-diethylaminoethylchloride hydrochloride (0 0719 g, 0 42 mmol), potassium carbonate (0 1157 g, 0 84 mmol), sodium iodide (0 0031 g, 0 021 mmol) and DMF (1 mL) are heated at 85 °C for 4 h After the mixture had cooled, it is partitioned between water and ether

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The combined organic layers are dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (30 mL) using methanol/dichloromethane (1/99 to 2/98 to 4/96) to give 0.0675 g (62%) of the title compound. mp 73.5-75 °C. MS (ESI+) for $C_{25}H_{27}ClN_2O$ m/z 407.3 ($M+H$)⁺, IR (drift) 2966, 1588, 1499, 1454, 1413, 1355, 1337, 1266, 1124, 1027, 789, 732, 727, 717, 697 cm^{-1} , ¹H NMR ($CDCl_3$) δ 1.13, 2.72, 3.10, 4.33, 5.99, 6.71, 6.96, 7.10, 7.15, 7.26, 7.33, 8.33. Anal. Calcd for $C_{25}H_{27}ClN_2O$: C, 73.79; H, 6.69; N, 6.88. Found: C, 73.47; H, 6.81; N, 6.76.

Preparation 7 8-Chloro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydro-4H-carbazol-4-one

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8-Chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.1973 g, 0.90 mmol) is added to a slurry of pentane-washed NaH (0.0286 g, 0.72 mmol) in DMF (1 mL) and, after stirring for 22 min, p-fluorobenzyl bromide (0.14 mL, 0.0011 mol) is added. Starting material remained after 30 min, so additional NaH (0.0165 g, 0.42 mmol) and DMF (1.8 mL) are added. The mixture is stirred for 1 h, at which time the mixture is partitioned between aq. sodium bicarbonate and ethyl acetate. The organic layer is dried over sodium sulfate and concentrated to dryness. The resulting solids are recrystallized from 30% ethyl acetate/hexane and dichloromethane to give 0.2088 g (71%) of the title compound, mp 166-166.5 °C, MS (ESI+) for $C_{19}H_{15}ClFNO$ m/z 328.1 ($M+H$)⁺, IR (drift) 1639, 1607, 1510, 1485, 1449, 1426, 1413, 1226, 1189, 1157, 1108, 1095, 830, 790, 734 cm^{-1} , ¹H NMR ($CDCl_3$) δ 2.22, 2.59, 2.84, 5.78, 6.97, 7.19, 8.27. Anal. Calcd for $C_{19}H_{15}ClFNO$: C, 69.62; H, 4.61; N, 4.27. Found: C, 69.44; H, 4.55; N, 4.34.

Preparation 8 8-Chloro-9-(4-fluorobenzyl)-9H-carbazol-4-ol

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Pyridinium bromide perbromide (0.1988 g, 0.62 mmol) is added to a solution of 8-chloro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydro-4H-carbazol-4-one in THF (0.7 mL) and DMF (0.5 mL) and the mixture is heated to 75 °C. After stirring for 5.5 h, THF is removed under reduced pressure and the residue is partitioned between dichloromethane and brine. The combined organic layers are washed with dilute sodium sulfate/brine and the aqueous layer is backwashed with dichloromethane. The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to give a residue. A mixture of the resulting residue, lithium bromide (0.0976 g, 0.0011 mol), lithium carbonate (0.0762 g, 0.0010 mol) and DMF (2 mL) is heated at 120 °C for two hours. The DMF is then removed.

5 $C_{19}H_{13}ClFNO$ m/z 324 1 (M-H) IR (drift) 3521 1591 1508, 1457, 1416, 1351; 1337, 1311, 1269, 1226, 1218, 1110, 852, 791, 736 cm^{-1} , ^1H NMR ($CDCl_3$) δ 5.38, 5.94 6.60, 6.93 7.06, 7.18, 7.26, 7.36, 8.29 Anal Calcd for $C_{19}H_{13}ClFNO$ C, 70.05, H 4.02, N, 4.30 Found C, 69.26 H 4.05 N 4.20

CCN(CC)CCOc1ccc2c(c1)c3ccccc3n2Cc4ccc(F)cc4

25 Preparation 9 8-Methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one

O-Tolylhydrazine hydrochloride (1.3957 g, 0.0091 mol) is added in portions to a solution of 1,3-cyclohexanedione (1.0113 g, 0.0090 mol) in water (17.5 mL). The mixture is allowed to stir overnight at room temperature. The resulting slurry is filtered, washed with water and vacuum dried at 50 °C for 30 min and then overnight at room temperature to

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give the hydrazone. The hydrazone is then heated at reflux in trifluoroacetic acid (9 mL). After stirring for 3 h, the mixture is cooled and then partitioned between ice water and dichloromethane. The organic layer is washed with aq. sodium bicarbonate and the aqueous layer is backwashed with dichloromethane. The combined organic layers are then dried over sodium sulfate and concentrated to a foam. Product is precipitated from the foam by adding methanol/dichloromethane (2/98). After collecting the solids by filtration, the filtrate is concentrated and again more product is precipitated using methanol/dichloromethane (2/98). These solids are collected by filtration and the filtrate is chromatographed on silica gel (150 mL) using acetone/dichloromethane (2/98 4/96 and 8/92) to give product. All of the solids are combined and recrystallized from dichloromethane/methanol and hexane to give 0.3550 g, (20%) for a first crop and 0.1261 g (7%) for a second crop of the title compound. mp >247 °C, MS (ESI-) for $C_{13}H_{13}NO$ m/z 198.0 (M-H), IR (drift) 3187, 3159, 3088, 2940, 1612, 1475, 1454, 1410, 1216, 1183, 1140, 1068, 1013, 791, 756 cm^{-1} . ^1H NMR ($CDCl_3$) δ 2.26, 2.50, 2.60, 3.00, 7.04, 7.17, 8.06, 8.39. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36, H, 6.58, N, 7.03. Found: C, 78.05, H, 6.61, N, 7.05.

Preparation 10 9-Benzyl-8-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one

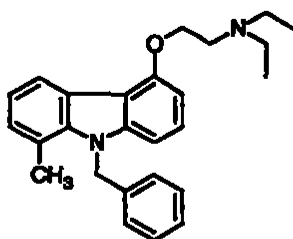
8-Methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.1967 g, 0.99 mmol) is added to a slurry of pentane-washed NaH (0.0485 g, 0.0012 mol) in DMF (2 mL) and after stirring for 30 min, benzyl bromide (0.14 mL, 0.0012 mol) is added. After 3 h starting material still remained so additional benzyl bromide (0.015 mL, 0.013 mmol) is added and the mixture is stirred overnight at room temperature. The mixture is then partitioned between aq. sodium bicarbonate and ethyl acetate and the organic layer is dried over sodium sulfate and concentrated to dryness. The resulting solids are recrystallized from ethyl acetate/hexane/dichloromethane to give 0.2076 g (73%) of the title compound. mp 165-166 °C, MS (ESI+) for $C_{20}H_{19}NO$ m/z 290.2 (M+H)⁺, IR (drift) 2940, 1637, 1599, 1538, 1494, 1462, 1447, 1416, 1357, 1322, 1121, 787, 752, 727, 697 cm^{-1} . ^1H NMR ($CDCl_3$) δ 2.21, 2.51, 2.59, 2.82, 5.58, 6.89, 6.95, 7.16, 7.29, 8.23. Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01, H, 6.62, N, 4.84. Found: C, 82.53, H, 6.62, N, 4.86.

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Preparation 11 9-Benzyl-8-methyl-9H-carbazol-4-ol

Pyridinium bromide perbromide (0 2032 g 0 64 mmol) is added to a mixture of 9-benzyl-8-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one in THF (0 7 mL) and DMF (0 5 mL) and the mixture is heated to 75 °C After stirring for 8 h THF is removed under reduced pressure and the residue is partitioned between dichloromethane and brine The combined organic layers are washed with dilute sodium thiosulfate/brine and the aqueous layer is backwashed with dichloromethane The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to give a residue A mixture of the resulting residue, lithium bromide (0 1005 g, 0 0012 mol) lithium carbonate (0 0768 g 0 0010 mol) and DMF (2 mL) is heated at 120 °C for two hours. The DMF is removed under high vacuum and the residue is partitioned between dichloromethane and water The combined organic layers are dried over sodium sulfate and concentrated to an oil The oil is chromatographed on silica gel (75 mL) using ethyl acetate/heptane (10/90) to give 0 0888 g (59%) of the title compound The product is then recrystallized from ethyl acetate/hexane, MS (ESI+) for $C_{20}H_{17}NO$ m/z 288 1 (M+H)⁺, IR (drift) 3537, 1587, 1492, 1451, 1351, 1338, 1315, 1271, 1236, 1205, 963, 792, 745, 729, 720 cm^{-1} , ¹H NMR (CDCl₃) δ 2 64 5 32, 5 76, 6 58, 6 88, 7 02, 7 15-7 26, 8 24 Anal Calcd for $C_{20}H_{17}NO$ C, 83 59, H, 5 96, N, 4 87 Found C, 80 86 H, 5 73, N, 4 72

20 Example 4 N-{2-[(9-Benzyl-8-methyl-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine



9-Benzyl-8-methyl-9H-carbazol-4-ol (0 0566 g, 0 20 mmol), 2-diethylaminoethylchloride hydrochloride (0 0505 g, 0 29 mmol), potassium carbonate (0 0922 g, 0 67 mmol), sodium iodide (0 0029 g, 0 019 mmol) and DMF (1 mL) are heated at 85 °C for 4 h. After the mixture had cooled, it is partitioned between water and ether The combined organic layers are dried over magnesium sulfate and concentrated to an oil The oil is chromatographed on silica gel (15 mL) using methanol/dichloromethane (1/99 to 2/98 to 4/96) to give 0 0248 g (32%) of the title compound MS (ESI+) for $C_{26}H_{30}N_2O$ m/z 387 2 (M+H)⁺, IR (drift)

2966 1585 1497 1449 1353 1336, 1268 1251 1140, 1106, 1069, 791 743, 725, 715 cm⁻¹, ¹H NMR (CDCl₃) δ 1.18, 2.64, 2.81, 3.20, 4.41, 5.77, 6.69, 6.91, 6.99, 7.13, 7.22-7.33, 8.28. Anal. Calcd for C₂₆H₃₀N₂O: C, 80.79, H, 7.82, N, 7.25. Found: C, 79.00, H, 7.76, N, 7.10.

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Preparation 12 9-(4-Fluorobenzyl)-8-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one

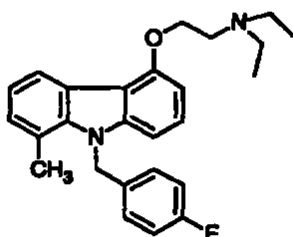
8-Methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.1967 g, 0.99 mmol) is added to a slurry of pentane-washed NaH (0.0449 g, 0.0011 mol) in DMF (2 mL). After stirring for 10 30 min, p-fluorobenzyl bromide (0.15 mL, 0.0012 mol) is added. Starting material is still present after 3 h, so additional p-fluorobenzyl bromide (0.015 mL, 0.12 mmol) is added and the mixture is stirred overnight. The mixture is then partitioned between aq. sodium bicarbonate and ethyl acetate and the organic layer is dried over sodium sulfate and concentrated to dryness. The resulting solids are chromatographed on silica gel (75 mL) 15 using methanol/dichloromethane (2/98). The impure fractions are rechromatographed on silica gel (60 mL) using methanol/dichloromethane (2/98). The pure fractions are combined and recrystallized from ethyl acetate/hexane/dichloromethane to give 0.1021 g (34%) of the title compound, mp 154-155 °C. MS (ESI+) for C₂₀H₁₈FNO *m/z* 308.2 (M+H)⁺, IR (neat) 1635, 1602, 1539, 1510, 1462, 1449, 1414, 1226, 1159, 835, 826, 801, 20 786, 756, 747 cm⁻¹, ¹H NMR (CDCl₃) δ 2.21, 2.51, 2.59, 2.81, 5.55, 6.87, 6.98, 7.17, 8.23. Anal. Calcd for C₂₀H₁₈FNO: C, 78.15, H, 5.90, N, 4.56. Found: C, 77.72, H, 5.95, N, 4.64.

Preparation 13 9-(4-Fluorobenzyl)-8-methyl-9H-carbazol-4-ol

25 Pyridinium bromide perbromide (0.0800 g, 0.25 mmol) is added to a solution of 9-(4-fluorobenzyl)-8-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one in THF (0.4 mL) and DMF (0.3 mL) and the mixture is heated to 75 °C. After stirring for 8 h, THF is removed under reduced pressure and the residue is partitioned between dichloromethane and brine. The combined organic layers are washed with dilute sodium sulfate/brine and the aqueous 30 layer is backwashed with dichloromethane. The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to give a residue. A mixture of the resulting residue, lithium bromide (0.0391 g, 0.45 mmol), lithium carbonate (0.0358 g, 0.48 mmol) and DMF (1.2 mL) is heated at 120 °C for two hours. The DMF is then

removed under high vacuum and the residue is partitioned between dichloromethane and water. The combined organic layers are dried over sodium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (30 mL) using ethyl acetate/heptane (10/90) to give 0.0321 g (52%) of the title compound. MS (ESI+) for $C_{20}H_{16}FNO$ m/z 306.1 ($M+H$)⁺, IR (drift) 3545, 1588, 1508, 1453, 1408, 1336, 1316, 1269, 1234, 1227, 1203, 819, 791, 743, 720 cm^{-1} , ^1H NMR ($CDCl_3$) δ 2.63, 5.36, 5.72, 6.58, 6.85, 6.96, 7.15-7.22, 8.25. Anal. Calcd for $C_{20}H_{16}FNO$: C, 78.67, H, 5.28, N, 4.59. Found: C, 74.98, H, 5.05, N, 4.37.

- 10 Example 5 *N,N*-Diethyl-*N*-(2-([9-(4-fluorobenzyl)-8-methyl-9H-carbazol-4-yl]oxy)ethyl)amine



- 9-(4-Fluorobenzyl)-8-methyl-9H-carbazol-4-ol (0.0176 g, 0.058 mmol), 2-diethylaminoethylchloride hydrochloride (0.0144 g, 0.084 mmol), potassium carbonate (0.0332 g, 0.24 mmol), sodium iodide (0.0008 g, 0.0053 mmol) and DMF (1 mL) are heated at 85 °C for 4 h. After the mixture had cooled, it is partitioned between water and ethyl acetate. The aqueous layer is also washed with dichloromethane. The combined organic layers are dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (10 mL) using methanol/dichloromethane (1/99 and 2/98) to give 0.0148 g (55%) of the title compound, MS (ESI+) for $C_{26}H_{29}FN_2O$ m/z 405.2 ($M+H$)⁺, ^1H NMR ($CDCl_3$) δ 1.23, 2.65, 2.88, 3.26, 4.47, 5.75, 6.73, 6.95, 7.15, 7.33, 8.29. Anal. Calcd for $C_{26}H_{29}FN_2O$: C, 77.20, H, 7.22, N, 6.93. Found: C, 73.47, H, 7.06, N, 6.53.

Preparation 14 9-Benzyl-4-(2-bromoethoxy)-9H-carbazole

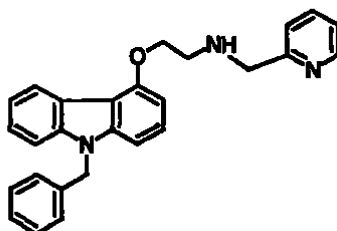
- 25 To a mixture of 9-benzyl-9H-carbazol-4-ol (2.46 g, 9.00 mmol), potassium carbonate (5.11 g, 27.0 mmol), and DMF (10 mL) is added dibromoethane (3.90 mL, 45.0 mmol). The mixture is stirred at 80 °C for 4.5 h and then allowed to cool and stir the remainder of the night. The mixture is then stirred at 85 °C, after about 2 h an additional 1.0 mL of dibromoethane is added. After 5.5 h the mixture is cooled and the solvent and

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excess dibromoethane are removed in vacuo. The residue is partitioned between Et₂O, water and brine. The organic layers are dried over MgSO₄ and taken to dryness. Chromatography on silica gel (250 mL) using EtOAc-heptane (10/90 to 20/80) to give 1.80 g (53%) after crystallization from CH₂Cl₂-hexane. IR (drift) 1583, 1458, 1446, 1342, 1333, 1281, 1270, 1245, 1154, 1147, 1114, 783, 753, 734, 719 cm⁻¹, ¹H NMR (CDCl₃) δ 3.87, 4.58, 5.51, 6.66, 7.02, 7.12, 7.2-7.4, 8.43. Anal. Calcd for C₂₁H₁₈BrNO: C, 66.33, H, 4.77, N, 3.68, Br, 21.01. Found: C, 66.30, H, 4.76, N, 3.62.

Example 6 N-{2-[(9-Benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-(2-pyridinylmethyl)amine

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A mixture of 9-benzyl-4-(2-bromoethoxy)-9H-carbazole (0.0622 g, 0.1635 mmol), diisopropylethylamine (0.0211 g, 0.1635 mmol), 2-(2-aminomethylpyridine) (0.0531 g, 0.4907 mmol), and DMF (0.5 mL) is stirred at 100 °C for 30 min. After cooling, the solvent is removed and the residue partitioned between CH₂Cl₂ and aq. sodium bicarbonate. The organic layers are dried over sodium sulfate, chromatography on silica gel (40 mL) using CH₃OH-CH₂Cl₂ (2/98) gave 0.0539 g (81%) of the title compound, IR (drift) 1586, 1457, 1342, 1269, 1237, 1153, 1145, 1118, 1047, 782, 776, 753, 745, 718, 710 cm⁻¹, ¹H NMR (CDCl₃) δ 3.32, 4.13, 4.44, 5.51, 6.70, 6.99, 7.12, 7.2-7.4, 7.66, 8.39, 8.60. Anal. Calcd for C₂₇H₂₅N₃O: C, 79.58, H, 6.18, N, 10.31. Found: C, 79.66, H, 6.41, N, 10.28.

Preparation 15 8-Fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one

2-Fluorophenylhydrazine hydrochloride (4.74 g, 0.0291 mol) is added in portions to a solution of 1,3-cyclohexanedione (3.20 g, 0.0285 mol) in water (60 mL). The mixture is allowed to stir overnight at room temperature. The resulting solids are collected by filtration, washed with water followed by a small hexane wash and vacuum dried at 50 °C for 40 min and then overnight at room temperature, to give the hydrazone. The hydrazone, p-toluene sulfonic acid monohydrate (5.8557 g, 0.031 mol) and trimethylbenzene (43 mL) are heated at 160 °C for 52 min. After cooling, the mixture is partitioned between water

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and dichloromethane. The aqueous layer is also washed once with chloroform. The combined organic layers are washed with aq sodium bicarbonate, dried over sodium sulfate and concentrated to a residue. The resulting residue is chromatographed on silica gel (400 mL) using ethyl acetate/hexane (20/80, 40/60 and 60/40 to give 0.8221 g (15%) of the title compound, mp 225-226 °C, MS (ESI-) for $C_{12}H_{10}FNO$ 202.0 (M-H), IR (drift) 3117, 3078, 3049, 3015, 2952, 2867, 1615, 1475, 1235, 1219, 1184, 1143, 864, 786, 735 cm^{-1} , ^1H NMR ($CDCl_3$) δ 2.27, 2.61, 3.02, 6.95, 7.16, 7.97, 8.82. Anal. Calcd for $C_{12}H_{10}FNO$: C, 70.93, H, 4.96, N, 6.89. Found: C, 71.40, H, 5.00, N, 6.92.

10 Preparation 16 9-Benzyl-8-fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one

8-Fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one (2.23 g, 0.011 mol) is added to a slurry of pentane-washed NaH (0.59 g, 0.015 mol) in DMF (18 mL) and after stirring for 20 min benzyl bromide (1.7 mL, 0.014 mol) is added. The mixture is stirred for 1 h at which time the mixture is partitioned between water and ethyl acetate. The combined organic layers are dried over sodium sulfate and concentrated to dryness. The resulting residue is chromatographed on silica gel (200 mL) using methanol/dichloromethane (1/99). The solids are then recrystallized from ethyl acetate/dichloromethane/hexane to give 2.25 g (70%) of the title compound, mp 183-184 °C. MS (ESI-) for $C_{19}H_{16}FNO$ m/z 292.1 (M-H), IR (drift) 1639, 1631, 1495, 1459, 1434, 1359, 1246, 1219, 1193, 1125, 798, 789, 736, 730, 698 cm^{-1} , ^1H NMR ($CDCl_3$) δ 2.23, 2.58, 2.87, 5.51, 6.92, 7.03, 7.16, 7.29, 8.07. Anal. Calcd for $C_{19}H_{16}FNO$: C, 77.80; H, 5.50, N, 4.78. Found: C, 77.58, H, 5.59, N, 4.79.

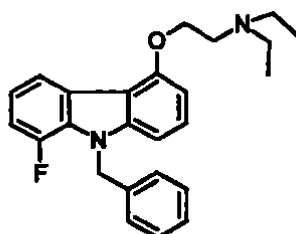
Preparation 17 9-Benzyl-8-fluoro-9H-carbazol-4-ol

Pyridinium bromide perbromide (2.9945 g, 0.0094 mol) is added to a mixture of 9-benzyl-8-fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one (2.1145 g, 0.0072 mol) in THF (22 mL) and DMF (16 mL) and the mixture is heated to 75 °C. After stirring for 5.5 h, THF is removed under reduced pressure and the residue is partitioned between ethyl acetate and brine. The combined organic layers are washed with dilute sodium thiosulfate/brine and the aqueous layer is backwashed with ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue is recrystallized from ethyl acetate/heptane and the resulting solids are combined with lithium bromide (1.1338 g, 0.013 mol), lithium carbonate (0.8831 g, 0.012 mol) and DMF (24 mL) and heated to 120 °C. After 1.5 h the mixture is partitioned between ethyl

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acetate and brine. The combined organic layers are washed with dilute brine and then dried over sodium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (150 mL) using dichloromethane (100) to give 1.0857 g (52%) of the title compound, mp 155-156 °C, MS (ESI-) for $C_{19}H_{14}FNO$ m/z 290.1 (M-H), IR (drift) 3524, 1581, 1498, 1456, 1432, 1343, 1318, 1272, 1239, 1134, 966, 790, 731, 714, 698 cm^{-1} , ^1H NMR (CDCl₃) δ 5.33, 5.69, 6.59, 6.98, 7.14, 7.25, 8.10. Anal. Calcd for $C_{19}H_{14}FNO$: C, 78.33, H, 4.84, N, 4.81. Found: C, 77.67, H, 4.90, N, 4.71.

Example 7 N-{2-[(9-Benzyl-8-fluoro-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine



9-Benzyl-8-fluoro-9H-carbazol-4-ol (0.0273 g, 0.0940 mmol), 2-diethylaminoethylchloride hydrochloride (0.0237 g, 0.14 mmol), potassium carbonate (0.0396 g, 0.29 mmol), sodium iodide (0.0013 g, 0.0087 mmol) and DMF (1 mL) are heated at 80 °C for 3 h. After the mixture had cooled, it is partitioned between water and ethyl acetate. The organic layer is dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (20 mL) using methanol/dichloromethane (1/99 to 2/98 to 3/97) to give 0.0206 g (56%) of the title compound, mp 60-60.5 °C, MS (ESI+) for $C_{25}H_{27}FN_2O$ m/z 391.3 (M+H)⁺, ^1H NMR (CDCl₃) δ 1.17, 2.79, 3.17, 4.39, 5.53, 6.73, 7.02, 7.13, 7.25, 7.38, 8.15. Anal. Calcd for $C_{25}H_{27}FN_2O$: C, 76.89, H, 6.97, N, 7.17. Found: C, 76.33, H, 7.18, N, 7.13.

Preparation 18 2-[(9-Benzyl-8-fluoro-9H-carbazol-4-yl)oxy]acetonitrile

A mixture of 9-benzyl-8-fluoro-9H-carbazol-4-ol (1.0775 g, 0.0037 mol), potassium carbonate (0.6284 g, 0.0046 mol), bromoacetonitrile (0.6 mL, 0.0086 mol) and DMF (12 mL) is stirred at room temperature for 4 h. The mixture is then partitioned between water and dichloromethane. The aqueous layer is also washed with ethyl acetate. The combined organic layers are dried over sodium sulfate and concentrated to a residue which is then partitioned between water and ethyl acetate. The combined organic layers are

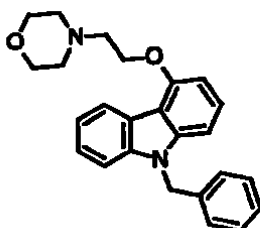
11/18

dried over magnesium sulfate and concentrated to a residue. The resulting residue is chromatographed on silica gel (100 mL) using ethyl acetate/hexane (20/80) followed by dichloromethane (100 %). The solids are recrystallized from ethyl acetate/heptane to give 0.8869 g (73%) of the title compound, mp 134-134.25 °C. MS (ESI+) for $C_{21}H_{15}FN_2O$ m/z 353.1 ($M+Na$)⁺, IR (dry ft) 1578, 1500, 1458, 1439, 1369, 1344, 1335, 1323, 1278, 1235, 1144, 1080, 793, 739, 695 cm^{-1} , ¹H NMR ($CDCl_3$) δ 5.05, 5.71, 6.75, 7.16, 7.24, 7.41, 8.07. Anal. Calcd for $C_{21}H_{15}FN_2O$: C, 76.35, H, 4.58, N, 8.48. Found: C, 76.15, H, 4.63, N, 8.35.

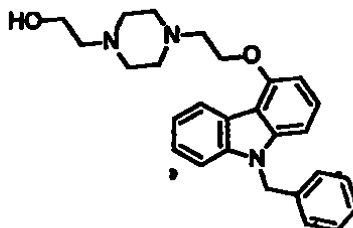
10 Examples 8-32

A mixture of 9-benzyl-4-(2-bromoethoxy)-9H-carbazole (0.020 g, 0.0526 mmol), an appropriate amine (0.0631 mmol), diisopropylethylamine (0.0631 mmol), and DMF (0.2 or 0.4 mL) is stirred in 7 mL capped glass vials (at room temperature for volatile amines and at 70 °C for the remainder). When TLC showed most of the starting material had been consumed (3-4 days for room temperature reactions and overnight for heated reactions), the vials (minus caps) are placed in a vacuum oven for removal of solvent. The residues are chromatographed on silica gel (using disposable glass Pasteur pipettes as columns), eluting with $CH_3OH-CH_2Cl_2$ (2/98 to 8/92, depending on the polarity of the product). Product fractions are combined and the eluent is allowed to evaporate.

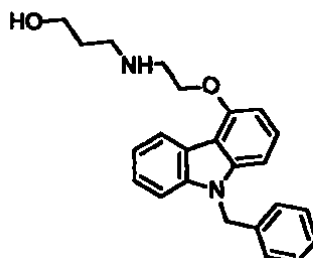
20 Example 8 9-benzyl-4-[2-(4-morpholinyl)ethoxy]-9H-carbazole ms (m + H) at 387



Example 9 2-(4-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-1-piperazinyl)-1-ethanol ms (m + H) at 430

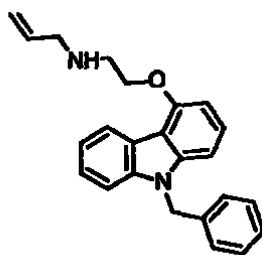


Example 10 3-({2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}amino)-1-propanol
ms (m + H) at 375

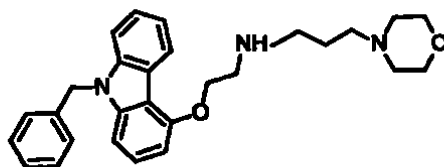


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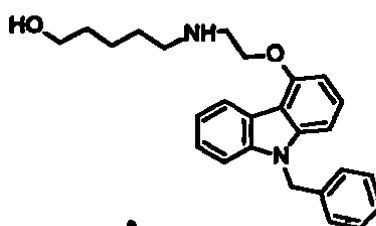
Example 11 N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-2-propen-1-amine
ms (m + H) at 357



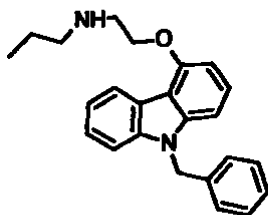
10 Example 12 N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-3-(4-morpholinyl)-1-propanamine ms (m + H) at 444



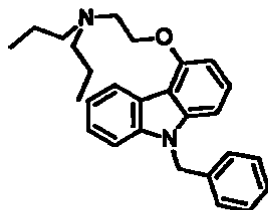
15 Example 13 5-({2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}amino)-1-pentanol
ms (m + H) at 403



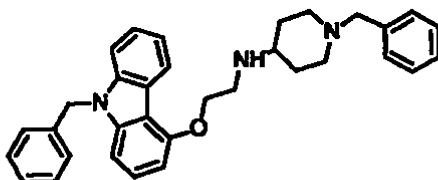
Example 14 N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-1-propanamine
ms (m + H) at 359



5 Example 15 N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-propyl-1-propanamine
ms (m + H) at 401

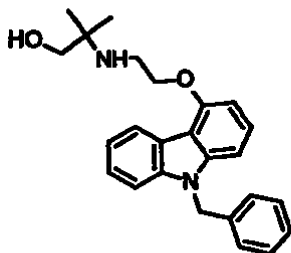


Example 16 1-benzyl-N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-4-piperidinamine
ms (m + H) at 490

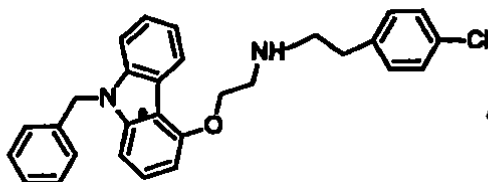


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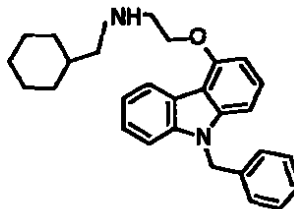
Example 17 2-({2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}amino)-2-methyl-1-propanol
ms (m + H) at 389



Example 18 2-[(9-benzyl-9H-carbazol-4-yl)oxy]-N-(4-chlorophenethyl)-1-ethanamine
15 ms (m + H) at 455

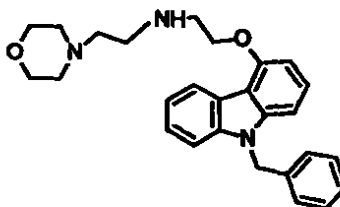


Example 19 2-[(9-benzyl-9H-carbazol-4-yl)oxy]-N-(cyclohexylmethyl)-1-ethanamine
ms (m + H) at 413

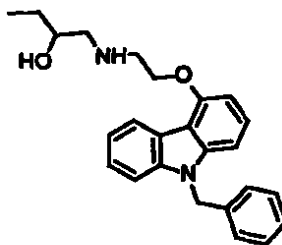


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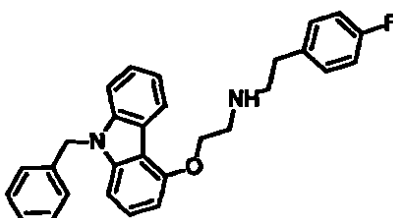
Example 20 2-[(9-benzyl-9H-carbazol-4-yl)oxy]-N-[2-(4-morpholinyl)ethyl]-1-ethanamine ms (m + H) at 430



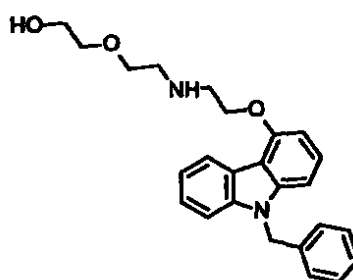
10 Example 21 1-({2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}amino)-2-butanol ms (m + H) at 389



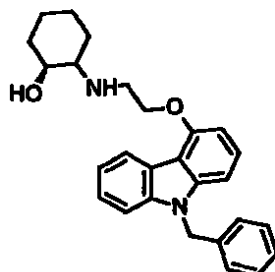
Example 22 2-[(9-benzyl-9H-carbazol-4-yl)oxy]-N-(4-fluorophenethyl)-1-ethanamine
15 ms (m + H) at 439



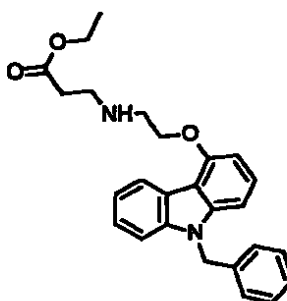
Example 23 2-[2-({2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}amino)ethoxy]-1-ethanol
ms (m + H) at 405



Example 24 (1S,2S)-2-({2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}amino)cyclohexanol
5 ms (m + H) at 415

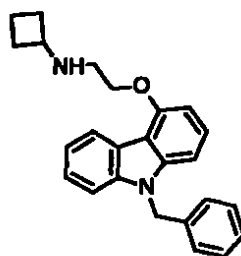


Example 25 ethyl 3-({2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}amino)propanoate
ms (m + H) at 417

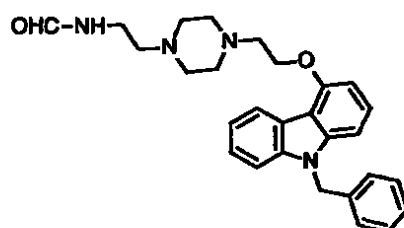


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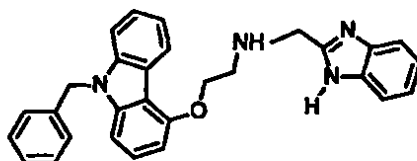
Example 26 N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}cyclobutanamine
ms (m + H) at 371



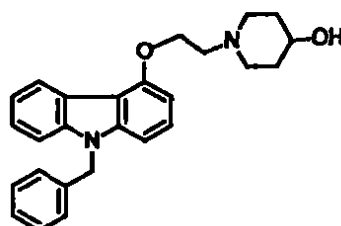
Example 27 2-(4-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-1-piperazinyl)ethylformamide
 ethylformamide ms (m + H) at 457



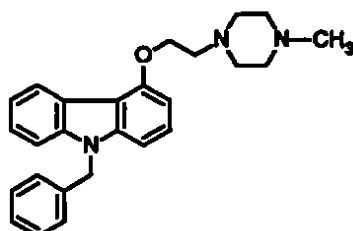
Example 28 N-(1H-benzimidazol-2-ylmethyl)-2-[(9-benzyl-9H-carbazol-4-yl)oxy]-1-ethanamine
 5 ethanamine ms (m + H) at 447



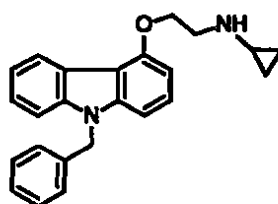
Example 29 1-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-4-piperidinol
 H) at 401 ms (m +



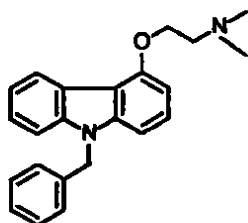
Example 30 9-benzyl-4-[2-(4-methyl-1-piperazinyl)ethoxy]-9H-carbazole
 H) at 400 ms (m +



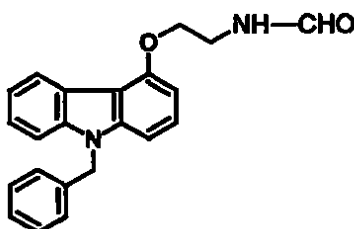
Example 31 N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-cyclopropylamine
 ms (m + H) at 357



Example 32 N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N,N-dimethylamine
ms (m + H) at 345

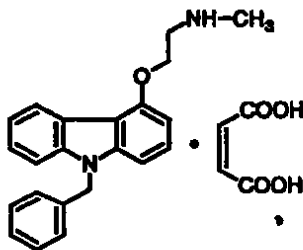


5 Example 33 N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}formamide



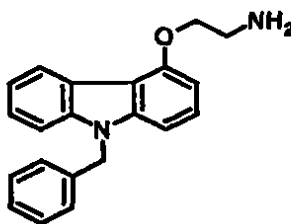
A mixture of 2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethylamine (0.0714 g, 0.226 mmol) and ethyl formate (3 mL) is stirred at 65-70 °C for 45 min. After cooling, excess ethyl formate is removed in vacuo and the residue is partitioned between CH₂Cl₂ and aq sodium sulfate. The organic layers are dried over sodium sulfate and concentrated, the residue is crystallized from CH₂Cl₂-EtOAc-hexane to give 0.0585 g (75%) of the title compound as a white, crystalline solid, mp 161-162 °C, MS (ESI+) for m/z 345 (M+H)⁺, 367 (M+Na), ¹H NMR (CDCl₃) δ 3.95, 4.38, 5.52, 6.13, 6.68, 7.03, 7.10, 7.2-7.4, 8.27, 8.29, IR (drift) 3297, 1659, 1459, 1385, 1341, 1332, 1269, 1255, 1145, 1116, 780, 747, 737, 717, 700 cm⁻¹. Anal. Calcd for C₂₂H₂₀N₂O₂: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.53; H, 5.99; N, 8.09.

Example 34 N-{2-[(9-Benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-methylamine, maleic acid salt



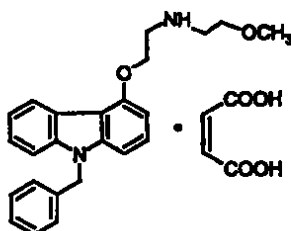
A mixture of 9-benzyl-4-(2-bromoethoxy)-9H-carbazole (0.165 g, 0.434 mmol) and methylamine (40% in H₂O, 0.4 mL) in acetonitrile (3 mL) is stirred in a glass pressure vessel with a screw top cap at 95 °C for 3.5 h after which it is allowed to cool and stir at room temperature overnight. The solvent is then removed and the residue is chromatographed on silica gel using CH₃OH-CH₂Cl₂ (4/96 to 8/92) to give 0.125 g (87%) of product as the free base. The free base and maleic acid (0.0439 g) are dissolved in CH₂Cl₂ and CH₃OH, concentrated, and crystallized from CH₂Cl₂/hexane to give 0.119 g of the title compound. mp 182.5-184.5 °C. ¹H NMR (free base) (CDCl₃) δ 2.61, 3.21, 4.40, 5.51, 6.71, 6.99, 7.12, 7.2-7.4, 8.30. Anal. Calcd for C₂₂H₂₂N₂O•C₄H₄O₄: C, 69.94, H, 5.87, N, 6.27. Found: C, 69.71, H, 5.79, N, 6.21.

Example 35 2-[(9-Benzyl-9H-carbazol-4-yl)oxy]ethylamine



Sodium hydride (60% in oil, 0.934 g, 23.36 mmol) is washed three times with pentane. DMF (5 mL) is added, followed by 9-benzyl-9H-carbazol-4-ol (1.52 g, 5.56 mmol) dissolved in DMF (10 mL) added over 10 min. The mixture is stirred an additional 5 min and then cooled in an ice-water bath. A solution of 2-chloroethylamine hydrochloride (1.29 g, 11.12 mmol) dissolved in DMF (5 mL) is added dropwise over about 5 min. The cooling bath is removed and the mixture is allowed to stir at room temperature over the weekend. Aq. sodium bicarbonate is added and the mixture partitioned between EtOAc, brine, and aq. sodium bicarbonate. The organic layers are dried over MgSO₄ and taken to dryness. The residue is chromatographed on silica gel (120 mL) using CH₃OH-CH₂Cl₂ (4/96) to give 1.26 g (72%) of the title compound as a white solid. An aliquot is crystallized from CH₂Cl₂-EtOAc-hexane, IR (dnft) 1597, 1587, 1458, 1441, 1342, 1329, 1269, 1156, 1145, 1110, 1045, 860, 785, 749, 726 cm⁻¹. ¹H NMR (CDCl₃) δ 3.30, 4.29, 5.51, 6.70, 7.00, 7.12, 7.2-7.4, 8.34. Anal. Calcd for C₂₁H₂₀N₂O: C, 79.72, H, 6.37, N, 8.85. Found: C, 78.70; H, 6.41, N, 8.70.

Example 36 N-{2-[(9-Benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-(2-methoxyethyl)amine

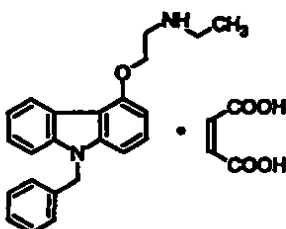


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A mixture of 2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethylamine (0.103 g, 0.327 mmol), 2-bromoethylmethyl ether (0.050 g, 0.359 mmol), diisopropylethylamine (0.0464 g, 0.359 mmol), acetonitrile (1 mL), and THF (1 mL) is stirred at room temperature for 40 min and then at 70 °C for 43 h. After cooling, the solvents are removed and the residue is chromatographed on silica gel (15 mL) using CH₃OH/CH₂Cl₂ (4/96). The pure product fractions are concentrated to dryness to give 0.044 g (36%) of an oil. Maleic acid (0.013 g) is added and the salt is crystallized from CH₂Cl₂/CH₃OH/hexane to give the title compound, mp 175.0-175.5 °C, ¹H NMR (CDCl₃) δ 2.98, 3.26, 3.39, 3.57, 4.38, 5.51, 6.70, 6.99, 7.12, 7.2-7.4, 8.33. Anal. Calcd for C₂₄H₂₆N₂O₂·C₄H₄O₄: C, 68.56, H, 6.16, N, 5.71. Found: C, 68.54, H, 6.22, N, 5.81.

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Example 37 N-Ethyl-N-([(1-phenyl-1,2-dihydro[1,4]oxazino[2,3,4-jk]carbazol-7-yl)oxy]ethyl)amine, maleic acid salt



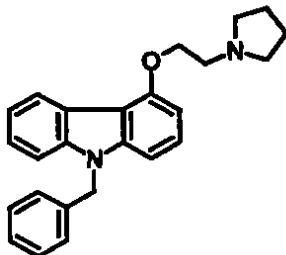
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To a mixture of N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}acetamide (0.3043 g, 0.849 mmol) and dry THF (7 mL) is added borane-methylsulfide complex (0.24 mL, 2.55 mmol) while under argon atmosphere. The mixture is refluxed at 85 °C for 18 h. Methanol is slowly added to consume unreacted borane complex. The mixture is stripped of solvent, then MeOH (5.0 mL) is added then stripped. The oil is dissolved in methanol/CH₂Cl₂ (10/1), to which is added concentrated hydrochloric acid (1.0 mL). The mixture is heated at

25

65 °C for 0.5 h. Water (50 ml) is added and the mixture neutralized with potassium carbonate then partitioned between CH₂Cl₂ and water. The organic layer is washed with water and dried over magnesium sulfate. Column chromatography (50g silica gel) using methanol/CH₂Cl₂ (5/95) gave an oil, which is converted to the maleic acid salt to give
 5 0.1445 g (60%) of the title compound. ¹H NMR (300 MHz, DMSO-d₆) δ 1.24, 3.16, 3.55, 4.47, 5.64, 5.99, 6.78, 7.09, 7.24, 7.37, 7.57, 8.30, 8.61. Anal. Calcd for C₂₃H₂₄N₂O•C₄H₄O₄: C, 70.42; H, 6.13; N, 6.08. Found: C, 70.27; H, 6.22; N, 6.03.

Example 38 9-Benzyl-4-[2-(1-pyrrolidinyl)ethoxy]-9H-carbazole

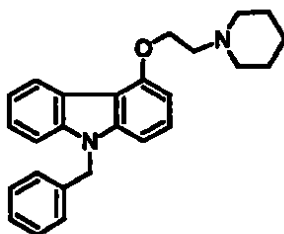


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A mixture of 9-benzyl-4-(2-bromoethoxy)-9H-carbazole (0.020 g, 0.0526 mmol), pyrrolidine (0.040 g, 0.562 mmol), and acetonitrile (1.0 mL) is stirred over the weekend at room temperature. Much starting material remained so the mixture is heated at 75 °C in a capped vial for 24 h. After cooling and removal of the solvent, the residue is partitioned
 15 between CH₂Cl₂ and aq. sodium bicarbonate. The organic layers are dried over sodium sulfate, chromatography on silica gel eluting with CH₃OH-CH₂Cl₂ (4/96) gave 0.0165 g (85%) of the title compound as a waxy solid. ¹H NMR (CDCl₃) δ 1.97, 3.04, 3.36, 4.59, 5.30, 6.71, 7.02, 7.12, 7.2-7.4, 8.32. Anal. Calcd for C₂₅H₂₆N₂O: C, 81.05; H, 7.07; N, 7.56. Found: C, 79.84; H, 7.02; N, 7.44.

20

Example 39 9-Benzyl-4-[2-(1-piperidinyl)ethoxy]-9H-carbazole



In the same manner as for 9-Benzyl-4-[2-(1-pyrrolidinyl)ethoxy]-9H-carbazole, 80 (0.020 g) and piperidine (0.040 g) gave 0.0196 g (97%) of the title compound, mp 113.5-
 25 114.5 °C. ¹H NMR (CDCl₃) δ 1.52, 1.73, 2.78, 3.14, 4.50, 5.51, 6.70, 7.00, 7.12, 7.2-7.4.

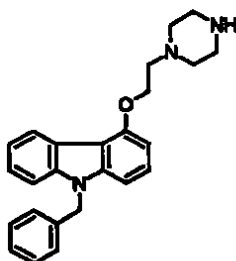
8 35 Anal Calcd for $C_{26}H_{28}N_2O$ C, 81.21, H, 7.34, N, 7.28 Found C, 80.59, H, 7.31, N, 7.22 CH, CH

Preparation 19 tert-Butyl 4-{2-[(9-Benzyl-9H-carbazol-4-yl)oxy]ethyl}-1-

5 piperazinecarboxylate

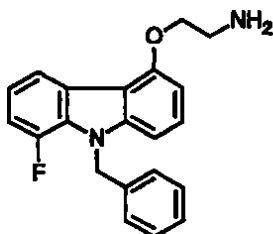
A mixture of 9-benzyl-4-(2-bromoethoxy)-9H-carbazole (0.0647 g, 0.170 mmol), Boc-piperazine (0.0380 g, 0.204 mmol), triethylamine (0.0206 g, 0.204 mmol), and acetonitrile (2 mL) is heated at reflux for 24 h. After cooling, the mixture is partitioned between CH_2Cl_2 and aq. sodium bicarbonate. The organic layers are dried over sodium sulfate, chromatography on silica gel eluting with $CH_3OH-CH_2Cl_2$ (2/98) gave poor separation of product and impurities. Re-chromatography (silica gel, 20 mL) using acetone-hexane (10/90 to 20/80) gave 0.0650 g (83%) of the title compound. IR (drift) 1693, 1457, 1420, 1365, 1341, 1332, 1291, 1266, 1243, 1174, 1154, 1145, 1129, 1112, 752 cm^{-1} , ^1H NMR ($CDCl_3$) δ 1.46, 2.65, 3.06, 3.48, 4.41, 5.51, 6.69, 6.99, 7.12, 7.2-7.4, 8.37. Anal Calcd for $C_{30}H_{35}N_3O_3$ C, 74.20, H, 7.26, N, 8.65 Found C, 73.82, H, 7.41, N, 8.52.

Example 40 9-Benzyl-4-{2-(1-piperazinyloxy)ethyl}-9H-carbazole



A mixture of tert-Butyl 4-{2-[(9-Benzyl-9H-carbazol-4-yl)oxy]ethyl}-1-piperazinecarboxylate (0.0450 g, 0.0927 mmol), trifluoroacetic acid (2.5 mL), and CH_2Cl_2 (2.5 mL) is stirred at room temperature for 1 h. Trifluoroacetic acid and CH_2Cl_2 are then removed in vacuo and the residue is partitioned between CH_2Cl_2 and aq. sodium bicarbonate. The organic layers are dried over sodium sulfate and taken to dryness to give 0.0326 g (91%) of the title compound, IR (drift) 2935, 2821, 1584, 1456, 1353, 1342, 1332, 1271, 1245, 1154, 1145, 1112, 783, 750, 715 cm^{-1} , ^1H NMR ($CDCl_3$) δ 2.70, 2.95, 3.04, 4.41, 5.50, 6.69, 6.99, 7.12, 7.2-7.4, 8.39. Anal Calcd for $C_{25}H_{27}N_3O$ C, 77.89, H, 7.06, N, 10.90 Found C, 76.35, H, 7.20, N, 10.30.

Example 41 2-[(9-Benzyl-8-fluoro-9H-carbazol-4-yl)oxy]ethylamine



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A mixture of 2-[(9-benzyl-8-fluoro-9H-carbazol-4-yl)oxy]acetonitrile (0.7685 g, 0.0023 mol), dry THF (20 mL) and borane-methyl sulfide (0.71 mL, 0.0075 mol) is stirred at room temperature for 3.5 h. Additional borane-methyl sulfide (0.20 mL, 0.0021 mol) is added and the mixture is stirred overnight. The excess borane is cautiously quenched with methanol and the mixture is concentrated under reduced pressure. Methanol and dichloromethane are added to the residue and the solution is again concentrated under reduced pressure (repeated twice). The solids are then dissolved in methanol/dichloromethane and conc. HCl (3 mL) is added. After the mixture is stirred for 50 min, the solvent is removed under reduced pressure and the residue is partitioned between dichloromethane and aq. sodium bicarbonate. The combined organic layers are dried over sodium sulfate and concentrated to dryness. The residue is chromatographed on silica gel (100 mL) using methanol/dichloromethane (2/98 and 4/96) and recrystallized from ethyl acetate/dichloromethane/heptane to give 0.333 g (43%) of the title compound, mp 122.25-123 °C, MS (ESI+) for $C_{21}H_{19}FN_2O$ m/z 335.2 ($M+H$)⁺, IR (drift) 1602, 1577, 1498, 1456, 1443, 1352, 1337, 1325, 1269, 1254, 1242, 1228, 1141, 792, 736 cm^{-1} , ¹H NMR (CDCl₃) δ 3.30, 4.28, 5.30, 6.70, 7.01, 7.11, 7.22, 7.36, 8.10, NH₂ not seen. Anal. Calcd for $C_{21}H_{19}FN_2O$: C, 75.43, H, 5.73, N, 8.38. Found: C, 75.25, H, 5.79, N, 8.28.

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Preparation 20 8-Fluoro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydro-4H-carbazol-4-one

8-Fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.1416 g, 0.70 mmol) is added to a slurry of pentane-washed NaH (0.0400 g, 0.0010 mol) in DMF (2 mL) and after stirring for 30 min, p-fluorobenzyl bromide (0.11 mL, 0.88 mmol) is added. After the mixture had stirred for 2.3 h, it is partitioned between aq. sodium bicarbonate and ethyl acetate. The

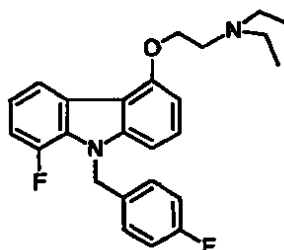
organic layer is dried over sodium sulfate and concentrated to dryness. The resulting solids are chromatographed on silica gel (100 mL) using first dichloromethane (100%) and then methanol/dichloromethane (2/98). The product fractions are combined and rechromatographed on silica gel (50 mL) using acetone/heptane/ NH_4OH (15/85/0.25) and then recrystallized using ethyl acetate/hexane to give 0.0932 g (43%) of the title compound, mp 177-178 °C. MS (ESI-) for $\text{C}_{19}\text{H}_{13}\text{F}_2\text{NO}$ m/z 310.1 (M-H). IR (dnft) 1638, 1630, 1509, 1496, 1459, 1436, 1413, 1361, 1249, 1222, 1194, 1158, 1125, 830, 790 cm^{-1} . ^1H NMR (CDCl_3) δ 2.24, 2.58, 2.86, 5.47, 6.89-7.02, 7.16, 8.06. Anal. Calcd for $\text{C}_{19}\text{H}_{13}\text{F}_2\text{NO}$: C, 73.30; H, 4.86; N, 4.50. Found: C, 73.40; H, 4.83; N, 4.50.

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Preparation 21 8-Fluoro-9-(4-fluorobenzyl)-9H-carbazol-4-ol

Pyridinium bromide perbromide (0.0860 g, 0.27 mmol) is added to a solution of 8-fluoro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydro-4H-carbazol-4-one in THF (0.5 mL) and DMF (0.5 mL) and the mixture is heated to 75 °C. After stirring for 4.5 h, THF is removed under reduced pressure and the residue is partitioned between ethyl acetate and dilute brine. The combined organic layers are washed with dilute sodium sulfate/brine and the aqueous layer is backwashed with ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to give a residue. A mixture of the resulting residue, lithium bromide (0.0428 g, 0.49 mmol), lithium carbonate (0.0311 g, 0.42 mmol) and DMF (1 mL) is heated at 120 °C for two hours. The mixture is partitioned between ethyl acetate and brine. The combined organic layers are dried over sodium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (20 mL) using ethyl acetate/heptane (5/95 and 10/90) to give 0.0460 g (71%) of the title compound, MS (ESI-) for $\text{C}_{19}\text{H}_{13}\text{F}_2\text{NO}$ m/z 308.1 (M-H), IR (dnft) 1580, 1508, 1461, 1434, 1329, 1274, 1242, 1235, 1221, 1157, 1129, 907, 788, 755, 732 cm^{-1} . ^1H NMR (CDCl_3) δ 5.37, 5.64, 6.60, 6.94, 7.14, 7.28, 8.10. Anal. Calcd for $\text{C}_{19}\text{H}_{13}\text{F}_2\text{NO}$: C, 73.78; H, 4.24; N, 4.53. Found: C, 72.52; H, 4.18; N, 4.37.

Example 42 N,N-Diethyl-N-(2-([8-fluoro-9-(4-fluorobenzyl)-9H-carbazol-4-yl]oxy)ethyl)amine



8 Fluoro-9-(4-fluorobenzyl)-9H-carbazol-4-ol (0.0226 g, 0.073 mmol), 2-diethylaminoethylchloride hydrochloride (0.0202 g, 0.12 mmol) potassium carbonate (0.0330 g, 0.24 mmol), sodium iodide (0.0018 g, 0.012 mmol) and DMF (1 mL) are heated
 5 at 80 °C for 3 h. After the mixture had cooled it is partitioned between water and ethyl acetate. The organic layer is dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (20 mL) using methanol/dichloromethane (2/98 and 4/96) to give 0.0222 g (74%) of the title compound. mp 59-60 °C, MS (ESI+) for $C_{25}H_{27}F_2N_2O$ m/z 409.3 (M+H)⁺, ¹H NMR (CDCl₃) δ 1.21, 2.87, 3.22, 4.45, 5.67, 6.74, 6.94, 7.02, 7.14, 7.39, 8.11. Anal. Calcd for $C_{25}H_{26}F_2N_2O$ C 73.51 H 6.41 N 6.86 Found C, 73.05, H, 6.61 N, 6.83.

Preparation 22 6-Chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one

4-Chlorophenylhydrazine hydrochloride (5.3766 g, 0.0300 mol) is added portion-
 15 wise to a solution of 1,3-cyclohexanedione (3.29 g, 0.029 mol) in water (58 mL) and the mixture is allowed to stir over night at room temperature. The resulting solids are collected by filtration, washed with water, and vacuum dried at 50 °C overnight to give the hydrazone. The hydrazone (0.5249 g, 0.0022 mol) is then heated at reflux in trifluoroacetic acid (3 mL) for 7 h, at which time the heat is turned off and the mixture is allowed to stir
 20 overnight at room temperature. Additional trifluoroacetic acid (1 mL) then is added and the mixture is stirred at reflux another 7h and stored in the refrigerator overnight. The mixture is partitioned between water and dichloromethane. The organic layer is washed with aq sodium bicarbonate and the aqueous layer is backwashed with dichloromethane. The combined organic layers are then dried over magnesium sulfate and concentrated to solids.
 25 The solids are chromatographed on silica gel (100 mL) using ethyl acetate/dichloromethane and then recrystallized from ethyl acetate/dichloromethane/methanol to give 0.0872 g (15%) of the title compound, MS_s(ESI-) for $C_{12}H_{10}ClNO$ m/z 218.0 (M-H), IR (drift) 3201, 3172, 3137, 3109, 3063, 2954, 2933, 1631, 1578, 1472, 1373, 1013, 879, 811, 623.

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cm⁻¹ ¹H NMR (CD₃OD) δ 2.22, 2.54, 3.00, 7.16, 7.32, 7.97, NH not seen Anal Calcd for C₁₂H₁₀ClNO C 65.61, H 4.59, N 6.38 Found C 65.49 H 4.51 N 6.32

Preparation 23 9-Benzyl-6-chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one

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6-Chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.4010 g, 0.0018 mol) is added to a slurry of pentane-washed NaH (0.0902 g, 0.0023 mol) in DMF (2 mL) and after stirring for 27 min, benzyl bromide (0.26 mL, 0.0022 mol) is added. After stirring for 2.5 h at room temperature, the mixture is partitioned between aq. sodium bicarbonate and ethyl acetate. The combined organic layers are dried over sodium sulfate and concentrated to dryness. The resulting solids are chromatographed on silica gel (200 mL) using dichloromethane/heptane (60/40 and 100/0) to give 0.5158 g (91%) of the title compound. An aliquot (0.0625 g) is recrystallized from ethyl acetate/heptane to give 0.0415 g of product, mp 196.5-197 °C, MS (ESI+) for C₁₉H₁₆ClNO *m/z* 310.1 (M+H)⁺, ¹H NMR (CDCl₃) δ 2.24, 2.58, 2.87, 5.31, 6.99, 7.16, 7.29, 8.28 Anal Calcd for C₁₉H₁₆ClNO C, 73.66, H, 5.20, N, 4.52 Found C 73.18, H, 5.19 N 4.58

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Preparation 24 9-Benzyl-6-chloro-9H-carbazol-4-ol

Pyridinium bromide perbromide (0.5495 g, 0.0017 mol) is added to a solution of 9-benzyl-6-chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.4406 g, 0.0014 mol) in THF (2.8 mL) and DMF (1.5 mL) and the mixture is heated to 75 °C. After stirring for 5 h, THF is removed under reduced pressure and the residue is partitioned between dichloromethane and brine. The combined organic layers are washed with dilute sodium thiosulfate/brine and the aqueous layer is backwashed with dichloromethane. The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to give a residue. A mixture of the resulting residue, lithium bromide (0.2799 g, 0.0032 mol), lithium carbonate (0.2286 g, 0.0031 mol) and DMF (6 mL) is heated at 120 °C for two hours. The DMF is removed under high vacuum and the residue is partitioned between dichloromethane and water. The combined organic layers are dried over sodium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (100 mL) using dichloromethane (100%) to give 0.3139 g (72%) of the title compound. An aliquot (0.0391) is recrystallized from dichloromethane/methanol/hexane to give 0.0272 g of product, MS (ESI-) for C₁₉H₁₄ClNO *m/z* 306.0 (M-H) IR (drift) 1470, 1452, 1334, 1293

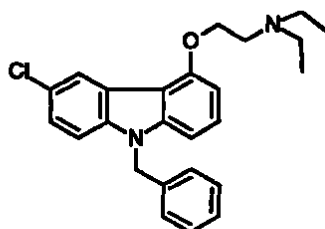
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1284 1266, 1231 1146, 1112 885 796 777 746, 717 702 cm^{-1} ^1H NMR (CDCl_3) δ 5.41
5.49, 6.60 6.97 7.13 7.28 7.35 8.33 Anal Calcd for $\text{C}_{19}\text{H}_{14}\text{ClNO}$ C, 74.15, H, 4.59, N,
4.55 Cl 11.52 Found C, 73.07 H, 4.63 N, 4.59

- 5 Example 43 N-(2-[(9-Benzyl-6-chloro-9H-carbazol-4-yl)oxy]ethyl)-N,N-diethylamine



- 9-Benzyl-6-chloro-9H-carbazol-4-ol (0.0616 g, 0.20 mmol), 2-diethylaminoethylchloride hydrochloride (0.0517 g, 0.30 mmol), potassium carbonate
10 (0.0863 g, 0.62 mmol), sodium iodide (0.0027 g, 0.018 mmol) and DMF (1 mL) are heated
at 85 °C for 3.5 h. After the mixture had cooled, it is partitioned between water and ether.
The combined organic layers are dried over magnesium sulfate and concentrated to an oil.
The oil is chromatographed on silica gel (60 mL) using methanol/dichloromethane (1/99 to
2/98 to 4/96) to give 0.0665 g (82%) of the title compound, mp 96-97.5 °C, MS (ESI+) for
15 $\text{C}_{25}\text{H}_{27}\text{ClN}_2\text{O}$ m/z 407.3 ($\text{M}+\text{H}$) $^+$, IR (drift) 2966, 1583, 1466, 1453, 1340, 1268, 1242
1149, 1124, 1069, 795, 780, 745, 718, 708 cm^{-1} , ^1H NMR (CDCl_3) δ 1.16, 2.75, 3.12, 4.34,
5.47, 6.69, 6.97, 7.08, 7.21-7.38, 8.34 Anal Calcd for $\text{C}_{25}\text{H}_{27}\text{ClN}_2\text{O}$ C, 73.79, H, 6.69,
N, 6.88 Found C, 73.39, H, 6.73, N, 6.78

- 20 Preparation 25 6-Chloro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydro-4H-carbazol-4-one

- 6-Chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.4042 g, 0.0018 mol) is added to a
slurry of pentane-washed NaH (0.091 g, 0.0023 mol) in DMF (2 mL) and after stirring for
20 min, p-fluorobenzyl bromide (0.28 mL, 0.0023 mol) is added. Additional DMF (1 mL)
25 is added and the mixture is stirred for 4 h, at which time the mixture is partitioned between
aq. sodium bicarbonate and ethyl acetate. The combined organic layers are washed with
water, dried over sodium sulfate and concentrated to dryness. The resulting solids are
• chromatographed on silica gel (200 mL) using dichloromethane/heptane (60/40 and 80/20)
to give 0.5519 g (92%) of the title compound, mp 207-207.5 °C, MS (ESI+) for

$C_{19}H_{15}ClFNO$ m/z 328.1 ($M+H$)⁺, IR (drift) 1628, 1511, 1467, 1448, 1360, 1226, 1218, 1145, 1096, 878, 849, 840, 804, 764, 649 cm^{-1} , ^1H NMR ($CDCl_3$) δ 2.23, 2.58, 2.86, 5.27, 6.99, 7.16, 8.27. Anal. Calcd for $C_{19}H_{15}ClFNO$: C, 69.62; H, 4.61; N, 4.27. Found (av): C, 69.08; H, 4.50; N, 4.26.

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Preparation 26 6-Chloro-9-(4-fluorobenzyl)-9H-carbazol-4-ol

Pyridinium bromide perbromide (0.6155 g, 0.0019 mol) is added to a solution of 6-chloro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydro-4H-carbazol-4-one in THF (2.2 mL) and DMF (1.5 mL) and the mixture is heated to 75 °C. After stirring for 3.5 h, the THF is removed under reduced pressure and the residue is partitioned between dichloromethane and brine. The combined organic layers are washed with dilute sodium thiosulfate/brine and the aqueous layer is backwashed with dichloromethane. The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to give a residue. A mixture of the resulting residue, lithium bromide (0.3077 g, 0.0036 mol), lithium carbonate (0.2376 g, 0.0032 mol) and DMF (6 mL) is heated at 120 °C for two hours. The DMF is removed under high vacuum and the residue is partitioned between dichloromethane and water. The combined organic layers are dried over sodium sulfate and concentrated to dryness. The residue is chromatographed on silica gel (125 mL) using dichloromethane (100%) to give 0.3773 g (73%) of the title compound. An aliquot is recrystallized from dichloromethane/hexane, MS (ESI-) for $C_{19}H_{13}ClFNO$ m/z 324.1 ($M-H$). IR (drift) 1510, 1468, 1444, 1335, 1297, 1263, 1232, 1218, 1147, 1116, 832, 822, 791, 778, 745 cm^{-1} , ^1H NMR ($CDCl_3$) δ 5.37, 5.43, 6.59, 6.94, 7.07, 7.23, 7.33, 8.31. Anal. Calcd for $C_{19}H_{13}ClFNO$: C, 70.05; H, 4.02; N, 4.30; Cl, 10.88. Found: C, 68.51; H, 3.96; N, 4.27.

25 Preparation 27 N-(2-([6-Chloro-9-(4-fluorobenzyl)-9H-carbazol-4-yl]oxy)ethyl)-N,N-diethylamine

6-Chloro-9-(4-fluorobenzyl)-9H-carbazol-4-ol (0.0619 g, 0.19 mmol), 2-diethylaminoethylchloride hydrochloride (0.0494 g, 0.29 mmol), potassium carbonate (0.0750 g, 0.54 mmol), sodium iodide (0.0021 g, 0.014 mmol) and DMF (1 mL) are heated at 85 °C for 4 h. After the mixture had cooled, it is partitioned between water and ether. The aqueous layer is also extracted with ethyl acetate several times. The combined organic layers are dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (75 mL) using methanol/dichloromethane (1/99 to 2/98 to

4/96) to give 0.0591 g (73%) of the title compound, mp 99-99.5 °C MS (ESI+) for $C_{25}H_{26}ClFN_2O$ m/z 425.2 ($M+H$)⁺, IR (drift) 2972, 1588, 1507, 1467, 1454, 1342, 1270, 1221, 1151, 1123, 817, 799, 778, 740, 714 cm^{-1} , ¹H NMR (CDCl₃) δ 1.15, 2.75, 3.12, 4.33, 5.44, 6.71, 6.93, 7.04, 7.20, 7.34, 8.33. Anal. Calcd for $C_{25}H_{26}ClFN_2O$ C, 70.66, H, 6.17, N, 6.59. Found C, 70.23, H, 6.05, N, 6.61.

Preparation 28 6-Fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one

4-Fluorophenylhydrazine hydrochloride (4.5697 g, 0.0281 mol) is added in portions to a solution of 1,3-cyclohexanedione (3.11 g, 0.0277 mol) in water (55 mL). The mixture is allowed to shake overnight at room temperature. Additional 4-fluorophenylhydrazine hydrochloride (0.1052 g, 0.65 mmol) is added and the mixture is shaken another 6 h. After sitting at room temperature overnight the mixture is extracted with ethyl acetate. The organic layer is washed with water and the aqueous layer is backwashed with ethyl acetate. The combined organic layers are dried over sodium sulfate and concentrated to give the hydrazone. The hydrazone and trifluoroacetic acid (37 mL) are heated at 85 °C for 3.5 h. After cooling, the mixture is partitioned between water and dichloromethane. The combined organic layers are washed with aq. sodium bicarbonate and the aqueous layer is washed with dichloromethane. The combined organic layers are dried over magnesium sulfate and concentrated to a foam. The foam is chromatographed on silica gel (200 mL) using ethyl acetate/dichloromethane (5/95 to 10/90 to 20/80) and recrystallized from ethyl acetate/methanol/hexane to give 0.6197 g (11%) for a first crop and 0.3281 g (6%) for a second crop of the title compound, MS (ESI-) for $C_{12}H_{10}FNO$ m/z 202.0 ($M-H$). IR (drift) 3231, 3183, 2942, 1638, 1623, 1482, 1468, 1377, 1203, 1173, 1131, 914, 856, 804, 793 cm^{-1} , ¹H NMR (CD₃OD) δ 2.22, 2.54, 3.00, 6.95, 7.32, 7.66, NH not seen. Anal. Calcd for $C_{12}H_{10}FNO$ C, 70.93, H, 4.96, N, 6.89. Found C, 70.76, H, 5.05, N, 6.85.

Preparation 29 9-Benzyl-6-fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one

6-Fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.3938 g, 0.0019 mol) is added to a slurry of pentane-washed NaH (0.0970 g, 0.0024 mol) in DMF (3 mL) and after stirring for 10 min, benzyl bromide (0.28 mL, 0.0024 mol) is added. After stirring for 4 h at room temperature, the mixture is partitioned between water and ethyl acetate. The combined organic layers are dried over sodium sulfate and concentrated to dryness. The resulting solids are chromatographed on silica gel (200 mL) using dichloromethane/heptane (60/40 to

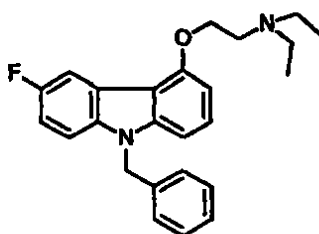
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80/20 to 100/0) to give 0.3681 g (65%) of the title compound. An aliquot is recrystallized from ethyl acetate/heptane, MS (ESI+) for $C_{19}H_{16}FNO$ m/z 294.2 ($M+H$)⁺, IR (drift) 1634, 1523, 1483, 1466, 1447, 1357, 1254, 1138, 900, 868, 803, 799, 759, 729, 700 cm^{-1} , ¹H NMR (CDCl₃) δ 2.22, 2.59, 2.88, 5.32, 6.95, 7.01, 7.15, 7.30, 7.96. Anal. Calcd for $C_{19}H_{16}FNO$: C, 77.80, H, 5.50, N, 4.78. Found: C, 77.65, H, 5.39, N, 4.69.

Preparation 30 9-Benzyl-6-fluoro-9H-carbazol-4-ol

Pyridinium bromide perbromide (0.4620 g, 0.0014 mol) is added to a mixture of 9-benzyl-6-fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.3271 g, 0.0011 mol) in THF (3.4 mL) and DMF (2.4 mL) and the mixture is heated to 75 °C. After stirring for 6.5 h, the mixture is stored in the freezer overnight. Heating is resumed for an additional 2.5 h at which time THF is removed under reduced pressure and the residue is partitioned between dichloromethane and brine. The combined organic layers are washed with dilute sodium thiosulfate/brine and the aqueous layer is backwashed with dichloromethane. The combined organic layers are dried over sodium sulfate and concentrated under reduced pressure to give a residue. The residue is heated to 120 °C in DMF (5 mL) with lithium bromide (0.2348 g, 0.0027 mol) and lithium carbonate (0.1813 g, 0.0025 mol). After 2 h, DMF is removed under high vacuum and the mixture is partitioned between dichloromethane and water. The combined organic layers are washed with water and the aqueous layer is backwashed with dichloromethane. The combined organic layers are dried over sodium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (100 mL) using dichloromethane/hexane (30/70 and 50/50) to give 0.1893 g (58%) of the title compound. An aliquot is precipitated from hexane/ether; MS (ESI+) for $C_{19}H_{14}FNO$ m/z 292.2 ($M+H$)⁺, IR (drift) 1483, 1466, 1451, 1337, 1304, 1174, 1157, 1138, 884, 859, 794, 777, 745, 713, 700 cm^{-1} , ¹H NMR (CDCl₃) δ 5.34, 5.47, 6.56, 6.95, 7.13, 7.20-7.30, 8.01. Anal. Calcd for $C_{19}H_{14}FNO$: C, 78.33, H, 4.84, N, 4.81. Found: C, 78.17, H, 4.83, N, 4.78.

Example 44 N-{2-[(9-Benzyl-6-fluoro-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine



9-Benzyl-6-fluoro-9H-carbazol-4-ol (0.0587 g, 0.20 mmol), 2-diethylaminoethylchloride hydrochloride (0.0524 g, 0.30 mmol), potassium carbonate (0.0872 g, 0.63 mmol), sodium iodide (0.0062 g, 0.041 mmol) and DMF (2 mL) are heated at 85 °C for 3 h. After the mixture had cooled, it is partitioned between water and ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (50 mL) using methanol/dichloromethane (1/99 to 3/97) to give 0.0485 g (62%) of the title compound, mp 68–69 °C, MS (ESI+) for $C_{25}H_{27}FN_2O$ m/z 391.3 ($M+H$)⁺, IR (drift) 2966, 1584, 1483, 1463, 1345, 1268, 1185, 1162, 1145, 1052, 799, 778, 741, 726, 713 cm^{-1} , ¹H NMR (CDCl₃) δ 1.14, 2.73, 3.10, 4.33, 5.48, 6.68, 6.97, 7.11, 7.21, 7.35, 8.03. Anal. Calcd for $C_{25}H_{27}FN_2O$: C, 76.89, H, 6.97, N, 7.17. Found: C, 77.16, H, 7.28, N, 7.16.

Preparation 31 6-Fluoro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydro-4H-carbazol-4-one

6-Fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.3940 g, 0.0019 mol) is added to a slurry of pentane-washed NaH (0.0966 g, 0.0024 mol) in DMF (3 mL) and after stirring for 10 min, p-fluorobenzyl bromide (0.29 mL, 0.0023 mol) is added. After stirring for 4 h at room temperature, the mixture is partitioned between water and ethyl acetate. The combined organic layers are dried over sodium sulfate and concentrated to dryness. The resulting solids are chromatographed on silica gel (100 mL) using methanol/dichloromethane (0.5/99.5) to give 0.5678 g (94%) of the title compound. An aliquot is recrystallized from ethyl acetate/heptane, mp 182.5–183 °C, MS (ESI+) for $C_{19}H_{15}F_2NO$ m/z 312.2 ($M+H$)⁺, IR (drift) 1631, 1511, 1483, 1466, 1449, 1256, 1228, 1218, 1137, 1094, 867, 836, 813, 808, 802 cm^{-1} , ¹H NMR (CDCl₃) δ 2.24, 2.58, 2.86, 5.28, 6.94, 7.13, 7.96. Anal. Calcd for $C_{19}H_{15}F_2NO$: C, 73.30, H, 4.86, N, 4.50. Found: C, 73.27, H, 4.92, N, 4.54.

Preparation 32 6-Fluoro-9-(4-fluorobenzyl)-9H-carbazol-4-ol

Pyridinium bromide perbromide (0.7068 g, 0.0022 mol) is added to a mixture of 6-fluoro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.5245 g, 0.0017 mol) in THF (4 mL) and DMF (4 mL) and the mixture is heated to 75 °C. After stirring for 6.5 h, the mixture is stored in the freezer overnight. Heating is resumed for an additional 2.5 h, at which time THF is removed under reduced pressure and the residue is partitioned between dichloromethane and brine. The combined organic layers are washed with dilute sodium thiosulfate/brine and the aqueous layer is backwashed with dichloromethane. The combined organic layers are dried over sodium sulfate and concentrated under reduced pressure to give a residue. The residue is heated to 120 °C in DMF (8 mL) with lithium bromide (0.3412 g, 0.0039 mol) and lithium carbonate (0.2548 g, 0.0035 mol). After 2 h, DMF is removed under high vacuum and the mixture is partitioned between dichloromethane and water. The combined organic layers are washed with water, dried over sodium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (100 mL) using dichloromethane/hexane (30/70 to 50/50) to give 0.2706 g (52%) of the title compound, MS (ESI-) for $C_{19}H_{13}F_2NO$ m/z 308.0 (M-H), IR (drift) 1511, 1483, 1465, 1450, 1336, 1222, 1215, 1172, 1157, 1138, 883, 858, 791, 777, 744 cm^{-1} , ^1H NMR ($CDCl_3$) δ 5.35, 5.44, 6.57, 6.95, 7.06-7.30, 8.01. Anal. Calcd for $C_{19}H_{13}F_2NO$ C, 73.78, H, 4.24, N, 4.53. Found C, 72.65, H, 4.20, N, 4.45.

Preparation 33 **N,N-Diethyl-N-(2-([6-fluoro-9-(4-fluorobenzyl)-9H-carbazol-4-yl]oxy)ethyl)amine**

6-Fluoro-9-(4-fluorobenzyl)-9H-carbazol-4-ol (0.0584 g, 0.19 mmol), 2-diethylaminoethylchloride hydrochloride (0.0593 g, 0.35 mmol), potassium carbonate (0.0926 g, 0.63 mmol), sodium iodide (0.0061 g, 0.041 mmol) and DMF (2 mL) are heated at 85 °C for 3 h. After the mixture had cooled, it is partitioned between water and ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (50 mL) using methanol/dichloromethane (1/99) to give 0.0471 g (61%) of the title compound, mp 75-76 °C, MS (ESI+) for $C_{23}H_{26}F_2N_2O$ m/z 409.3 (M+H)⁺, IR (drift) 1585, 1507, 1481, 1461, 1343, 1269, 1221, 1159, 1145, 871, 820, 799, 776, 739, 712 cm^{-1} , ^1H NMR ($CDCl_3$) δ 1.14, 2.73, 3.10, 4.33, 5.44, 6.69, 6.93, 7.04-7.18, 7.36, 8.03. Anal. Calcd for $C_{23}H_{26}F_2N_2O$ C, 73.51, H, 6.41, N, 6.86. Found C, 73.30, H, 6.59, N, 6.77.

Preparation 34 6-Methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one

p-Tolylhydrazine hydrochloride (8 6693 g, 0 0547 mol) is added in portions to a solution of 1,3-cyclohexanedione (6 00 g, 0 053 mol) in water (100 mL). The mixture is allowed to stir for three days at room temperature. The resulting solids are collected by filtration, washed with water and vacuum dried at 56 °C for 30 min and then overnight at room temperature to give the hydrazone. The hydrazone, p-toluene sulfonic acid monohydrate (8 31 g, 0,044 mol) and toluene (350 mL) are heated at 120 °C for 2 5 h. After cooling, the toluene layer is decanted and washed with water and aq. sodium bicarbonate, then dried over sodium sulfate and concentrated to dryness. The residue left behind in the round bottom flask is dissolved in dichloromethane and washed with water and aq. sodium bicarbonate (emulsion observed) and the organic layer is dried over sodium sulfate and concentrated to dryness. The solids in the emulsion are collected and washed with water, followed by ether and vacuum dried at room temperature to give 3 2168 g (39%) of the title compound. The solids obtained from the extractions are combined and chromatographed on silica gel (250 mL) using methanol/dichloromethane (0/100 to 2/98 to 4/96) and then triturated in ethyl acetate/dichloromethane/methanol/heptane to give 0 4377 g (5%) of the title compound. An aliquot is chromatographed on silica gel (15 mL) using dichloromethane (100 %) and then precipitated from dichloromethane/methanol/hexane, mp > 255 °C. MS (ESI-) for C₁₃H₁₃NO m/z 198 0 (M-H), IR (drift) 3182, 3155, 3121, 3079, 3062, 3027, 2936, 1615, 1586, 1471, 1377, 1215, 1185, 1123, 798 cm⁻¹, ¹H NMR (CD₃OD) δ 2 21, 2 41, 2 53, 2 98, 7 02, 7 23, 7 83, NH not seen. Anal. Calcd for C₁₃H₁₃NO C, 78 36, H, 6 58, N, 7 03. Found (av) C, 77 70, H, 6 55, N, 6 96.

Preparation 35 9-Benzyl-6-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one

6-Methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one (7 6342 g, 0 038 mol) is added to a slurry of pentane-washed NaH (1 9563 g, 0 049 mol) in DMF (43 mL) and, after stirring for 20 min, benzyl bromide (0 58 mL, 0 0011 mol) is added. The mixture is cooled with a cold water bath and additional DMF (9 mL) is added to thin the slurry. After the slurry is stirred for 34 min, it is partitioned between water and ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated to dryness. The resulting solids are recrystallized from ethyl acetate/dichloromethane/heptane to give 9 23 g (83%) of the title compound. The filtrate from the recrystallization is chromatographed on silica gel (225 mL) using methanol/dichloromethane (1/99) to give 1 14 g (10%) of the title compound.

mp 179-179.5 °C MS (ESI+) for $C_{20}H_{19}NO$ m/z 290 1 (M+H)⁺ IR (drift) 2938 1631, 1521 1468, 1447, 1386, 1360, 1189, 1105, 953, 795, 757, 731, 702 654 cm^{-1} , ¹H NMR (CDCl₃) δ 2.21 2.46 2.58 2.86 5.30 7.03 7.14, 7.28 8.11 Anal Calcd for $C_{20}H_{19}NO$ C 83.01, H 6.62 N 4.84 Found C 82.61 H, 6.75 N, 4.76

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Preparation 36 9-Benzyl-6-methyl-9H-carbazol-4-ol

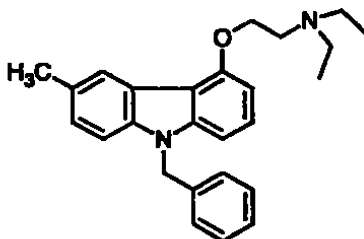
Pyridinium bromide perbromide (11.9436 g, 0.0373 mol) is added to a mixture of 9-benzyl-6-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one (8.93 g 0.0309 mol) in dry THF (42 mL) and dry DMF (30 mL) and the mixture is heated to 75 °C After stirring for 6 h, THF is removed under reduced pressure and the residue is partitioned between dichloromethane and brine The combined organic layers are washed with dilute sodium thiosulfate/brine and the combined organic layers are dried over magnesium sulfate and concentrated under high vacuum to give an oil Hexane is added to the oil and solids precipitated. These solids are upgraded by precipitation from dichloromethane/ethyl acetate/hexane and vacuum dried at room temperature The solids are combined with lithium bromide (3.5386 g, 0.041 mol), lithium carbonate (2.7427 g, 0.037 mol) and dry DMF (72 mL) and heated at 120 °C for 1.5 h. DMF then is removed under high vacuum and the mixture is partitioned between dichloromethane and water The combined organic layers are washed with water and the aqueous layer is backwashed with dichloromethane. The combined organic layers are dried over sodium sulfate and concentrated to an oil The oil is chromatographed on silica gel (300 mL) using ethyl acetate/heptane (30/70) The product fractions are rechromatographed on silica gel (200 mL) using ethyl acetate/heptane (10/90) to give 3.75 g (42%) of 9-benzyl-6-methyl-9H-carbazol-4-ol containing a significant amount of 9-benzyl-3-bromo-6-methyl-9H-carbazol-4-ol as an impurity The material is purified by reduction of the bromide 9-Benzyl-6-methyl-9H-carbazol-4-ol The mixture (2.25 g, 0.0078 mol) is dissolved in dry THF (8 mL) is added to a slurry of lithium aluminum hydride (0.7604 g, 0.020 mol) in dry THF (42 mL) The mixture is stirred overnight at 75-80 °C The mixture then is cooled and water (0.8 mL) is added followed by 15% NaOH (0.8 mL) and then water (2.4 mL) The solids are removed by filtration and washed with THF The filtrate is concentrated to dryness and the residue is chromatographed on silica gel (50 mL) using dichloromethane (100 %) Recrystallization from dichloromethane/hexane give 1.48 g (52%) of the title compound, mp 160-161 °C, MS (ESI+) for $C_{20}H_{17}NO$ m/z 288 2 (M+H)⁺ IR (drift) 3294, 1468 1450 1338 1302 1281 1238 1147 1117, 790, 779 746 720 714 703 cm^{-1} ¹H

197-201

NMR (CDCl₃) δ 2.54, 5.29, 5.47, 6.57, 6.93, 7.12, 7.23, 8.12. Anal. Calcd for C₂₀H₁₇NO: C, 83.59, H 5.96, N 4.87. Found: C 83.51, H 6.03, N 4.94.

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Example 45 N-{2-[(9-Benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine



9-Benzyl-6-methyl-9H-carbazol-4-ol (0.0597 g, 0.21 mmol), 2-diethylaminoethylchloride hydrochloride (0.0565 g, 0.33 mmol), potassium carbonate (0.1007 g, 0.73 mmol), sodium iodide (0.0054 g, 0.036 mmol) and DMF (1 mL) are heated at 85 °C for 4.5 h. After the mixture had cooled, it is partitioned between water and ether. The aqueous layer is also washed twice with ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated to dryness. The residue is chromatographed on silica gel (60 mL) using methanol/dichloromethane (1/99 to 3/97 to 5/95) to give 0.0605 g (75%) of the title compound containing N-{2-[(9-benzyl-3-bromo-6-methyl-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine as an impurity. Attempts at purifying this material through recrystallization are unsuccessful, MS (ESI+) for C₂₆H₃₀N₂O *m/z* 387.3 (M+H)⁺. ¹H NMR (CDCl₃) δ 1.17, 2.53, 2.78, 3.17, 4.37, 5.47, 6.68, 6.96, 7.11, 7.21-7.34, 8.17.

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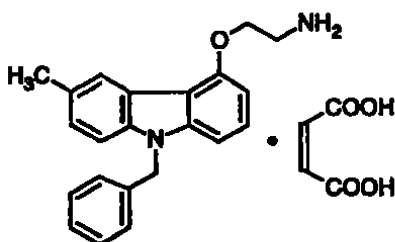
Preparation 37 2-[(9-Benzyl-6-methyl-9H-carbazol-4-yl)oxy]acetonitrile

A mixture 9-benzyl-6-methyl-9H-carbazol-4-ol (1.4172 g, 0.0049 mol), potassium carbonate (0.8184 g, 0.0059 mol), bromoacetonitrile (0.75 mL, 0.011 mol) and DMF (18 mL) is stirred at room temperature for 3 h. The mixture is then partitioned between water and dichloromethane and the combined organic layers are dried over sodium sulfate and concentrated to a residue. Water is added to the residue and solids precipitated. The solids are collected by filtration and washed with water followed by a little hexane, and then vacuum dried at room temperature. The solids are chromatographed on silica gel (150 mL) using dichloromethane (100 %) to give 1.4723 g (91%) of the title compound. An aliquot is

recrystallized from ethyl acetate/hexane, chromatographed on silica gel (50 mL) using ethyl acetate/hexane (20/80) and then recrystallized again from ethyl acetate/dichloromethane/hexane, mp 188-188.25 °C MS (ESI+) for C₂₂H₁₈N₂O m/z 327.2 (M+H)⁺ IR (drift) 1497, 1467, 1447, 1365, 1340, 1305, 1264, 1237, 1152, 1126, 1053, 799, 781, 754, 711 cm⁻¹ ¹H NMR (CDCl₃) δ 2.54, 5.06, 5.49, 6.73, 7.10, 7.25, 7.36, 8.10. Anal. Calcd for C₂₂H₁₈N₂O C, 80.96, H, 5.56, N, 8.58. Found. C, 80.62, H, 5.68, N, 8.55.

Example 46 2-[(9-Benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethylamine

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Borane-methyl sulfide (1.2 mL, 0.013 mol) is added to a mixture of 2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]acetonitrile (1.3337 g, 0.0041 mol) in dry THF (35 mL) and the mixture is allowed to stir at room temperature for 5.5 h. The excess borane then is cautiously quenched with methanol and the mixture is concentrated under reduced pressure. Methanol and dichloromethane are added to the residue and the solution is again concentrated under reduced pressure (repeated twice). The solids are then dissolved in methanol/dichloromethane with heating and 4N HCl (10 mL) is added. The mixture is stirred for 15 min while being warmed slightly. The solvent is then removed under reduced pressure and the residue is partitioned between dichloromethane and aq. sodium bicarbonate. The combined organic layers are dried over sodium sulfate and concentrated to dryness. The residue is chromatographed on silica gel (300 mL) using methanol/dichloromethane (2/98 and 6/94) to give 0.89 g (66%) of the title compound. The salt of 2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethylamine (0.2310 g, 0.70 mmol) is formed with maleic acid in dichloromethane and recrystallized from methanol/dichloromethane/hexane to give 0.2051 g (66%) of the maleic acid salt, mp 187.5-188 °C, MS (ESI+) for C₂₂H₂₂N₂O m/z 331.3 (M+H)⁺, IR (drift) 3027, 2984, 2926, 2887, 1601, 1579, 1497, 1483, 1465, 1364, 1344, 1267, 1150, 865, 747 cm⁻¹, ¹H NMR (CD₃OD) δ 2.52, 3.59, 4.52, 5.54, 6.23, 6.77, 7.09, 7.22, 7.33, 8.16. NH₂ not seen. Anal.

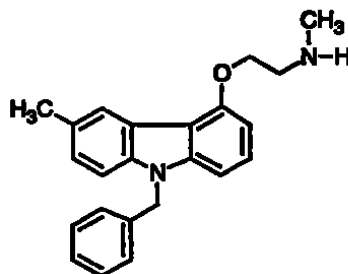
Calcd for $C_{22}H_{22}N_2O \cdot C_4H_4O_4$ C 69.94, H 5.87, N 6.27 Found C, 69.93 H 5.90, N, 6.29

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Preparation 38 2-[(9-Benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethylformamide

A mixture of 2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethylamine (0.2974 g, 0.90 mmol), dichloromethane (4 mL) and ethyl formate (4 mL) is heated at 62 °C. Additional dichloromethane (6 mL) and ethyl formate (6 mL) are added. After 4 h, the mixture is concentrated to dryness and the residue is chromatographed on silica gel (100 mL) using methanol/dichloromethane (4/96). The resulting solids are recrystallized from ethyl acetate/dichloromethane/hexane to give 0.2716 g (84%) of the title compound. ^1H NMR ($CDCl_3$) δ 2.55, 3.94, 4.36, 5.48, 6.11, 6.64, 6.99, 7.11, 7.24, 7.32, 8.06, 8.28.

Example 47 N-(2-[(9-Benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethyl)-N-methylamine



Borane-methyl sulfide (0.12 mL, 0.0013 mol) is added to a mixture of 2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethylformamide (0.1565 g, 0.0013 mol) in dry THF (3 mL) and the mixture is stirred overnight at room temperature. The excess borane is cautiously quenched with methanol and the mixture is concentrated under reduced pressure. Methanol and dichloromethane are added to the residue and the solution is again concentrated under reduced pressure (repeated twice). The solids are then dissolved in methanol/dichloromethane and conc. HCl (27 drops) is added. After the mixture had stirred for 1.3 h, the solvent is removed under reduced pressure and the residue is partitioned between dichloromethane and aq. sodium bicarbonate. The combined organic layers are dried over sodium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (40 mL) using acetone/dichloromethane/0.25% NH_4OH (10/90, 20/80 and 50/50) to give 0.1300 g (86%) of the title compound, mp 96-96.75 °C. MS (ESI+) for $C_{23}H_{24}N_2O$ m/z

345.2 (M+H)⁺ IR (drift) 1600, 1580, 1467, 1449, 1341, 1307, 1268, 1242, 1151, 1128, 794, 779, 744, 718, 708 cm⁻¹, ¹H NMR (CDCl₃) δ 2.54, 2.61, 3.22, 4.39, 5.48, 6.68, 6.96, 7.11, 7.24, 7.31, 8.09. Anal. Calcd for C₂₃H₂₄N₂O: C, 80.20; H, 7.02; N, 8.13. Found: C, 79.88; H, 7.15; N, 8.12.

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Preparation 39 9-(4-Fluorobenzyl)-6-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one

6 Methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.5457 g, 0.0027 mol) is added to a slurry of pentane-washed NaH (0.1369 g, 0.0034 mol) in DMF (3 mL) and after stirring for 10 20 min, p-fluorobenzyl bromide (0.42 mL, 0.0034 mol) is added followed by additional DMF (2 mL). After the slurry had stirred for 2.5 h, it is partitioned between water and ethyl acetate. The combined organic layers are washed with water, dried over sodium sulfate and concentrated to dryness. The resulting solids are chromatographed on silica gel (200 mL) using dichloromethane (100%) to give 0.6929 g (82%) of the title compound. An aliquot is 15 recrystallized from ethyl acetate/heptane, mp 209.5–210 °C, MS (ESI+) for C₂₀H₁₈FNO *m/z* 308.2 (M+H)⁺, IR (drift) 2939, 1629, 1510, 1467, 1449, 1413, 1362, 1225, 1219, 1190, 1158, 1107, 1094, 832, 797 cm⁻¹, ¹H NMR (CDCl₃) δ 2.23, 2.47, 2.59, 2.85, 5.27, 6.99, 7.05, 7.12, 8.11. Anal. Calcd for C₂₀H₁₈FNO: C, 78.15; H, 5.90; N, 4.56. Found: C, 77.64; H, 5.87; N, 4.44.

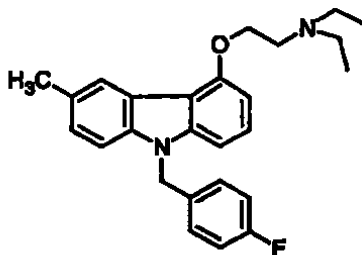
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Preparation 40 9-(4-Fluorobenzyl)-6-methyl-9H-carbazol-4-ol

Pyridinium bromide perbromide (0.8153 g, 0.0026 mol) is added to a mixture of 9-(4-fluorobenzyl)-6-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.6351 g, 0.0021 mol) in dry THF (4.2 mL) and dry DMF (3 mL) and the mixture is heated to 75 °C. After stirring 25 for 6 h, additional pyridinium bromide perbromide (0.0951 g, 0.30 mmol) is added and the mixture is stirred another hour. After storing in the freezer overnight, the mixture is again heated for another 40 min. THF is removed under reduced pressure and the residue is partitioned between dichloromethane and brine. The combined organic layers are washed with dilute sodium thiosulfate/brine and the aqueous layer is backwashed with 30 dichloromethane. The combined organic layers are dried over magnesium sulfate and concentrated to dryness. The residue is combined with lithium bromide (0.4092 g, 0.0047 mol), lithium carbonate (0.3652 g, 0.0049 mol) and dry DMF (12 mL) and heated at 120 °C for 1.5 h. DMF is removed under high vacuum and the mixture is partitioned between

dichloromethane and water. The combined organic layers are dried over sodium sulfate and concentrated to dryness. The residue is chromatographed on silica gel (100 mL) using hexane (100%, to remove oil from sample) followed by ethyl acetate (100%). The residue is chromatographed again on silica gel (125 mL) using ethyl acetate/heptane (10/90) to give 0.0505 g (8%) of the title compound. MS (ESI-) for $C_{20}H_{16}FNO$ m/z 304.1 (M-H), ^1H NMR ($CDCl_3$) δ 2.54, 5.33, 5.43, 6.57, 6.93, 7.08, 7.24, 8.12.

Example 48 N,N -Diethyl- N -(2-([9-(4-fluorobenzyl)-6-methyl-9H-carbazol-4-yl]oxy)ethyl)amine



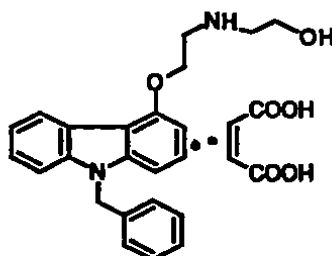
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9-(4-Fluorobenzyl)-6-methyl-9H-carbazol-4-ol (0.0505 g, 0.17 mmol), 2-diethylaminoethylchloride hydrochloride (0.0411 g, 0.24 mmol), potassium carbonate (0.1018 g, 0.74 mmol), sodium iodide (0.0046 g, 0.031 mmol) and DMF (3 mL) are heated at 85 °C for 3 h. After the mixture had cooled, it is partitioned between water and ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated to dryness. The residue is chromatographed on silica gel (60 mL) using methanol/dichloromethane (1/99 to 2/98 to 4/96) to give 0.0332 g (50%) of the title compound, MS (ESI+) for $C_{26}H_{29}FN_2O$ m/z 405.3 (M+H)⁺, IR (drift) 2966, 1601, 1506, 1460, 1339, 1269, 1242, 1218, 1150, 1127, 1054, 790, 781, 746, 717 cm^{-1} , ^1H NMR ($CDCl_3$) δ 1.90, 2.55, 2.80, 3.18, 4.39, 5.46, 6.71, 6.94, 7.07, 7.22, 7.33, 8.19. Anal. Calcd for $C_{26}H_{29}FN_2O$: C, 77.20, H, 7.22, N, 6.93. Found: C, 75.79, H, 7.61, N, 6.55.

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Example 49 2-([2-([9-benzyl-9H-carbazol-4-yl]oxy)ethyl]amino)-1-ethanol and its maleic acid salt



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To a mixture of 9-benzyl-4-(2-bromoethoxy)-9H-carbazole (0.2350 g, 0.618 mmol), ethanolamine (0.41 ml, 0.68 mmol) and acetonitrile (10 ml) is added diisopropylethylamine (0.118 ml, 0.68 mmol). The mixture is refluxed at 85 °C for 24 h. The mixture is then concentrated, partitioned between CH₂Cl₂ and brine. The organic layer is washed with water and dried over magnesium sulfate. Column chromatography (30 ml silica gel) using methanol/CH₂Cl₂ (5/95) gave an oil, which is converted to the maleic acid salt to give 0.108 g (37 %) of the title compound. mp 160 °C, IR (drift) 1580, 1532, 1499, 1487, 1458, 1380, 1356, 1343, 1334, 1268, 1146, 1113, 748, 714, 705 cm⁻¹, ¹H NMR (300 MHz, DMSO-d₆) δ 3.18, 3.30, 3.69, 4.50, 5.27, 5.64, 5.99, 6.78, 7.09, 7.19, 7.36, 7.57, 8.30, 8.66. Anal. Calcd for C₂₃H₂₄N₂O₂·C₄H₄O₄·0.5 H₂O. C, 66.79; H, 6.02; N, 5.77. Found C, 66.58; H, 5.89; N, 5.69.

Preparation 41 9H-Carbazol-4-ol

1,2,3,9-Tetrahydro-4H-carbazol-4-one (11.59 g, 0.063 mol), anhydrous lithium chloride (10.76 g, 0.255 mol), anhydrous copper (II) chloride (17.73 g, 0.132 mol) and DMF (70 mL) are combined and heated at 62 °C for 28 h. The mixture is cooled and the resulting solids are collected and washed with water followed by hexane. The solids are triturated four times in ethyl acetate at 80 °C. Each time the filtrate is washed with water and the organic layer is dried over sodium sulfate and concentrated to dryness. The solids collected by filtration are then dissolved in dichloromethane/methanol, dried over sodium sulfate and concentrated to dryness. The combined solids gave 12.29 g of the chloro intermediate. A mixture of the chloro intermediate (6.52 g, 0.030 mol), lithium bromide (5.464 g, 0.063), lithium carbonate (4.530, 0.061 mol) and dry DMF (80 mL) is heated at 120 °C for 7.5 h and then stirred for two days at room temperature. The mixture is partitioned between water and dichloromethane and the combined organic layers are washed with brine, dried over sodium sulfate and concentrated to dryness. The resulting residue is chromatographed on silica gel (300 mL) using ethyl acetate/hexane (20/80) to give 2.543 g (42%) of the title compound, MS (ESI+) for C₁₂H₉NO *m/z* 184.1 (M+H)⁺, ¹H NMR (CDCl₃) δ 5.32, 6.60, 7.04, 7.27, 7.43, 8.07, 8.29.

Preparation 42 2-(9H-Carbazol-4-yloxy)acetonitrile

A mixture of 9H-carbazol-4-ol (2.543 g, 0.014 mol), potassium carbonate (0.2386 g, 0.017 mol), bromoacetonitrile (2.5 mL, 0.036 mol) and DMF (42 mL) is stirred at room

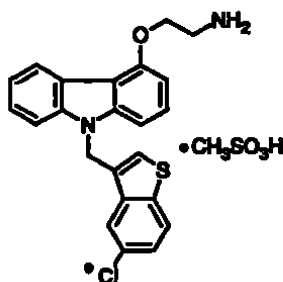
temperature for 4 h. The mixture is then partitioned between water and ethyl acetate. The combined organic layers are dried over sodium sulfate and concentrated to a residue. The resulting residue is chromatographed on silica gel (200 mL) using ethyl acetate/hexane (20/80) to give 0.703 g (23%) of the title compound, mp 120-120.5 °C. MS (ESI-) for

5 $C_{14}H_{10}N_2O$ m/z 221.0 (M-H) IR (drift) 3399, 1605, 1585, 1508, 1452, 1346, 1336, 1269, 1242, 1212, 1106, 785, 757, 750, 723 cm^{-1} . ^1H NMR ($CDCl_3$) δ 5.07, 6.76, 7.21, 7.29, 7.38-7.47, 8.18, 8.28. Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.53; N, 12.60. Found: C, 75.41; H, 4.52; N, 12.48.

10 **Preparation 43** 2-({9-[(5-Chloro-1-benzothiophen-3-yl)methyl]-9H-carbazol-4-yl}oxy)acetonitrile

2-(9H-Carbazol-4-yloxy)acetonitrile (0.146 g, 0.66 mmol) is added to a slurry of pentane-washed NaH (0.0441 g, 0.0011 mol) in DMF (1 mL) and allowed to stir for 20 min at room temperature. 3-(Bromomethyl)-5-chlorobenzothiophene (0.229 g, 0.88 mmol) is
15 added and after stirring for 1 h the mixture is partitioned between ethyl acetate and water. The combined organic layers are dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (75 mL) using ethyl acetate/hexane (20/80) and solids are precipitated using dichloromethane/hexane to give 0.148 g (56%) of the title compound, MS (ESI+) for $C_{23}H_{15}ClN_2OS$ m/z 425.2 (M+Na), IR (drift) 1581, 1460, 1439,
20 1332, 1279, 1232, 1221, 1155, 1148, 1115, 1079, 833, 780, 752, 717 cm^{-1} . ^1H NMR ($CDCl_3$) δ 5.10, 5.70, 6.72, 6.80, 7.12, 7.28-7.47, 7.80, 7.87, 8.36. Anal. Calcd for $C_{23}H_{15}ClN_2OS$: C, 68.57; H, 3.75; N, 6.95. Found: C, 68.87; H, 4.22; N, 6.56.

Example 50 2-({9-[(5-Chloro-1-benzothiophen-3-yl)methyl]-9H-carbazol-4-yl}oxy)ethylamine, methane sulfonate salt
25



A mixture of 2-({9-[(5-chloro-1-benzothiophen-3-yl)methyl]-9H-carbazol-4-yl}oxy)acetonitrile (0.0915 g, 0.23 mmol), dry THF (2 mL) and borane-methyl sulfide (0.07
- 65 -

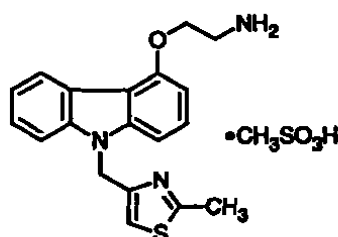
mL 0.77 mmol) is stirred at 83 °C for 1.5 h. The mixture is then cooled the excess borane is cautiously quenched with methanol and the mixture is concentrated under reduced pressure. Twice more methanol and dichloromethane are added to the residue and the solution is again concentrated under reduced pressure. The solids are slurried in
 5 methanol/dichloromethane and conc. HCl (approx 1.5 mL) is added and the mixture is heated at 64 °C for 40 min. After cooling, the mixture is concentrated to dryness under reduced pressure and the residue is partitioned between dichloromethane and aq. sodium bicarbonate. The combined organic layers are dried over sodium sulfate and concentrated to dryness. The residue is chromatographed on silica gel (50 mL) using
 10 methanol/dichloromethane (2/98 and 4/96 and 6/94) to give the desired free base. The methane sulfonate salt is formed by dissolving the free base (0.0547 g, 0.13 mmol) in dichloromethane/methanol and adding methanesulfonic acid (0.0013 g, 0.14 mmol) to the solution. Solids crystallized and are collected, washed with dichloromethane and vacuum dried at room temperature to give 0.0481 g (42%) of the title compound, mp >256 °C, MS
 15 (ESI+) for $C_{23}H_{19}ClN_2OS$ m/z 407.2 (M+H)⁺ IR (drift) 1585, 1457, 1328, 1269, 1240, 1221, 1197, 1180, 1165, 1149, 1044, 783, 772, 750, 717 cm^{-1} . ¹H NMR (CD₃OD) δ 2.71, 3.61, 4.55, 5.82, 6.85, 7.00, 7.20-7.53, 7.86, 8.43.
 Anal. Calcd for $C_{23}H_{19}ClN_2OS \cdot CH_4O_3S$ C, 57.30; H, 4.61; N, 5.57. Found C, 56.90; H, 4.68; N, 5.49.

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Preparation 44 2-({9-[(2-methyl-1,3-thiazol-4-yl)methyl]-9H-carbazol-4-yl}oxy)acetonitrile

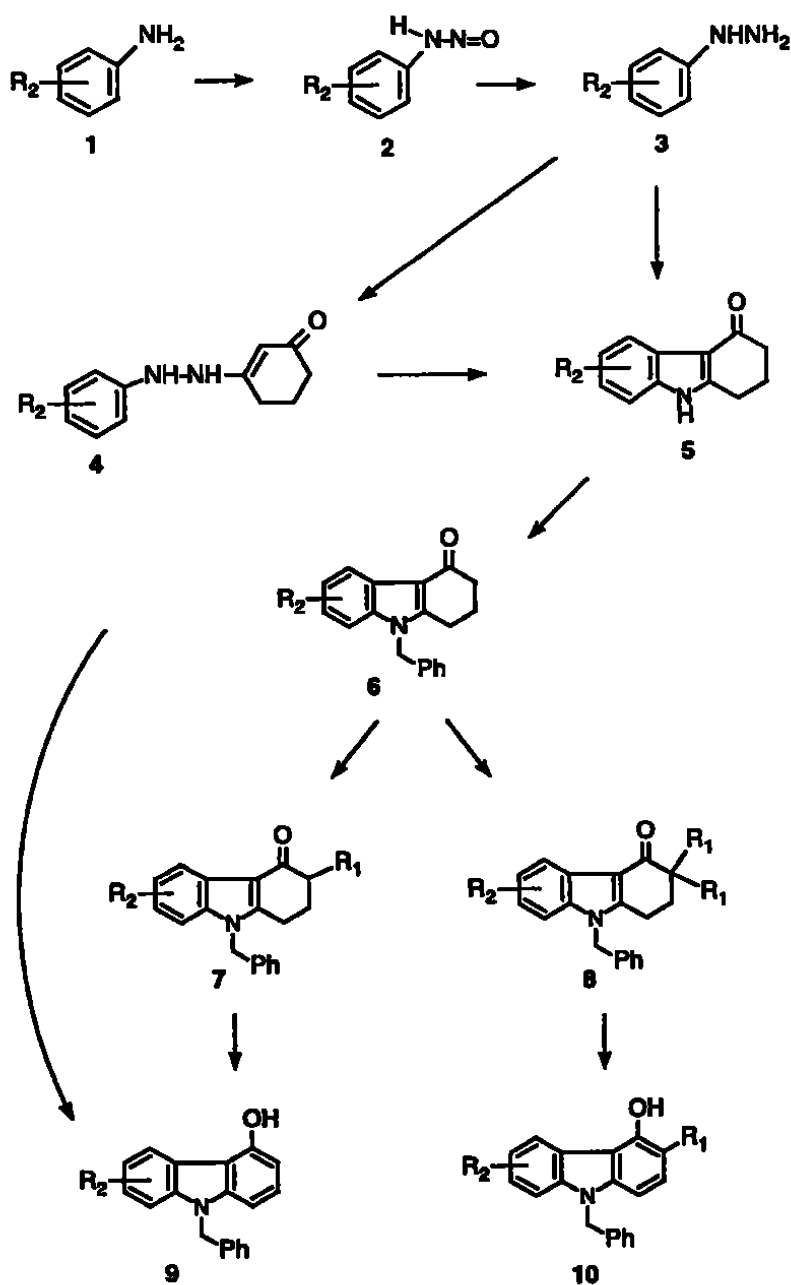
2-(9H-Carbazol-4-yloxy)acetonitrile (0.143 g, 0.64 mmol) is added to a slurry of pentane-washed NaH (0.0825 g, 0.0021 mol) in DMF (1 mL) and allowed to stir for 20 min
 25 at room temperature. 4-Chloromethyl-2-methylthiazole hydrochloride (0.163 g, 0.89 mmol) is added and after stirring for 2 h the mixture is partitioned between ethyl acetate and water. The combined organic layers are dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (75 mL) using ethyl acetate/hexane (20/80 and 40/60) and solids are crystallized from dichloromethane/ether to give 0.162 g (76%) of the
 30 title compound, MS (ESI+) for $C_{19}H_{15}N_3OS$ m/z 334.2 (M+H)⁺ IR (drift) 1581, 1459, 1440, 1341, 1333, 1275, 1228, 1215, 1182, 1157, 1151, 1113, 782, 754, 718 cm^{-1} , ¹H NMR (CDCl₃) δ 2.74, 5.09, 5.62, 6.38, 6.78, 7.19, 7.31, 7.44, 8.32. Anal. Calcd for $C_{19}H_{15}N_3OS$ C, 68.45; H, 4.53; N, 12.60. Found C, 68.27; H, 4.53; N, 12.33.

Example 51 2-((9-[(2-Methyl-1,3-thiazol-4-yl)methyl]-9H-carbazol-4-yl)oxy)ethylamine, methane sulfonate salt



A mixture of 2-((9-[(2-methyl-1,3-thiazol-4-yl)methyl]-9H-carbazol-4-yl)oxy)acetonitrile (0.1229 g, 0.37 mmol), dry THF (3 mL) and borane-methyl sulfide (0.11 mL, 0.0012 mol) is stirred at 83 °C for 3 h. The mixture is then cooled, the excess borane is cautiously quenched with methanol and the mixture is concentrated under reduced pressure. Methanol and dichloromethane are added to the residue and the solution is again concentrated under reduced pressure (repeated twice). The solids are heated at 60 °C in methanol/dichloromethane and conc. HCl (2 mL) for 1 h. After cooling, the mixture is concentrated to dryness under reduced pressure and partitioned between dichloromethane and aq. sodium bicarbonate. The combined organic layers are dried over sodium sulfate and concentrated to dryness. The oil is chromatographed on silica gel (30 mL) using methanol/dichloromethane (2/98 and 4/96) to give 0.0754 g (61%) of the desired free base. The methane sulfonate salt is formed by dissolving the free base (0.0696 g, 0.21 mmol) in dichloromethane and adding methanesulfonic acid (0.0201 g, 0.21 mmol) to the solution. The solution is concentrated and the solids are recrystallized from ethyl acetate/dichloromethane/methanol to give 0.0400 g (45%) of the title compound. mp 228.5–229.0 °C, MS (ESI+) for $C_{19}H_{19}N_3OS$ m/z 338.2 ($M+H$)⁺, IR (drift) 1458, 1343, 1335, 1269, 1239, 1223, 1182, 1165, 1155, 1119, 1043, 782, 770, 751, 713 cm^{-1} . ¹H NMR (CD_3OD) δ 2.65, 2.69, 3.58, 4.52, 5.60, 6.75, 6.81, 7.23, 7.39, 7.51, 8.38. Anal. Calcd for $C_{19}H_{19}N_3OS \cdot CH_4O_3S$: C, 55.41; H, 5.35; N, 9.69. Found: C, 55.08; H, 5.39; N, 9.54.

CHART A



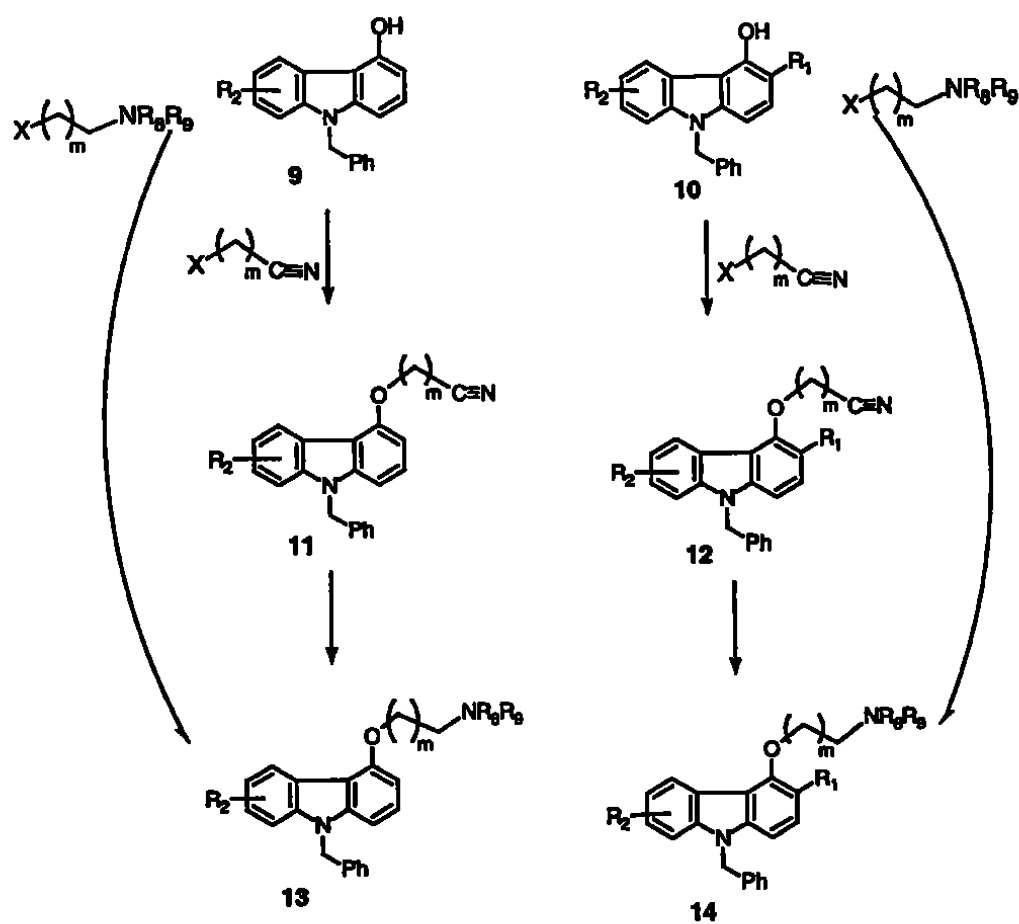
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CHART B

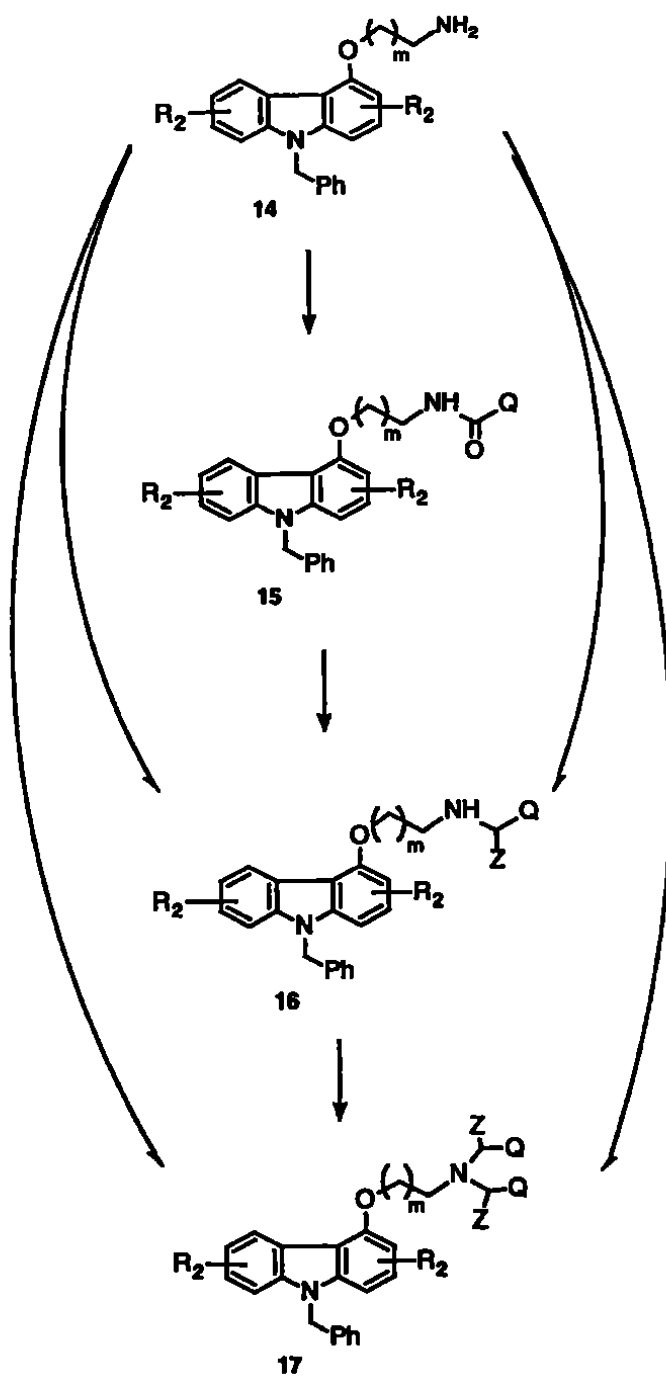


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CHART C

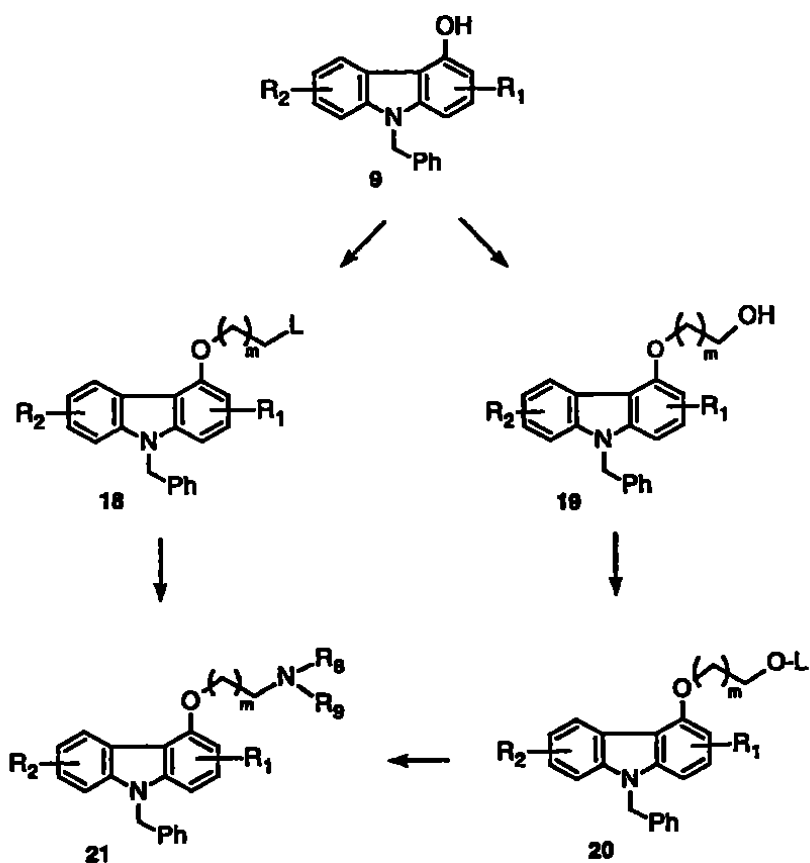


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CHART D

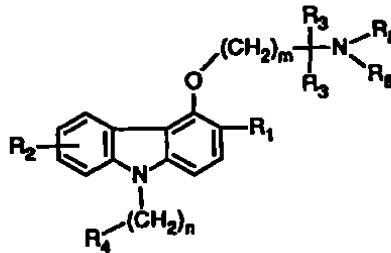


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CLAIMS

What is claimed is

1 A compound of formula I



I

wherein

R₁ is

- (a) H,
- (b) halo, or
- (c) C₁₋₆ alkyl,

R₂ is

- (a) H
- (b) halo,
- (c) -OH,
- (d) -CN
- (e) -CF₃
- (f) -O(C₁₋₆)alkyl,
- (g) C₁₋₆ alkyl,
- (h) C₃₋₆ cycloalkyl,
- (i) -NR₅R₆,
- (j) -CONR₅R₆,
- (k) -SO₂NR₅R₆,
- (l) -COOR₇,
- (m) -OCF₃, or
- (n) phenyl, optionally substituted with halo, OH, O(C₁₋₄) alkyl, or C₁₋₆ alkyl,

each R₃ is independently

- (a) H
- (b) C₁₋₆ alkyl, or
- (c) C₃₋₆ cycloalkyl

R₄ is

- (a) aryl, or
- (b) heteroaryl,

5 R₅ and R₆ are independently

- (a) H
- (b) C₁₋₆ alkyl or
- (c) C₃₋₆ cycloalkyl,

R₇ is

- 10 (a) H,**
- (b) C₁₋₆ alkyl, or**
- (c) (C₁₋₃ alkyl)-phenyl wherein phenyl may be substituted with R₃,**

R₈ and R₉ are independently

- (a) H,**
- 15 (b) C₁₋₆ alkyl, optionally substituted with aryl, heteroaryl, or C₃₋₆ cycloalkyl**
- (c) C₂₋₆ alkene,**
- (d) C₃₋₆ cycloalkyl,**
- (e) C₂₋₆ alkyl substituted with R₁₀,**
- (f) -CHO, provided that only one of the R₈ and R₉ is CHO, the other one is H,**
- 20 (g) aryl,**
- (h) heterocyclic, wherein heterocyclic is bonded via carbon atom to the nitrogen to which it is attached, or**
- (i) R₈ and R₉ taken together with the nitrogen to which they are attached form a heterocyclic ring wherein the heterocyclic ring may have one to two additional heteroatoms**
- 25 selected from the group consisting of oxygen, sulfur and N(Y) and wherein the carbon atoms of the heterocyclic ring is optionally substituted with one or two R₁₄,**

R₁₀ is

- (a) -OH,**
- (b) -O(C₁₋₄ alkyl), optionally alkyl is substituted with OH,**
- 30 (c) -O(C₁₋₄ alkyl)-NR₁₁R₁₂,**
- (d) heterocyclic, or**
- (e) -CO₂R₅,**

R₁₁ and R₁₂ are independently,

- Y 15

- 20 (e) -OH,

R₁₃ is

- (1) $-\text{OCF}_3$, or

R₁₄ IS

- 5

10 n is 1 2 3, or 4

15

- 20

3 A compound of claim 1 wherein R₁ is H, CH₃, fluoro or chloro

25

30

7 A compound of claim 1 wherein R₂ is H.

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- 8 A compound of claim 1 wherein R₂ chloro or fluoro
- 9 A compound of claim 1 wherein R₂ is methyl
- 5 10 A compound of claim 1 wherein m is 2
- 11 A compound of claim 1 wherein R₄ aryl or heteroaryl,
- 10 12 A compound of claim 1 wherein R₄ is phenyl
- 13 A compound of claim 1 wherein R₄ is phenyl substituted with fluoro or chloro
- 14 A compound of claim 1 wherein R₄ is pyridyl, thiophene, benzothiophene,
- 15 benzofuran, benzimidazole, imidazole or thiazole
- 15 A compound of claim 1 wherein R₄ is 2-methyl-1,3-thiazol-4-yl or 5-chloro-1-benzothiophn-3-yl
- 20 16 A compound of claim 1 wherein each R₃ is independently H, C₁₋₆ alkyl or C₃₋₆ cycloalkyl
- 17 A compound of claim 1 wherein each R₃ is independently H
- 25 18 A compound of claim 1 wherein R₈ and R₉ are independently
 - (a) H,
 - (b) C₁₋₆ alkyl, optionally substituted with aryl, hetroaryl, or C₃₋₆ cycloalkyl,
 - (c) C₂₋₆ alkene,
 - (d) C₃₋₆ cycloalkyl,
 - 30 (e) C₂₋₆ alkyl substituted with R₁₀,
 - (f) -CHO,
 - (g) aryl,

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- (h) heterocyclic, wherein heterocyclic is bonded via carbon atom to the nitrogen to which it is attached, or
- (i) R_8 and R_9 taken together with the nitrogen to which they are attached form a heterocyclic ring wherein the heterocyclic ring may have one to two additional heteroatoms selected from the group consisting of oxygen sulfur and N(Y) and wherein the carbon atoms of the heterocyclic ring is optionally substituted with one or two R_{14} , wherein R_{10} and Y are the same as defined in claim 1

- 19 A compound of claim 1 wherein R_8 is H, R_9 is H
- 20 A compound of claim 1 wherein R_8 is H, R_9 is C_{1-6} alkyl, C_{2-4} alkene, or $-CHO$
- 21 A compound of claim 1 wherein R_8 is H, R_9 is methyl
22. A compound of claim 1 wherein R_8 is H, R_9 is C_{1-6} alkyl substituted with C_{3-6} cycloalkyl, wherein cycloalkyl is optionally substituted with $-OH$, C_{1-4} alkyl or oxo
- 23 A compound of claim 22 wherein cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl
- 24 A compound of claim 1 wherein R_8 is H, R_9 is C_{2-6} alkyl substituted with $-OH$, $-O(C_{1-4}$ alkyl), $-O(C_{1-4}$ alkyl- $-OH$), or $-CO_2C_{1-4}$ alkyl,
- 25 A compound of claim 1 wherein R_8 is H, R_9 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, optionally substituted with $-OH$, C_{1-4} alkyl or oxo
- 26 A compound of claim 1 wherein R_8 is H, R_9 is C_{1-6} alkyl substituted with
- (a) phenyl, optionally substituted with fluoro or chloro,
 - (b) pyridyl, thiophene, benzothiophene, benzofuran, benzimidazole, imidazole or thiazole, or
 - (c) heterocyclic, which is bonded via carbon atom to the nitrogen to which it is attached.

- 27 A compound of claim 21 wherein R_8 is H, R_9 is C_{1-4} alkyl substituted with fluorophenyl chlorophenyl, pyridyl benzimidazole or 1-benzyl-piperidinyl
- 28 A compound of claim 1 wherein R_8 is H, R_9 is C_{2-6} alkyl substituted with
 5 azetidyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1-benzyl-piperidinyl 1-methyl-piperidinyl, dioxolane, imidazolidine, oxazolidinyl, oxathiolane, 4-hydroxyl-1-piperidinyl, 4-ethanol-1-piperazinyl-, 4-ethylformamide-1-piperazinyl-, or 4-methyl-1-piperazinyl
- 10 29 A compound of claim 1 wherein R_8 and R_9 taken together with the nitrogen to which they are attached form a heterocyclic ring wherein the heterocyclic ring may have one to two additional heteroatoms selected from the group consisting of oxygen, sulfur and N(Y) wherein Y is the same as defined in claim 1
- 15 30 A compound of claim 1 wherein R_8 and R_9 taken together with the nitrogen to which they are attached form 4-morpholinyl, 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl 4-hydroxyl-1-piperidinyl, 4-ethanol-1-piperazinyl-, 4-ethylformamide-1-piperazinyl- or 4-methyl-1-piperazinyl
- 20 31 A compound of claim 1 wherein R_8 and R_9 are independently H methyl ethyl, propyl, 1-propanol, 2-propen, 1-pentanol, 2-methyl-1-propanol, 2-butanol, 1-ethanol ethoxyl-1-ethanol, $-CH_2CH_2CO_2$ ethyl, 2-methoxyethyl, 4-chlorophenethyl, or 4-fluorophenethyl
- 25 32 A compound of claim 1 wherein R_8 and R_9 taken together with the nitrogen to which they are attached form 4-methyl-1-piperazinyl
- 33 A compound of claim 1 which is
 30 a) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine,
 b) N-{2-[(9-benzyl-8-chloro-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine
 c) N-(2-{[8-chloro-9-(4-fluorobenzyl)-9H-carbazol-4-yl]oxy}ethyl)-N,N-diethylamine,
 d) N-{2-[(9-benzyl-8-methyl-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine,

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- e) N,N-diethyl-N-(2-([9-(4-fluorobenzyl)-8-methyl-9H-carbazol-4-yl]oxy)ethyl)amine,
- f) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-(2-pyridinylmethyl)amine,
- g) N-{2-[(9-benzyl-8-fluoro-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine,
- 5 h) 9-benzyl-4-[2-(4-morpholinyl)ethoxy]-9H-carbazole,
- i) 2-(4-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-1-piperazinyl)-1-ethanol,
- j) 3-((2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)amino)-1-propanol,
- k) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-2-propen-1-amine
- l) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-3-(4-morpholinyl)-1-propanamine
- 10 m) 5-((2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)amino)-1-pentanol,
- n) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-1-propanamine,
- o) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-propyl-1-propanamine,
- p) 1-benzyl-N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-4-piperidinamine,
- q) 2-((2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)amino)-2-methyl-1-propanol,
- 15 r) 2-[(9-benzyl-9H-carbazol-4-yl)oxy]-N-(4-chlorophenethyl)-1-ethanamine,
- s) 2-[(9-benzyl-9H-carbazol-4-yl)oxy]-N-(cyclohexylmethyl)-1-ethanamine,
- t) 2-[(9-benzyl-9H-carbazol-4-yl)oxy]-N-[2-(4-morpholinyl)ethyl]-1-ethanamine,
- u) 1-((2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)amino)-2-butanol,
- v) 2-[(9-benzyl-9H-carbazol-4-yl)oxy]-N-(4-fluorophenethyl)-1-ethanamine,
- 20 w) 2-[2-((2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)amino)ethoxy]-1-ethanol,
- x) (1S,2S)-2-((2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)amino)cyclohexanol,
- y) ethyl 3-((2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)amino)propanoate,
- z) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}cyclobutanamine,
- aa) 2-(4-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-1-piperazinyl) ethylformamide,
- 25 bb) N-(1H-benzimidazol-2-ylmethyl)-2-[(9-benzyl-9H-carbazol-4-yl)oxy]-1-ethanamine,
- cc) 1-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-4-piperidinol,
- dd) 9-benzyl-4-[2-(4-methyl-1-piperazinyl)ethoxy]-9H-carbazole,
- ee) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-cyclopropylamine,
- 30 ff) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N,N-dimethylamine
- gg) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}formamide
- hh) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-methylamine, or its maleic acid salt,
- ii) 2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethylamine,

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- jj) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-(2-methoxyethyl)amine,
kk) N-ethyl-N-[[[(1-phenyl-1,2-dihydro[1,4]oxazino[2,3,4-jk]carbazol-7-yl)oxy]ethyl]amine or its maleic acid salt,
ll) 9-benzyl-4-[2-(1-pyrrolidinyl)ethoxy]-9H-carbazole
5 mm) 9-benzyl-4-[2-(1-piperidinyl)ethoxy]-9H-carbazole,
nn) 9-benzyl-4-[2-(1-piperazinyl)ethoxy]-9H-carbazole,
oo) 2-[(9-benzyl-8-fluoro-9H-carbazol-4-yl)oxy]ethylamine,
pp) N,N-diethyl-N-(2-[[8-fluoro-9-(4-fluorobenzyl)-9H-carbazol-4-yl]oxy]ethyl)amine,
qq) N-{2-[(9-benzyl-6-chloro-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine,
10 rr) N-{2-[(9-benzyl-6-fluoro-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine,
ss) N-{2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine,
tt) 2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethylamine,
uu) N-{2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethyl}-N-methylamine,
vv) N,N-diethyl-N-(2-[[9-(4-fluorobenzyl)-6-methyl-9H-carbazol-4-yl]oxy]ethyl)amine,
15 ww) 2-((2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)amino)-1-ethanol or its maleic acid salt,
xx) 2-((9-[(5-Chloro-1-benzothiophen-3-yl)methyl]-9H-carbazol-4-yl)oxy)ethylamine or its methane sulfonate salt, or
20 yy) 2-((9-[(2-Methyl-1,3-thiazol-4-yl)methyl]-9H-carbazol-4-yl)oxy)ethylamine or its methane sulfonate salt.
- 34 A compound of claim 1 which is
25 a) 2-[(9-benzyl-8-fluoro-9H-carbazol-4-yl)oxy]ethylamine, or
b) 2-[(9-benzyl-8-fluoro-9H-carbazol-4-yl)oxy]ethylamine.
- 35 A compound of claim 1 which is
a) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-methylamine or its maleic acid salt,
30 b) 9-benzyl-4-[2-(4-methyl-1-piperazinyl)ethoxy]-9H-carbazole, or
c) N-{2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethyl}-N-methylamine.

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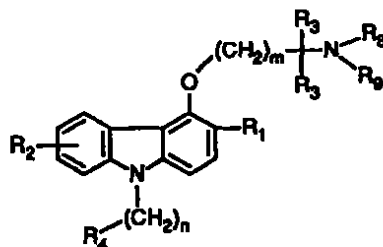
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ABSTRACT

The present invention provides aminoalkoxy carbazole derivatives and more specifically provides compounds of formula (I)



5

I

wherein R_1 , R_2 , R_3 , R_4 , R_8 and R_9 are described herein. These compounds are 5-HT ligands, and are useful for treating diseases wherein modulation of 5-HT activity is desired.

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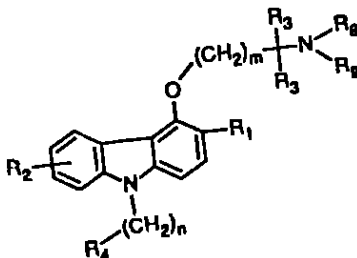
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REIVINDICACIONES

1 Un compuesto de la formula



I

donde

R₁ es

- (a) H,
- (b) halo, o —
- (c) alquilo C₁₋₆, (

R₂ es

- (a) H,
- (b) halo,
- (c) -OH,
- (d) -CN,
- (e) -CF₃,
- (f) -O(C₁₋₆)alquilo,
- (g) alquilo C₁₋₆,
- (h) cicloalquilo C₃₋₆,
- (i) -NR₅R₆,
- (j) -CONR₅R₆,
- (k) -SO₂NR₅R₆,
- (l) -COOR₇,
- (m) fenilo, sustituido opcionalmente por halo, OH,

alquilo O(C₁₋₄), o alquilo C₁₋₆,

donde cada R₃ es independientemente

- (a) H,
- (b) alquilo C₁₋₆, o
- (c) cicloalquilo C₃₋₆,

R₄ es

- (a) arilo, o
- (b) heteroarilo,

R₅ y R₆ son independientemente

- (a) H,
- (b) alquilo C₁₋₆, o
- (c) cicloalquilo C₃₋₆,

R₇ es

- (a) H,
- (b) alquilo C₁₋₆, o
- (c) fenilo-(alquilo C₁₋₃) donde el fenilo puede sustituirse por R₃,

R₈ y R₉ son independientemente

- (a) H,
- (b) alquilo C₁₋₆, sustituido opcionalmente por arilo, heteroarilo, o cicloalquilo C₃₋₆,
- (c) alqueno C₂₋₆,
- (d) cicloalquilo C₃₋₆,
- (e) alquilo C₂₋₆ sustituido por R₁₀,
- (f) -CHO, con la condición de que tan solo uno de los R₈

y R_9 sea CHO, y el otro sea H,

- (g) arilo,
- (h) heterocíclico, donde el heterocíclico se enlaza por medio del átomo de carbono al nitrógeno al cual se encuentra adherido, o

(1) R_8 y R_9 tomados conjuntamente con el nitrógeno al cual se adhieren forman un anillo heterocíclico donde el anillo heterocíclico puede tener de uno a dos heteroátomos adicionales que se seleccionan a partir del grupo conformado por oxígeno, azufre y N(Y) y donde los átomos de carbono del anillo heterocíclico se sustituyen opcionalmente por uno o dos R_{14} ,

R_{10} es

- (a) -OH,
- (b) -O(alquilo C_{1-4}), alquilo opcionalmente sustituido por OH,
- (c) -O(alquilo C_{1-4})- $NR_{11}R_{12}$,
- (d) heterocíclico, o
- (e) -CO₂ R_3 ,

R_{11} y R_{12} son independientemente,

- (c) H, o
- (d) alquilo C_{1-4} ,

arilo es fenilo o naftilo, sustituido opcionalmente por uno o más R_{13} ,

heteroarilo es un radical de un anillo aromático monocíclico de cinco o seis miembros que tiene uno o dos heteroátomos y cada uno se selecciona a partir del grupo conformado por oxígeno, azufre, y N(X), o un radical de un anillo aromático bicíclico

orto-fusionado de nueve o diez miembros que tiene uno, dos o tres heteroátomos, donde cada uno se selecciona a partir del grupo conformado por oxígeno, azufre, y N(X),

donde los átomos de carbono del heteroarilo pueden estar sustituidos por R₁₃,

el heterocíclico es un radical de un anillo heterocíclico parcialmente saturado o insaturado de cinco, seis o siete miembros que tiene uno, dos o tres heteroátomos que se selecciona a partir del grupo conformado por oxígeno, azufre y N(Y) donde los átomos de carbono del anillo heterocíclico pueden sustituirse por R₁₄,

X está ausente, H o alquilo C₁₋₄,

Y es

- (a) H,
- (b) alquilo C₁₋₆, sustituido opcionalmente por arilo o heteroarilo,
- (c) cicloalquilo C₃₋₆, o
- (d) alquilo C₂₋₆ sustituido por -OH, -O(alquilo C₁₋₄), -O(alquilo C₁₋₄)-NR₁₁R₁₂, -CO₂R₅, o NHCHO, o
- (e) -OH,

R₁₃ es

- (a) halo,
- (b) -OH,
- (c) -CN,
- (d) -CF₃,
- (e) -O(C₁₋₆)alquilo,
- (f) alquilo C₁₋₆,
- (g) cicloalquilo C₃₋₆,

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- (h) $-NR_5R_6$,
- (i) $-CONR_5R_6$,
- (j) $-SO_2NR_5R_6$,
- (k) $-COOR_7$,
- (l) $-OCF_3$, o
- (m) fenilo, sustituido opcionalmente por halo, OH, O(C₁₋₄)alquilo, o alquilo C₁₋₆,

R₁₄ es

- (a) alquilo C₁₋₆,
- (b) cicloalquilo C₃₋₆,
- (c) alquilo C₂₋₆ sustituido por -OH, -O(alquilo C₁₋₄), -O(alquilo C₁₋₄)-NR₁₁R₁₂, o -CO₂R₅,
- (d) -OH, o
- (e) oxo (=O),

m es 1, 2, 3 o 4,

n es 1, 2, 3 o 4,

Cicloalquilo C₃₋₆ en cada una de las definiciones dadas anteriormente, pueden sustituirse cada uno y en forma independiente por OH, alquilo C₁₋₄, u oxo (=O), con las siguientes condiciones

- (a) cuando R₄ es arilo sustituido por fluoro, R₂ no puede ser fluoro ni cloro en la posición C-6 de la formula I,
 - (b) cuando R₄ es 4-tiazolilo, no se puede sustituir por 4-clorofenilo,
- o una sal farmacéuticamente aceptable, racemate, solvato, tautomero, isomero óptico o sus derivados de precursores de drogas,

(c) cuando R₄ es heteroarilo, heteroarilo no es 4-piridilo

2 Un compuesto de la reivindicación 1 donde R₁ es H, halo, o alquilo C₁₋₆

3 Un compuesto de la reivindicación 1 donde R₁ es H, CH₃, fluoro o cloro

4 Un compuesto de la reivindicación 1 donde R₁ es H

5 Un compuesto de la reivindicación 1 donde R₂ es H, halo, -OH, -CN, -CF₃, -O(C₁₋₆)alquilo, alquilo C₁₋₆, cicloalquilo C₃₋₆, -NR₅R₆, -CONR₅R₆, -SO₂NR₅R₆, -COOR₇, o fenilo, sustituido opcionalmente por halo, OH, O(C₁₋₄)alquilo, o alquilo C₁₋₆, donde R₅, R₆ y R₇ corresponden a la definición dada en la reivindicación 1

6 Un compuesto de la reivindicación 1 donde R₂ es H, halo, o alquilo C₁₋₆

7 Un compuesto de la reivindicación 1 donde R₂ es H

8 Un compuesto de la reivindicación 1 donde R₂ es cloro o fluoro

9 Un compuesto de la reivindicación 1 donde R₂ es metilo

10 Un compuesto de la reivindicación 1 donde m es 1

11 Un compuesto de la reivindicación 1 donde R_4 es arilo o heteroarilo

12 Un compuesto de la reivindicación 1 donde R_4 es fenilo

13 Un compuesto de la reivindicación 1 donde R_4 es fenilo sustituido por fluoro o cloro

14 Un compuesto de la reivindicación 1 donde R_4 es piridilo, tiofeno, benzotiofeno, benzofurano, benzimidazola, imidazola o tiazola

15 Un compuesto de la reivindicación 1 donde R_4 es metilo-1,3-tiazol-4-ilo o 5-cloro-1-benzotiofeno-3-ilo

16 Un compuesto de la reivindicación 1 donde cada R_3 es independientemente H, alquilo C_{1-6} , o cicloalquilo C_{3-6}

17 Un compuesto de la reivindicación 1 donde cada R_3 es independientemente H

18 Un compuesto de la reivindicación 1 donde R_8 y R_9 son independientemente

- (a) H,
- (b) alquilo C_{1-6} , sustituido opcionalmente por arilo, heteroarilo, o cicloalquilo C_{3-6} ,
- (c) alqueno C_{2-6} ,
- (d) cicloalquilo C_{3-6} ,

- (e) alquilo C₂₋₆ sustituido por R₁₀,
- (f) -CHO,
- (g) anillo,
- (h) heterocíclico, donde el heterocíclico se enlaza vía átomo de carbono con el nitrógeno al cual se adhiere, o

(1) R₈ y R₉ tomados conjuntamente con el nitrógeno al cual se adhieren forman un anillo heterocíclico donde dicho anillo heterocíclico puede tener de uno a dos heteroátomos adicionales que se seleccionan a partir del grupo conformado por oxígeno, azufre y N(Y) y donde los átomos de carbono del anillo heterocíclico se sustituyen opcionalmente por uno o dos R₁₄, donde R₁₀ y Y son iguales a la definición dada en la reivindicación 1

19 Un compuesto de la reivindicación 1 donde R₈ es H, R₉ es H

20 Un compuesto de la reivindicación 1 donde R₈ es H, R₉ es alquilo C₁₋₆, alqueno C₂₋₄, o -CHO

21 Un compuesto de la reivindicación 1 donde R₈ es H, R₉ es metilo

22 Un compuesto de la reivindicación 1 donde R₈ es H, R₉ es alquilo C₁₋₆ sustituido por cicloalquilo C₃₋₆, donde el cicloalquilo es sustituido opcionalmente por -OH, alquilo C₁₋₄, u oxo

23 Un compuesto de la reivindicación 22 donde el cicloalquilo es ciclopropilo, ciclobutilo, ciclopentilo, o ciclohexilo

24 Un compuesto de la reivindicación 1 donde R_3 es H, R_3 es alquilo C_{2-6} sustituido por -OH, -O(alquilo C_{1-4}), -O(alquilo C_{1-4} -OH), o -CO₂alquilo C_{1-4}

25 Un compuesto de la reivindicación 1 donde R_3 es H, R_3 es ciclopropilo, ciclobutilo, ciclopentilo, o ciclohexilo, sustituido opcionalmente por -OH, alquilo C_{1-4} u oxo

26 Un compuesto de la reivindicación 1 donde R_3 es H, R_3 es alquilo C_{1-6} sustituido por

- (a) fenilo, sustituido opcionalmente por fluoro o cloro,
- (b) piridilo, tiofeno, benzotiofeno, benzofurano, benzimidazola, imidazola o tiazola, o
- (c) heterocíclico, que se enlaza por medio del átomo de carbono al nitrógeno al que se le adhiere

27 Un compuesto de la reivindicación 21 donde R_3 es H, R_3 es alquilo C_{1-4} sustituido por fluorofenilo, clorofenilo, piridilo, benzimidazola, o 1-benzil-piperidinilo

28 Un compuesto de la reivindicación 1 donde R_3 es H, R_3 es alquilo C_{2-6} sustituido por acetidilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, 1-benzil-piperidinilo, 1-metil-piperidinilo, dioxolano, imidazolidina, oxazolidinilo, oxatolano, 4-hidroxi-1-piperidinilo, 4-etanol-1-piperazinilo-, 4-etilformamida-1-

piperazinilo-, o 4-metil-1-piperazinilo

29 Un compuesto de la reivindicación 1 donde R₈ y R₉ tomados conjuntamente con el nitrógeno al que se le adhieren forman un anillo heterocíclico, donde dicho anillo heterocíclico puede tener de uno a dos heteroátomos adicionales que se seleccionan a partir del grupo conformado por oxígeno, azufre y N(Y), donde Y corresponde a la definición dada en la reivindicación 1

30 Un compuesto de la reivindicación 1 donde R₈ y R₉ tomados conjuntamente con el nitrógeno al que se le adhieren forman 4-morfolinilo, 1-pirrolidinilo, 1-piperidinilo, 1-piperazinilo, 4-hidroxil-1-piperidinilo, 4-etanol-1-piperazinilo-, 4-etilformamida-1-piperazinilo-, o 4-metil-1-piperazinilo

31 Un compuesto de la reivindicación 1 donde R₈ y R₉ son independientemente H, metilo, etilo, propilo, 1-propanol, 2-propen, 1-pentanol, 2-metil-1-propanol, 2-butanol, 1-etanol, etoxi-1-etanol, -CH₂CH₂CO₂etilo, 2-metoxietilo, 4-clorofenetilo, o 4-fluorofenetilo

32 Un compuesto de la reivindicación 1 donde R₈ y R₉ tomados conjuntamente con el nitrógeno al que se le adhieren forman el 4-metil-1-piperazinilo

33 Un compuesto de la reivindicación que es

a) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-N,N-dietilamina,

- b) N-{2-[(9-benzil-8-cloro-9H-carbazol-4-il)oxi]etil}-N,N-dietilamina,
- c) N-(2-{[8-cloro-9-(4-fluorobenzil)-9H-carbazol-4-il]oxi}etil)-N,N-dietilamina,
- d) N-{2-[(9-benzil-8-metil-9H-carbazol-4-il)oxi]etil}-N,N-dietilamina,
- e) N,N-dietil-N-{2-[(9-(4-fluorobenzil)-8-metil-9H-carbazol-4-il)oxi]etil)amina,
- f) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-N-(2-piridinilmetil)amina,
- g) N-{2-[(9-benzil-8-fluoro-9H-carbazol-4-il)oxi]etil}-N,N-dietilamina,
- h) 9-benzil-4-[2-(4-morfolinil)etoxi]-9H-carbazola,
- i) 2-(4-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-1-piperazinil)-1-etanol,
- j) 3-({2-[(9-benzil-9H-carbazol-4-il)oxi]etil)amino)-1-propanol,
- k) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-2-propen-1-amina,
- l) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-3-(4-morfolinil)-1-propanamina,
- m) 5-({2-[(9-benzil-9H-carbazol-4-il)oxi]etil)amino)-1-pentanol,
- n) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-1-propanamina,
- o) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-N-propil-1-propanamina,
- p) 1-benzil-N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-4-piperidinamina,
- q) 2-({2-[(9-benzil-9H-carbazol-4-il)oxi]etil)amino)-2-metil-1-propanol,

- r) 2-[(9-benzil-9H-carbazol-4-il)oxi]-N-(4-clorofenetil)-1-etanamina,
- s) 2-[(9-benzil-9H-carbazol-4-il)oxi]-N-(ciclohexilmetil)-1-etanamina,
- t) 2-[(9-benzil-9H-carbazol-4-il)oxi]-N-[2-(4-morfolinil)etil]-1-etanamina,
- u) 1-({2-[(9-benzil-9H-carbazol-4-il)oxi]etil}amino)-2-butanol,
- v) 2-[(9-benzil-9H-carbazol-4-il)oxi]-N-(4-fluorofenetil)-1-etanamina,
- w) 2-[2-({2-[(9-benzil-9H-carbazol-4-il)oxi]etil}amino)etoxi]-1-etanol,
- x) (1S,2S)-2-({2-[(9-benzil-9H-carbazol-4-il)oxi]etil}amino)ciclohexanol,
- y) etil 3-({2-[(9-benzil-9H-carbazol-4-il)oxi]etil}amino)propanoato,
- z) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}ciclobutanamina,
- aa) 2-{4-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-1-piperazinil}etilformamida,
- bb) N-(1H-benzimidazol-2-ilmetil)-2-[(9-benzil-9H-carbazol-4-il)oxi]-1-etanamina,
- cc) 1-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-4-piperidinol,
- dd) 9-benzil-4-[2-(4-metil-1-piperazinil)etoxi]-9H-carbazola,
- ee) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-N-ciclopropilamina,
- ff) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-N,N-dimetilamina,
- gg) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}formamida,

- hh) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-N-metilamina, o su sal de ácido maleico,
- ii) 2-[(9-benzil-9H-carbazol-4-il)oxi]etilamina,
- jj) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-N-(2-metoxietil)amina,
- kk) N-etil-N-[(1-fenil-1,2-dihidro[1,4]oxazino[2,3,4-jk]carbazol-7-il)oxi]etil)amina, o su sal de ácido maleico,
- ll) 9-benzil-4-[2-(1-pirrolidinil)etoxi]-9H-carbazola,
- mm) 9-benzil-4-[2-(1-piperidinil)etoxi]-9H-carbazola,
- nn) 9-benzil-4-[2-(1-piperazinil)etoxi]-9H-carbazola,
- oo) 2-[(9-benzil-fluoro-9H-carbazol-4-il)oxi]etilamina,
- pp) N,N-dietil-N-(2-[(8-fluoro-9-(4-fluorobenzil)-9H-carbazol-4-il)oxi]etil)amina,
- qq) N-{2-[(9-benzil-6-cloro-9H-carbazol-4-il)oxi]etil}-N,N-dietilamina,
- rr) N-{2-[(9-benzil-6-fluoro-9H-carbazol-4-il)oxi]etil}-N,N-dietilamina,
- ss) N-{2-[(9-benzil-6-metil-9H-carbazol-4-il)oxi]etil}-N,N-dietilamina,
- tt) 2-[(9-benzil-6-metil-9H-carbazol-4-il)oxi]etilamina,
- uu) N-{2-[(9-benzil-6-metil-9H-carbazol-4-il)oxi]etil}-N-metilamina,
- vv) N,N-dietil-N-{2-[(9-(4-fluorobenzil)-6-metil-9H-carbazol-4-il)oxi]etil)amina,
- ww) 2-[(2-[(9-benzil-9H-carbazol-4-il)oxi]etil)amino)-1-etanol o su sal de ácido maleico,
- xx) 2-[(9-[(5-Cloro-1-benzotiofen-3-il)metil]-9H-carbazol-4-il)oxi]etilamina o su sal de sulfonato de metano, o

- yy) 2-((9-[(2-Metil-1,3-tiazol-4-il)metil]-9H-carbazol-4-il)oxi)etilamina o su sal de sulfonato de metano
- zz) 2-[(9-benzil-cloro-9H-carbazol-4-il)oxi]etilamina, sal de metanosulfonato,
- aaa) 2-[[9-(3-bromobenzil)-9H-carbazol-4-il]oxi]etilamina, sal de ácido maleico,
- bbb) 2-[[9-(3-fluorobenzil)-9H-carbazol-4-il]oxi]etilamina, sal de ácido maleico,
- ccc) 2-[[9-(2-bromobenzil)-9H-carbazol-4-il]oxi]etilamina, sal de ácido maleico,
- ddd) 2-[[9-(4-metilbenzil)-9H-carbazol-4-il]oxi]etilamina, sal de ácido maleico,
- eee) 2-[[9-(2-Fluorobenzil)-9H-carbazol-4-il]oxi]etilamina, sal de ácido maleico,
- fff) 2-[[9-(3-metoxibenzil)-9H-carbazol-4-il]oxi]etilamina, sal de ácido maleico,
- ggg) 2-[[9-(3,5-dimetoxibenzil)-9H-carbazol-4-il]oxi]etilamina, sal de ácido maleico,
- hhh) 2-[[9-(4-bromobenzil)-9H-carbazol-4-il]oxi]etilamina, sal de ácido maleico,
- iii) 2-[[9-(3-metilbenzil)-9H-carbazol-4-il]oxi]etilamina, sal de ácido maleico,
- jjj) 2-[[9-(2-metilbenzil)-9H-carbazol-4-il]oxi]etilamina, sal de ácido maleico,
- kkk) 2-[(9-benzil-6-metoxi-9H-carbazol-4-il)oxi]etilamina, o
- lll) 2-[(9-benzil-7-metoxi-9H-carbazol-4-il)oxi]etilamina

34 Un compuesto de la reivindicación 1 que es

- a) 2-[(9-benzil-8-fluoro-9H-carbazol-4-il)oxi]etilamina, o

b) 2-[(9-benzil-8-fluoro-9H-carbazol-4-il)oxi]etilamina

35 Un compuesto de la reivindicación 1 el cual es

- a) N-{2-[(9-benzil-9H-carbazol-4-il)oxi]etil}-N-metilamina o su sal de ácido maleico,
- b) 9-benzil-4-[2-(4-metil-1-piperazinil)etoxi]-9H-carbazol, o
- c) N-{2-[(9-benzil-6-metil-9H-carbazol-4-il)oxi]etil}-N-metilamina

36 Un método para el tratamiento o prevención de psicosis, parafrenia, depresión psicótica, manía, esquizofrenia, trastornos esquizofreniformes, trastorno esquisoafectivo, trastorno ilusorio, trastorno de pánico, fobia, trastorno obsesivo compulsivo, síndrome de estres post-traumático, depresión de sistema inmune, problema inducido por estres con respecto del tracto urinario, enfermedad relacionada con el estres, ansiedad, cefalea por migraña, drogadicción, trastornos convulsivos, trastornos de personalidad, síndrome de estres post-traumático, alcoholismo, ataques de pánico, trastorno obsesivo compulsivo, trastornos del sueño, trastornos del sistema gastrointestinal o cardiovascular (por ejemplo incontinencia por estres), trastornos neurodegenerativos, autismo, vómito inducido por quimioterapia, hipertensión, cefalea en racimo, disfunción sexual en mamífero (por ejemplo humanos), trastorno aditivo y síndrome de abstinencia, trastorno de ajuste, trastorno de aprendizaje asociado con la edad y trastorno mental, anorexia nervosa, apatía, trastorno de déficit de atención debido a condiciones médicas generales, trastorno de hiperactividad con déficit de atención, perturbación conductual (incluyendo agitación en condiciones

asociadas con cognición disminuida (por ejemplo demencia, retardo mental o delirio)), trastorno bipolar, bulimia nervosa, síndrome de fatiga crónica, trastorno de conducta, trastorno ciclotímico, trastorno distímico, fibromialgia y otros trastornos somatoformes, trastorno de inhalación, trastorno de intoxicación, trastorno de la movilidad (por ejemplo enfermedad de Huntington o Disquinesia Tardía), trastorno oposicional desafiante, neuropatía periférica, trastorno de estrés post-traumático, trastorno disfórico premestruar, trastorno psicótico (trastorno de duración breve y prolongada, trastorno psicóticos debidos a condiciones médicas, trastorno psicótico NOS), trastorno afectivo (trastorno de depresión mayor o bipolar con características psicóticas), trastorno afectivo estacional, trastorno específico del desarrollo, trastorno de agitación, inhibición de recaptación de la serotonina selectiva (SSRI) síndrome de "poop out" o trastornos de Tic (por ejemplo síndrome de la Tourette), que comprende la administración a un mamífero que necesite de dicho tratamiento de una cantidad terapéuticamente eficaz de un compuesto de la fórmula (I) o de una de sus sales farmacéuticamente aceptables

37 Un método para el tratamiento de enfermedad o condición en un mamífero donde el receptor 5-HT está implicado y la modulación de la función 5-HT es deseable y comprende la administración de una cantidad terapéuticamente eficaz de un compuesto de uno de los productos descritos en la reivindicación 1 al mamífero

38 El método de la reivindicación 36 donde el receptor es receptor 5-HT₆

39 El método de la reivindicación 36 donde la enfermedad o condición es antiedad, depresión, esquisofrenia, enfermedad relacionada con el estrés, trastorno de pánico, fobia, trastorno obsesivo compulsivo, síndrome de estrés post-traumático, depresión del sistema inmune, psicosis, parafrenia, manía, trastornos convulsivos, desórdenes de la personalidad, cefalea de migraña, drogadicción, alcoholismo, obesidad, trastornos de la alimentación, o trastornos del sueño

40 El método de la reivindicación 36 donde la enfermedad o condición es síntoma psicótico, afectivo, vegetativo y psicomotor de esquisofrenia y efectos colaterales motores extrapiramidales de otros medicamentos antipsicóticos

41 El método de la reivindicación 36 donde la enfermedad es ansiedad, obesidad, depresión o enfermedad relacionada con el estrés

42 Un método para la modulación de la función del receptor 5-HT₁, que comprende la puesta en contacto del receptor con una cantidad inhibitoria eficaz de un compuesto de la reivindicación 1

43 El método de la reivindicación 42 donde el receptor es receptor 5-HT₁

La anterior es Traducción Oficial de un documento presentado originalmente en inglés Esta traducción fue realizada por **GABRIEL RUEDA CHADID (Traductor Oficial)** Resolución 5996 del Minjusticia, por lo cual estampo mi Sello y Firma

Santafé de Bogotá D C , Agosto 28 del 2000

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August 15, 2000

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APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A
FILING DATE UNDER 35 USC 111**

APPLICATION NUMBER 60/203,771

FILING DATE May 12, 2000



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

T. Lawrence

**T. LAWRENCE
Certifying Officer**

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PROVISIONAL APPLICATION COVER SHEET

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CERTIFICATE OF MAILING (37 CFR 1.10)

"Express Mail" No: EM177639676 US Date of Deposit: May 12, 2000

I hereby certify that this transmittal together with the patent application referred to below is being deposited with the United States Postal Service Express Mail Post Office to Addressee service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, DC 20231

Julia K. Lyons, Legal Assistant
Name of Person Mailing Paper Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner of Patents and Trademarks
Washington, DC 20231

TRANSMITTAL OF A PROVISIONAL APPLICATION
UNDER 37 CFR 1.53(c)

Sir

This is a request for filing a provisional application under 37 CFR 1.53(c). The application is entitled Aminoalkoxy Carbazoles for the Treatment of CNS Diseases, our Docket No. 6219 1 and consists of

- [86] page(s) of Specification
- [11] page(s) of Claims
- [] page(s) of Drawings
- [] page(s) of Sequence Listings
- [1] page(s) of Abstract

- ☐ A disk containing nucleotide and/or amino acid sequences in a computer readable format is attached. The contents of the sequence listing in the application is the same as the document on the disk. (37 CFR 1.821(f) and MPEP 2422.06)
- ☒ The name(s) and residence address(es) of the inventor(s) are set forth on the attached Inventor Information Sheet
- ☐ As provided in 37 CFR 1.41(a)(3), instead of providing the names of the inventors at this time, the applicant identifier is PNU

This application is being sent by Express Mail under 37 CFR 1.10 and the required certificate appears above

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SPECIFIC DEPOSIT ACCOUNT AUTHORIZATION Please charge my Deposit Account No 21-0718 in the amount of the total Provisional Application filing fee for a large entity (\$150 00 or such greater or lesser amount as the Commissioner may require) Triplicate copies of this sheet are enclosed for this purpose

The undersigned hereby requests that all correspondence and telephone communications in connection with this application be directed to the undersigned person at the mailing address and telephone number shown below

Respectfully submitted,

Lucy X. Yang
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Date 5-12-00

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Enclosures

- ☒ Patent Application
- ☐ Disk containing Nucleotide and/or Amino Acid Sequence Listing
- ☒ Inventor Information Sheet

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INVENTOR INFORMATION SHEET

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AMINOALKOXY CARBAZOLES FOR THE TREATMENT OF CNS DISEASES

FIELD OF THE INVENTION

5 The present invention provides aminoalkoxy carbazole derivatives, and more specifically provides compounds of formula (I) described herein below. These compounds are 5-HT ligands, and are useful for treating diseases wherein modulation of 5-HT activity is desired.

BACKGROUND OF THE INVENTION

10 Many diseases of the central nervous system are influenced by the adrenergic, the dopaminergic, and the serotonergic neurotransmitter systems. For example, serotonin has been implicated in a number of diseases and conditions which originate in the central nervous system. These include diseases and conditions related to sleeping, eating, perceiving
15 pain, controlling body temperature, controlling blood pressure, depression, anxiety, schizophrenia, and other bodily states. R. W. Fuller, *Biology of Serotonergic Transmission*, 221 (1982), D. J. Boulton, *Serotonin in Mental Abnormalities* 1316 (1978), J. Barchas, et al., *Serotonin and Behavior* (1973). Serotonin also plays an important role in peripheral systems, such as the gastrointestinal system, where it has been found to mediate a variety of
20 contractile, secretory, and electrophysiologic effects.

 As a result of the broad distribution of serotonin within the body, there is a tremendous interest in drugs that affect serotonergic systems. In particular, receptor-specific agonists and antagonists are of interest for the treatment of a wide range of
25 disorders including anxiety, depression, hypertension, migraine, obesity, compulsive disorders, schizophrenia, autism, neurodegenerative disorders (e.g., Alzheimer's disease, Parkinsonism, and Huntington's chorea), and chemotherapy-induced vomiting. M. D. Gershon, et al., *The Peripheral Actions of 5-Hydroxytryptamine*, 246 (1989), P. R. Saxena, et al., *Journal of Cardiovascular Pharmacology* 15 Supplement 7 (1990).

 The major classes of serotonin receptors (5-HT₁₋₇) contain fourteen to eighteen
30 separate receptors that have been formally classified. See Glennon, et al., *Neuroscience and Behavioral Reviews*, 1990, 14, 35, and D. Hoyer, et al., *Pharmacol. Rev.* 1994, 46, 157-203. Recently discovered information regarding subtype identity, distribution, structure, and

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function suggests that it is possible to identify novel subtype specific agents, having improved therapeutic profiles (e.g. fewer side effects)

For example The 5-HT₆ receptor was identified in 1993 (Monsma et al. *Mol Pharmacol* 1993, 43, 320-327 and Ruat M. et al. *Biochem. Biophys. Res. Commun.* 1993, 193, 269-276). Several antidepressants and atypical antipsychotics bind to the 5-HT₆ receptor with high affinity and this binding may be a factor in their profile of activities (Roth et al. *J. Pharm. Exp. Therapeut.* 1994, 268, 1403-1410, Sleight et al. *Exp. Opin. Ther. Patents* 1998, 8, 1217-1224, Bourson et al. *Brit. J. Pharm.* 1998, 125, 1562-1566, Boess et al. *Mol. Pharmacol.* 1998, 54, 577-583, Sleight et al. *Brit. J. Pharmacol.* 1998, 124, 556-562). In addition, the 5-HT₆ receptor has been linked to generalized stress and anxiety states (Yoshioka et al. *Life Sciences* 1998, 17/18, 1473-1477). Together these studies and observations suggest that compounds that antagonize the 5-HT receptor will be useful in treating disorders of the central nervous system.

Compounds of the present invention are 5-HT ligands (e.g. receptor-specific agonists or antagonists). Thus they are useful for treating diseases wherein modulation of 5-HT activity is desired. Specifically the compounds of this invention are useful in the treatment of psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, schizoaffective disorder, delusional disorder, panic disorder, a phobia, obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, a stress induced problem with the urinary, a stress related disease such as anxiety, migraine headache, drug addiction, convulsive disorders, personality disorders, post-traumatic stress syndrome, alcoholism, panic attacks, obsessive-compulsive disorders, sleep disorders, gastrointestinal or cardiovascular system (e.g. stress incontinence), neurodegenerative disorders, autism, chemotherapy-induced vomiting, hypertension, cluster headaches, sexual dysfunction in a mammal (e.g. a human), addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, behavioral disturbance (including agitation in conditions associated with diminished cognition (e.g., dementia, mental retardation or delirium)), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, an inhalation disorder, an intoxication disorder, movement disorder (e.g., Huntington's disease or Tardive Dyskinesia), oppositional defiant disorder, peripheral

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neuropathy post-traumatic stress disorder premenstrual dysphoric disorder a psychotic disorder (brief and long duration disorders psychotic disorder due to medical condition, psychotic disorder NOS) mood disorder (major depressive or bipolar disorder with psychotic features) seasonal affective disorder a specific developmental disorder, agitation disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome or a Tic disorder (e.g., Tourette's syndrome) More specifically, the compounds of this invention are useful to treat psychotic affective, vegetative and psychomotor symptoms of schizophrenia and the extrapyramidal motor side effects of other antipsychotic drugs. This last action will allow higher doses of antipsychotics to be used and thus greater antipsychotic efficacy to be obtained as a result of a reduction in side effects The compounds of this invention are also useful in the modulation of eating behavior and thus are useful in treating excess weight and associated morbidity and mortality

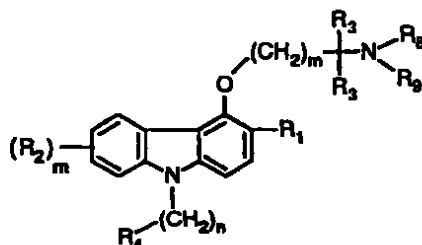
INFORMATION DISCLOSURE

- International Publication No WO95/03296 discloses carbazole and dibenzofuran hapten compounds
- Abstract of International Publication No WO/9747601 discloses new heterocyclic compounds useful for treating schizophrenia
- European Patent Application EP 839806 discloses tricyclic compounds useful for inhibiting sPLA2 mediated release of fatty acids for conditions such as septic shock.
- US Patent No 5,668 167 discloses carbazole derivatives useful for treating microbial infections
- US Patent No 4 503,067 discloses carbazoyl-(4)-oxypropanolamine compounds useful for treating cardiac diseases
- US Patent No 3,932 424 discloses carbazoles useful as antiviral agents
- US Patent No 3,896,145 discloses carbazoles useful as antiinflammatory, analgesic, and anti-rheumatic agents.
- US Patent No 3,759,948 discloses tricyclic carboxylic acid and ester derivatives useful as anti-inflammatory, anti-pyretic and analgesic agents
- DE 4330175 discloses beta carbolines useful for treating Parkinson's disease, Alzheimer's disease, senile dementia, epilepsy, schizophrenia migraine etc
- Abstract of Japanese Patent No 06228095 discloses carbazole derivatives useful for treating ischaemic encephalopathy

Abstract of French Patent No 2516512 discloses pyrido-indole derivatives useful for treating cardiac rhythm diseases

SUMMARY OF THE INVENTION

5 The present invention provides a compound of formula I



I

wherein

R₁ is

- 10 (a) H,
(b) halo or
(c) C₁₋₆ alkyl,

R₂ is

- 15 (a) H
(b) halo
(c) OH,
(d) -CN,
(e) -CF₃
(f) -O(C₁₋₆)alkyl,
20 (g) C₁₋₆ alkyl,
(h) C₃₋₆ cycloalkyl,
(i) -NR₅R₆
(j) -CONR₅R₆,
(k) SO₂NR₅R₆,
25 (l) -COOR₇,
(m) -OCF₃ or
(n) phenyl, optionally substituted with halo OH O(C₁₋₄) alkyl, or C₁₋₆ alkyl,

each R₃ is independently

- (a) H

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- (b) C₁₋₆ alkyl, or
- (c) C₃₋₆ cycloalkyl

R₄ is

- (a) aryl, or
- (b) heteroaryl,

R₅ and R₆ are independently

- (a) H
- (b) C₁₋₆ alkyl, or
- (c) C₃₋₆ cycloalkyl,

10 R₇ is

- (a) H,
- (b) C₁₋₆ alkyl, or
- (c) (C₁₋₃ alkyl)-phenyl wherein phenyl may be substituted with R₃

R₈ and R₉ are independently

- (a) H,
- (b) C₁₋₆ alkyl, optionally substituted with aryl, heteroaryl, or C₃₋₆ cycloalkyl
- (c) C₂₋₆ alkene
- (d) C₃₋₆ cycloalkyl,
- (e) C₂₋₆ alkyl substituted with R₁₀,
- (f) -CHO provided that only one of the R₈ and R₉ is CHO the other one is H,
- (g) aryl,
- (h) heterocyclic, which is bonded via carbon atom to the nitrogen to which it is attached or

25 * (i) R₈ and R₉ taken together with the nitrogen to which they are attached form a heterocyclic ring wherein the heterocyclic ring may have one to two additional heteroatoms selected from the group consisting of oxygen, sulfur and N(Y) and wherein the carbon atoms of the heterocyclic ring is optionally substituted with one or two R₁₄.

R₁₀ is

- (a) -OH,
- (b) -O(C₁₋₄ alkyl), optionally alkyl is substituted with OH
- (c) -O(C₁₋₄ alkyl)-NR₁₁R₁₂,
- (d) heterocyclic or
- (e) -CO₂R₃

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R_{11} and R_{12} are independently,

- (a) H, or
- (b) C_{1-4} alkyl,

aryl is phenyl or naphthyl optionally substituted with one or more R_{13}

- 5 heteroaryl is a radical of a five or six-membered monocyclic aromatic ring having one or two heteroatoms each selected from the group consisting of oxygen, sulfur and N(X) or a radical of a nine- or ten-membered ortho-fused bicyclic aromatic ring having one two or three heteroatoms each selected from the group consisting of oxygen, sulfur, and N(X), wherein carbon atoms of heteroaryl may be substituted with R_{13}
- 10 heterocyclic is a radical of a five- six-, or seven-membered partially saturated or unsaturated heterocyclic ring having one, two or three heteroatoms selected from the group consisting of oxygen, sulfur and N(Y) wherein the carbon atoms of the heterocyclic ring may be substituted with R_{14} ,
- X is absent, H or C_{1-4} alkyl,

15 Y is

- (a) H,
- (b) C_{1-6} alkyl optionally substituted with aryl or hetroaryl,
- (c) C_{3-6} cycloalkyl, or
- (d) C_{2-6} alkyl substituted with -OH -O(C_{1-4} alkyl) -O(C_{1-4} alkyl)-NR₁₁R₁₂
- 20 -CO₂R₅ or NHCHO or
- (e) -OH,

R_{13} is

- (a) halo
- (b) -OH,
- 25 (c) -CN,
- (d) -CF₃
- (e) -O(C_{1-6})alkyl,
- (f) C_{1-6} alkyl,
- (g) C_{3-6} cycloalkyl,
- 30 (h) -NR₅R₆,
- (i) -CONR₅R₆,
- (j) -SO₂NR₅R₆,
- (k) -COOR₇,

- (l) $-\text{OCF}_3$ or
- (m) phenyl, optionally substituted with halo, OH, $\text{O}(\text{C}_{1-4})$ alkyl, or C_{1-6} alkyl,

R_{14} is

- (a) C_{1-6} alkyl,
- 5 (b) C_{3-6} cycloalkyl,
- (c) C_{2-6} alkyl substituted with $-\text{OH}$ $-\text{O}(\text{C}_{1-4})$ alkyl $-\text{O}(\text{C}_{1-4})$ alkyl- $\text{NR}_{11}\text{R}_{12}$, or $-\text{CO}_2\text{R}_5$
- (d) $-\text{OH}$ or
- (e) oxo ($=\text{O}$),

10 m is 1, 2, 3 or 4,

n is 1, 2, 3, or 4,

C_{3-6} cycloalkyl in each of the above definitions may be each and independently substituted with $-\text{OH}$, C_{1-4} alkyl, or oxo ($=\text{O}$), and with the following provisos

- (a) when R_4 is aryl substituted with fluoro, R_2 cannot be fluoro or chloro at the C-6
- 15 position of formula I
- (b) when R_4 is 4-thiazolyl, it cannot be substituted with 4-chlorophenyl, or a pharmaceutically acceptable salt, racemate, solvate, tautomer optical isomer or prodrug derivative thereof
- (c) when R_4 is heteroaryl heteroaryl is not 4-pyridyl

20 In another aspect, the present invention also provides

a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient (the composition preferably comprises a therapeutically effective amount of the compound or salt)

25 a method for treating a disease or condition in a mammal (e.g. a human) wherein a 5-HT receptor is implicated and modulation of a 5-HT function is desired comprising administering a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof to the mammal,

30 a method for treating or preventing anxiety obesity depression, schizophrenia, a stress related disease (e.g. general anxiety disorder), panic disorder a phobia, obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, a stress induced problem with the gastrointestinal or cardiovascular system, eating disorders or sexual dysfunction in a mammal (e.g. a human) comprising administering a therapeutically

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effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof to the mammal,

5 a method of treating or preventing diseases or disorders of the central nervous system such as psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, schizoaffective disorder, delusional disorder, panic disorder, a phobia, obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, a stress induced problem with the urinary system, a stress related disease such as anxiety, migraine, headache, drug addiction, convulsive disorders, personality disorders, post-traumatic stress syndrome, alcoholism, panic attacks, obsessive-compulsive disorders, 10 sleep disorders, gastrointestinal or cardiovascular system (e.g., stress incontinence), neurodegenerative disorders, autism, chemotherapy-induced vomiting, hypertension, cluster headaches, sexual dysfunction in a mammal (e.g., a human), addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder, behavioral disturbance (including agitation in conditions associated with diminished cognition (e.g., dementia, mental retardation or delirium)), bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, an inhalation disorder, an intoxication disorder, movement disorder 20 (e.g., Huntington's disease or Tardive Dyskinesia), oppositional defiant disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder (brief and long duration disorders, psychotic disorder due to medical condition, psychotic disorder NOS), mood disorder (major depressive or bipolar disorder with psychotic features), seasonal affective disorder, a specific developmental disorder, agitation disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome or a Tic disorder (e.g., Tourette's syndrome), comprising administering to a mammal (e.g., a human) in need of such treatment, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof,

25 a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in medical diagnosis or therapy (e.g., the treatment or prevention of 5-HT related central nervous system diseases or disorders,

the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof to prepare a medicament for treating or preventing 5-HT related central nervous system

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diseases or disorders such as anxiety obesity depression, schizophrenia, a stress related disease (e.g. general anxiety disorder) panic disorder a phobia obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, a stress induced problem with the gastrointestinal or cardiovascular system, or sexual dysfunction in a mammal (e.g. a human), and

a method for modulating 5-HT (e.g. 5-HT₆) receptor function, comprising contacting (*in vitro* or *in vivo*) the receptor with an effective inhibitory amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

The invention also provides novel intermediates and processes disclosed herein that are useful for preparing compounds of formula I.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are generally named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art may be used (e.g. "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "h" for hour or hours and "rt" for room temperature)

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety i.e. the prefix C_{i-j} indicates a moiety of the integer 'i' to the integer 'j' carbon atoms, inclusive. Thus for example, C₁₋₇alkyl refers to alkyl of one to seven carbon atoms inclusive.

Specific and preferred values listed below for radicals substituents, and ranges are for illustration only, they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

The following definitions are used, unless otherwise described.

Halo is fluoro chloro bromo, or iodo

Alkyl denotes both straight and branched groups but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. Specifically, C₁₋₇ alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, or hexyl.

Alkene denotes both straight and branched groups have at least one double bond

C₃₋₆ cycloalkyl denotes a cycloalkyl having three to six carbon atoms. Specifically C₃₋₆ cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

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Aryl denotes a phenyl or a naphthyl radical. Optionally aryl is substituted with one or more halo, OH, CN, CF₃, O(C₁₋₆)alkyl, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, NR₅R₆, CONR₅R₆, SO₂NR₅R₆, COOR₇, OCF₃ or phenyl which in turn may be substituted with halo, OH, O(C₁₋₄) alkyl, or C₁₋₆ alkyl. R₅ and R₆ are the same as summarized above.

- 5 Heteroaryl denotes a radical of a five- or six-membered monocyclic aromatic ring having one or two heteroatoms each selected from the group consisting of oxygen, sulfur and N(X) or a radical of a nine- or ten-membered ortho-fused bicyclic aromatic ring having one, two or three heteroatoms each selected from the group consisting of oxygen, sulfur and N(X), wherein X is absent, H or C₁₋₄ alkyl, wherein carbon atoms of heteroaryl may be substituted with one or more halo, OH, CN, CF₃, O(C₁₋₆)alkyl, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, NR₅R₆, CONR₅R₆, SO₂NR₅R₆, COOR₇, OCF₃, or phenyl which in turn may be substituted with halo, OH, O(C₁₋₄) alkyl or C₁₋₆ alkyl. R₅, R₆ and R₇ are the same as summarized above. Examples of heteroaryl are pyridyl, thiophene, benzothiophene, benzofuran, benzimidazole, imidazole or thiazole.

- 15 Heterocyclic is a radical of a five-, six- or seven-membered partially-saturated or unsaturated heterocyclic ring having one, two or three heteroatoms selected from the group consisting of oxygen, sulfur and N(Y) wherein the carbon atoms of the heterocyclic ring is optionally substituted with R₁₄. Y and R₁₄ are the same as summarized above. Examples of heterocyclic is azetidyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1-benzyl-piperidinyl, 1-methyl-piperidinyl, dioxolane, imidazolidine, oxazolidinyl, 20 oxathiolane, 4-hydroxyl-1-piperidinyl, 4-ethanol-1-piperazinyl, 4-ethylformamide-1-piperazinyl- or 4-methyl-1-piperazinyl.

- Pharmaceutically acceptable salts denotes acid addition salts useful for administering the compounds of this invention and include hydrochloride, hydrobromide, hydroiodide, 25 sulfate, phosphate, acetate, propionate, lactate, mesylate, maleate, malate, succinate, tartrate, citric acid, 2-hydroxyethyl sulfonate, fumarate, methanesulfonic acid salt and etc. Specifically, pharmaceutically acceptable salts can be maleate, methanesulfonic acid salt and etc.

Mammal denotes human and animals.

- 30 A specific value for R₁ is H, halo or C₁₋₄ alkyl.

A specific value for R₁ is H.

A specific value for R₂ is H, halo, -OH, -CN, -CF₃, -O(C₁₋₆)alkyl, C₁₋₆ alkyl.

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C₃₋₆ cycloalkyl, -NR₅R₆, -CONR₅R₆, -SO₂NR₅R₆, COOR₇ or phenyl which may be substituted with halo, -OH, -O(C₁₋₄) alkyl, or C₁₋₆ alkyl wherein R₅ and R₆ is H, C₁₋₆ alkyl, or C₃₋₆ cycloalkyl, wherein R₇ is C₁₋₆ alkyl or (C₁₋₃ alkyl)-phenyl wherein phenyl may be substituted with R₂

5 A specific value for R₂ is H, halo, or C₁₋₆ alkyl

A specific value for R₂ is H, chloro, fluoro, or methyl

A specific value for R₂ is H.

A specific value for R₂ is fluoro or methyl.

A specific value for each R₃ is independently H, C₁₋₆ alkyl, or C₃₋₆ cycloalkyl.

10 A specific value for each R₃ is independently H

A specific value is wherein R₈ and R₉ are independently H, C₁₋₆ alkyl (optionally substituted with aryl, heteroaryl or C₃₋₆ cycloalkyl), C₂₋₆ alkene, C₃₋₆ cycloalkyl, C₂₋₆ alkyl substituted with R₁₀, -CHO (provided that only one of the R₈ and R₉ is -CHO, the other one is hydrogen), aryl, heterocyclic wherein heterocyclic is bonded via carbon atom to the nitrogen to which it is attached or R₈ and R₉ taken together with the nitrogen to which they are attached form a heterocyclic ring wherein the heterocyclic ring may have one to two additional heteroatoms selected from the group consisting of oxygen, sulfur and N(Y) and wherein the carbon atoms of the heterocyclic ring is optionally substituted with one or two R₁₃, wherein R₁₀, and Y are as defined above, wherein each C₃₋₆ cycloalkyl is optionally

20 substituted with -OH, C₁₋₄ alkyl, or oxo

A specific value is wherein R₈ is H, and R₉ is H, C₁₋₆ alkyl, C₂₋₄ alkene, C₁₋₆ alkyl substituted with phenyl, wherein phenyl is optionally substituted with fluoro or chloro

A specific value is wherein R₈ is H, and R₉ is C₁₋₆ alkyl substituted with C₃₋₆ cycloalkyl, wherein cycloalkyl is optionally substituted with -OH, C₁₋₄ alkyl or oxo

25 A specific value is wherein R₈ is H, and R₉ is C₂₋₆ alkyl substituted with -OH, -O(C₁₋₄ alkyl), -O(C₁₋₄ alkyl-OH) or -CO₂C₁₋₄ alkyl.

A specific value is wherein R₈ is H, and R₉ is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, all of which may be substituted with -OH, C₁₋₄ alkyl, oxo, or -CHO

A specific value is wherein R₈ is H, and R₉ is C₁₋₆ alkyl substituted with phenyl, pyridyl, thiophene, benzothienophene, benzofuran, benzimidazole, imidazole or thiazole

30 A specific value is wherein R₈ is H, and R₉ is heterocyclic wherein heterocyclic is bonded via carbon atom to the nitrogen to which it is attached

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A specific value is wherein R_8 is H and R_9 is pyridyl methyl, benzimidazole methyl, or 1-benzyl-piperidinyl.

A specific value is wherein R_8 is H, and R_9 is C_{2-6} alkyl substituted with azetidinyl pyrrolidinyl piperidinyl piperazinyl morpholinyl, thiomorpholinyl,

- 5 1 benzyl-piperidinyl, 1-methyl-piperidinyl dioxolane, imidazolidine oxazolidinyl, oxathiolane, 4-hydroxyl-1-piperidinyl, 4-ethanol-1-piperazinyl- 4-ethylformamide-1-piperazinyl-, or 4-methyl-1-piperazinyl.

- A specific value is wherein R_8 and R_9 taken together with the nitrogen to which they are attached form a heterocyclic ring wherein the heterocyclic ring may have one to two
10 additional heteroatoms selected from the group consisting of oxygen, sulfur and N(Y), wherein Y is the same as defined in claim 1

- A specific value is wherein R_8 and R_9 taken together with the nitrogen to which they are attached form 4-morpholinyl, 1-pyrrolidinyl, 1-piperidinyl 1-piperazinyl, 4-hydroxyl-1-piperidinyl, 4-ethanol-1-piperazinyl- 4-ethylformamide-1-piperazinyl-, or 4-
15 methyl-1-piperazinyl.

A specific value for R_8 and R_9 are independently H, methyl, ethyl, propyl 1-propanol, 2-propanol, 1-pentanol, 2-methyl-1-propanol, 2-butanol, 1-ethanol, ethoxyl-1-ethanol, $-CH_2CH_2CO_2$ ethyl, 2-methoxyethyl, 4-chlorophenethyl, or 4-fluorophenethyl.

- A specific value is wherein R_8 and R_9 are both hydrogen atoms
20 A specific value is wherein R_8 is H and R_9 is methyl.

A specific value is wherein R_8 and R_9 taken together with the nitrogen to which they are attached form 4-methyl-1-piperazinyl.

A specific value for R_4 is aryl, or heteroaryl, wherein aryl or heteroaryl are as defined as herein above

- 25 A specific value for R_4 is phenyl

A specific value for R_4 is pyridyl, thiophene, benzothiophene, benzofuran, benzimidazole, imidazole, thiazole pyridyl, thiophene, benzothiophene, benzofuran, benzimidazole, imidazole or thiazole

- A specific value for R_4 is 2-methyl-1,3-thiazol-4-yl, or 5-chloro-1-benzothiophen-3-yl.
30 A specific value for m is one

Examples of the present invention includes

- a) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine
b) N-{2-[(9-benzyl-8-chloro-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine.

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- c) N-(2-([8-chloro-9-(4-fluorobenzyl)-9H-carbazol-4-yl]oxy)ethyl)-N,N-diethylamine
- d) N-(2-((9-benzyl-8-methyl-9H-carbazol-4-yl)oxy)ethyl)-N,N-diethylamine,
- e) N,N-diethyl-N-(2-([9-(4-fluorobenzyl)-8-methyl-9H-carbazol-4-yl]oxy)ethyl)amine,
- f) N-(2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)-N-(2-pyridinylmethyl)amine,
- 5 g) N-(2-((9-benzyl-8-fluoro-9H-carbazol-4-yl)oxy)ethyl)-N,N-diethylamine
- h) 9-benzyl-4-[2-(4-morpholinyl)ethoxy]-9H-carbazole
- i) 2-(4-(2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)-1-piperazinyl)-1-ethanol,
- j) 3-((2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)amino)-1-propanol,
- k) N-(2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)-2-propen-1-amine
- 10 l) N-(2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)-3-(4-morpholinyl)-1-propanamine,
- m) 5-((2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)amino)-1-pentanol,
- n) N-(2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)-1-propanamine,
- o) N-(2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)-N-propyl 1-propanamine,
- p) 1-benzyl-N-(2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)-4-piperidinamine,
- 15 q) 2-((2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)amino)-2-methyl 1-propanol,
- r) 2-((9-benzyl-9H-carbazol-4-yl)oxy)-N-(4-chlorophenethyl)-1-ethanamine,
- s) 2-((9-benzyl-9H-carbazol-4-yl)oxy)-N-(cyclohexylmethyl)-1-ethanamine
- t) 2-((9-benzyl-9H-carbazol-4-yl)oxy)-N-[2-(4-morpholinyl)ethyl]-1-ethanamine,
- u) 1-((2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)amino)-2-butanol,
- 20 v) 2-((9-benzyl-9H-carbazol-4-yl)oxy)-N-(4-fluorophenethyl)-1-ethanamine
- w) 2-[2-((2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)amino)ethoxy]-1-ethanol,
- x) (1S,2S)-2-((2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)amino)cyclohexanol,
- y) ethyl 3-((2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)amino)propanoate,
- z) N-(2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)cyclobutanamine,
- 25 aa) 2-(4-(2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)-1-piperazinyl)ethylformamide,
- bb) N-(1H-benzimidazol-2-ylmethyl)-2-((9-benzyl-9H-carbazol-4-yl)oxy)-1-ethanamine,
- cc) 1-(2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)-4-piperidinol,
- dd) 9-benzyl-4-[2-(4-methyl-1-piperazyl)ethoxy]-9H-carbazole,
- ee) N-(2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)-N-cyclopropylamine,
- 30 ff) N-(2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl) N,N-dimethylamine,
- gg) N-(2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)formamide,
- hh) N-(2-((9-benzyl-9H-carbazol-4-yl)oxy)ethyl)-N-methylamine or its maleic acid salt,
- u) 2-((9-benzyl-9H-carbazol-4-yl)oxy)ethylamine

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- jj) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-(2-methoxyethyl)amine
- kk) N-ethyl-N-[(1-phenyl-1,2-dihydro[1,4]oxazino[2,3-d]carbazol-7-yl)oxy]ethyl)amine or its maleic acid salt
- ll) 9-benzyl-4-[2-(1-pyrrolidinyl)ethoxy]-9H-carbazole,
- 5 mm) 9-benzyl-4-[2-(1-piperidinyl)ethoxy]-9H-carbazole,
- nn) 9-benzyl-4-[2-(1-piperazinyl)ethoxy]-9H-carbazole,
- oo) 2-[(9-benzyl-8-fluoro-9H-carbazol-4-yl)oxy]ethylamine,
- pp) N,N-diethyl-N-(2-[(8-fluoro-9-(4-fluorobenzyl)-9H-carbazol-4-yl)oxy]ethyl)amine,
- qq) N-{2-[(9-benzyl-6-chloro-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine,
- 10 rr) N-{2-[(9-benzyl-6-fluoro-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine,
- ss) N-{2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine,
- tt) 2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethylamine,
- uu) N-{2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethyl}-N-methylamine,
- vv) N,N-diethyl-N-(2-[(9-(4-fluorobenzyl)-6-methyl-9H-carbazol-4-yl)oxy]ethyl)amine,
- 15 ww) 2-[(2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)amino]-1-ethanol or its maleic acid salt
- xx) 2-[(9-[(5-chloro-1-benzothiophen-3-yl)methyl]-9H-carbazol-4-yl)oxy]ethylamine or its methane sulfonate salt,
- yy) 2-[(9-[(2-methyl-1,3-thiazol-4-yl)methyl]-9H-carbazol-4-yl)oxy]ethylamine or its methane sulfonate salt
- 20 zz) 2-[(9-benzyl-3-chloro-9H-carbazol-4-yl)oxy]ethylamine, methane sulfonate salt,
- aaa) 2-[(9-(3-bromobenzyl)-9H-carbazol-4-yl)oxy]ethylamine, maleic acid salt,
- bbb) 2-[(9-(3-fluorobenzyl)-9H-carbazol-4-yl)oxy]ethylamine, maleic acid salt,
- ccc) 2-[(9-(2-bromobenzyl)-9H-carbazol-4-yl)oxy]ethylamine, maleic acid salt
- 25 ddd) 2-[(9-(4-methylbenzyl)-9H-carbazol-4-yl)oxy]ethylamine, maleic acid salt,
- eee) 2-[(9-(2-fluorobenzyl)-9H-carbazol-4-yl)oxy]ethylamine, maleic acid salt,
- fff) 2-[(9-(3-methoxybenzyl)-9H-carbazol-4-yl)oxy]ethylamine, maleic acid salt,
- ggg) 2-[(9-(3,5-dimethoxybenzyl)-9H-carbazol-4-yl)oxy]ethylamine, maleic acid salt,
- hhh) 2-[(9-(4-bromobenzyl)-9H-carbazol-4-yl)oxy]ethylamine, maleic acid salt
- 30 iii) 2-[(9-(3-methylbenzyl)-9H-carbazol-4-yl)oxy]ethylamine, maleic acid salt,
- iii) 2-[(9-(2-methylbenzyl)-9H-carbazol-4-yl)oxy]ethylamine, maleic acid salt,
- kkk) 2-[(9-benzyl-6-methoxy-9H-carbazol-4-yl)oxy]ethylamine, or
- lll) 2-[(9-benzyl-7-methoxy-9H-carbazol-4-yl)oxy]ethylamine

It will be appreciated by those skilled in the art that compounds of the invention may contain a chiral center therefore they may be isolated in optically active or racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present
5 invention encompasses any racemic, optically active, polymorphic, tautomeric, or stereoisomeric form, or mixture thereof of a compound of the invention which possesses the useful properties described herein. It is well known in the art to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by
10 synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation (using a chiral stationary phase, for example) and to determine 5-HT₆ activity using the standard tests described herein, or using other similar tests which are well known in the art.

The following Schemes describe the preparation of compounds of the present invention. All of the starting materials are commercially available or prepared by procedures
15 described in these schemes or by procedures that would be well known to one of ordinary skill in organic chemistry. The variables used in the Schemes are as defined above or as in the claims.

As shown in Chart A, hydrazines 3 can be prepared from commercially available anilines 1. Aniline 1 is stirred in an acidic medium such as TFA, acetic acid or aq. sulfuric
20 acid. A nitrite such as sodium nitrite, isoamyl nitrite, or n-butyl nitrite is added to give nitroso aniline 2. Nitroso aniline 2 is reduced with lithium aluminum hydride in ether or THF to give hydrazine 3. For a discussion of additional methods of preparing 3 see Sandler S R., Karo, W. *Organic Functional Group Preparations*, Academic Press New York, 1983, Vol. I, 2nd Ed., pp 434-465. Hydrazone 4 is prepared from hydrazine 3 and
25 cyclohexane-1,3-dione in solvents such as water, alcohols, or dichloromethane. Hydrazone 4 is then treated under the conditions of the Fischer indole synthesis using an acid and a solvent such as acetic acid, toluene, ethanol, or others, to give tetrahydrocarbazole 5. Alternatively hydrazine 3 and cyclohexane-1,3-dione may be reacted under Fischer indole conditions to directly give tetrahydrocarbazole 5. Many additional methods for the Fischer
30 indole synthesis are given in Sundberg R.J., *Indoles* Academic Press London, 1996, and in Hughes D.L. Progress in the Fischer Indole Reaction. A Review *Org Prep Proceed. Int* 1993 25 609-632. The nitrogen of tetrahydrocarbazole 5 is alkylated by methods well known to those versed in the art. For example treatment of tetrahydrocarbazole 5 with a

base such as sodium hydride followed by an alkyl halide such as benzyl chloride or benzyl bromide, gives benzyl tetrahydrocarbazole 6

Treatment of compound 6 in a single step using Raney nickel on Pd/carbon in solvents such as cumene mesitylene, 1,2,3-trimethylbenzene, 1,2,4-trimethylbenzene, decalin, carbitol, or diphenyl ether at temperatures between 130-270 °C provides phenol 9 directly. Alternatively, benzyl tetrahydrocarbazole 6 is first treated with a copper (II) halide, preferably CuCl₂ or CuBr₂, in solvents such as DMF, acetonitrile, EtOAc, chloroform, acetic acid, or acetic acid/water at temperatures between 50 and 120 °C to give halo tetrahydrocarbazoles 7 and 8. For a reference to this reaction, see Matsumoto M., Ishida, Y. Watanabe N. *Heterocycles* 1985, 23, 165-170. A third useful method is treatment of benzyl tetrahydrocarbazole 6 with pyridinium bromide perbromide or phenyltrimethylammonium tribromide in solvents such as DMF, acetonitrile, or THF to give halo tetrahydrocarbazoles 7 and 8. Halo tetrahydrocarbazoles 7 and 8 may be separated and carried on individually in the next steps or they may be carried forward as a mixture to phenols 9 and 10 and separated at that time. Halo tetrahydrocarbazoles 7 and 8 (separately or together) are then treated with lithium chloride or lithium bromide (anhydrous LiCl or LiBr is preferred, but hydrated forms also may be used) in the presence of lithium carbonate in a solvent such as DMF at 110-130 °C to give phenols 9 and 10.

Charts B and D disclose some of the ways phenols 9 and 10 may be alkylated with various alkylating agents and Chart C discloses further transformations of carbazole amine 13 to give alkyl amines 15, 16, and 17 directly or after several steps. Which method is used will depend on the type of amine that is desired and on the availability of alkylating agents. For clarity, only 13 is depicted in Chart C, but the reaction scheme applies equally well to 14. In chart D, only phenol 9 is depicted, but the reaction scheme applies equally well to phenol 10.

In Chart B, X refers to a halogen atom. Phenols 9 and 10 are alkylated with chloro or bromoethyl amine in the presence of bases such as sodium hydride, potassium carbonate, cesium carbonate, or sodium carbonate in solvents such as DMF, acetonitrile, or acetone at room temperature to 120 °C to give carbazole amines 13 and 14 directly. Alternatively, phenols 9 and 10 are alkylated with chloro or bromoacetonitrile in the presence of bases such as sodium hydride, potassium carbonate, cesium carbonate or sodium carbonate in solvents such as DMF, acetonitrile or acetone at room temperature to 120 °C to give nitriles 11 and 12. Reduction of nitriles 11 and 12 with borane in THF or borane-methyl

sulfide complex in THF at room temperature to 80 °C gives carbazole amines 13 and 14 (R8 and R9 are hydrogen atoms) Other methods for the reduction of the nitrile group to an amine may be found in March J *Advanced Organic Chemistry* 3rd ed , John Wiley and Sons New York 1985

5 Chart C discloses further functionalization of carbazole amine 14 by several methods In Chart C, Q refers to hydrogen, alkyl, or aryl. Z refers to hydrogen or alkyl. One method is acylation with acylating agents such as ethyl formate acetic anhydride, and the like to give acyl carbazole 15 The carbonyl function of acyl carbazole 15 is reduced to an alkyl group using reagents such as borane in THF or borane-methyl sulfide complex in THF at room
10 temperature to 80 °C to give monoalkylamino carbazole 16 or using lithium aluminum hydride in ethereal solvents to effect the reduction to monoalkylamino carbazole 16 A second method is reductive amination of 14 with an equivalent amount of an aldehyde or ketone in the presence of reducing agents such as sodium cyanoborohydride or sodium triacetoxyborohydride in solvents such as dichloromethane, dichloroethane, and THF at 0 to
15 80 °C, or Pd/C under a hydrogen atmosphere in solvents such as methanol, ethanol, or ethyl acetate to give monoalkylamino carbazole 16 A third method is alkylation of carbazole amine 14 with alkyl halides or mesylates or tosylates in the presence of base in solvents such as THF acetonitrile dichloromethane DMF and the like using methods well known to those versed in the art to give monoalkylamino carbazole 16

20 When dialkylamino carbazole 17 is desired a second equivalent of the same or a different aldehyde ketone or alkylating agent depending on the method used, is added to monoalkylamino carbazole 16 using the conditions described above Alternatively dialkylaminocarbazole 17 may be prepared directly from 14 using two equivalents of the aldehyde, ketone, or alkylating agent

25 Chart D describes another method of preparing mono or dialkylamino carbazole 21, wherein phenol 9 is alkylated by methods well-known to those versed in the art to give carbazole halide 18 or carbazole alcohol 19 In Chart D, L refers to a leaving group such as halo atom or a sulfonate group The alcohol group of carbazole alcohol 19 is converted to a leaving group with methane sulfonyl halide or toluene sulfonyl halide to give carbazole
30 sulfonate 20 The mesyl or tosyl group of carbazole sulfonate 20 or carbazole halide 18 is then displaced by amines to give ammo carbazole 21

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Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art for example by mixing a compound of the present invention with a suitable acid

Compounds of the present invention can conveniently be administered in a pharmaceutical composition containing the compound in combination with a suitable excipient. Such pharmaceutical compositions can be prepared by methods and contain excipients which are well known in the art. A generally recognized compendium of such methods and ingredients is Remington's Pharmaceutical Sciences by E W Martin (Mark Publ. Co., 15th Ed. 1975). The compounds and compositions of the present invention can be administered parenterally (for example, by intravenous, intraperitoneal or intramuscular injection), topically, orally, or rectally

For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained

The tablets, troches, pills, capsules and the like may also contain the following binders such as gum tragacanth, acacia, corn starch or gelatin, excipients such as dicalcium phosphate, a disintegrating agent such as corn starch, potato starch, alginic acid and the like, a lubricant such as magnesium stearate, and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry. Flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and

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substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The compounds or compositions can also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

Pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e. when they are liquids. However, it will generally be desirable to administer them to the skin

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as compositions or formulations, in combination with a dermatologically acceptable carrier which may be a solid or a liquid

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers. Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps and the like for application directly to the skin of the user.

Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice and other animals to humans are known to the art, for example see U.S. Pat. No. 4,938,949.

The compound is conveniently administered in unit dosage form, for example, containing about 0.05 mg to about 500 mg, conveniently about 0.1 mg to about 250 mg, most conveniently, about 1 mg to about 150 mg of active ingredient per unit dosage form. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete, loosely spaced administrations.

The compositions can conveniently be administered orally, sublingually, transdermally, or parenterally at dose levels of about 0.01 to about 150 mg/kg, preferably about 0.1 to about 50 mg/kg and more preferably about 0.1 to about 30 mg/kg of mammal body weight.

For parenteral administration the compounds are presented in aqueous solution in a concentration of from about 0.1 to about 10% more preferably about 0.1 to about 7%. The solution may contain other ingredients, such as emulsifiers, antioxidants or buffers.

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The exact regimen for administration of the compounds and compositions disclosed herein will necessarily be dependent upon the needs of the individual subject being treated the type of treatment and, of course, the judgment of the attending practitioner

Generally compounds of the invention are 5-HT ligands. The ability of a compound of the invention to bind or act at a 5-HT receptor or to bind or act selectively at a specific 5-HT receptor subtype can be determined using *in vitro* and *in vivo* assays that are known in the art. As used herein, the term "bind selectively" means a compound binds at least 2 times, preferably at least 10 times, and more preferably at least 50 times more readily to a given 5-HT subtype than to one or more other subtypes. Preferred compounds of the invention bind selectively to one or more 5-HT receptor subtypes.

The ability of a compound of the invention to act as a 5-HT receptor agonist or antagonist can also be determined using *in vitro* and *in vivo* assays that are known in the art. The invention provides compounds of formula I that act as either agonists or as antagonists of one or more 5-HT receptor subtypes.

5-HT₆ RECEPTOR BINDING ASSAY

Growth of Cells and Membrane Preparation

Hela cells containing the cloned human 5-HT₆ receptor were acquired from Dr David R. Sibley's laboratory in National Institute of Health (see Sibley D.R. J. Neurochemistry, 66, 47-56, 1996). Cells were grown in high glucose Dulbecco's modified Eagle's medium, supplemented with L-glutamine, 0.5% sodium pyruvate, 0.3% penicillin-streptomycin, 0.025% G-418 and 5% Gibco fetal bovine serum and then were harvested when confluent, in cold phosphate buffered saline.

Harvested intact cells were washed once in cold phosphate-buffered saline. The cells were pelleted and resuspended in 100 ml of cold 50 mM Tris, 5 mM EDTA and 5 mM EGTA, pH 7.4. Homogenization was with a Vir Tishear generator, 4 cycles for 30 seconds each at setting 50. The homogenized cells were centrifuged at 700 RPM (1000 X g) for 10 minutes and the supernatant was removed. The pellet was resuspended in 100 ml of the above buffer and rehomogenized for 2 cycles. The rehomogenized cells were then centrifuged at 700 RPM (1000 X g) for 10 minutes and the supernatant was removed. The combined supernatant (200ml) was centrifuged at 23 000 RPM (80 000 X g) for 1 hour in a Beckman Rotor (42.1 Ti). The membrane pellet was resuspended in 50-80 ml of assay buffer.

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containing HEPES 20 mM MgCl₂ 10 mM NaCl 150 mM EDTA 1mM, pH 7.4 and stored frozen in aliquots at -70°C

5-HT₆ Receptor Binding Assay

The radioligand binding assay used [³H]-lysergic acid diethylamide (LSD). The assay was carried out in Wallac 96-well sample plates by the addition of 11 µl of the test sample at the appropriate dilution (the assay employed 11 serial concentrations of samples run in duplicate), 11 µl of radioligand, and 178 µl of a washed mixture of WGA-coated SPA beads and membranes in binding buffer. The plates were shaken for about 5 minutes and then incubated at room temperature for 1 hour. The plates were then loaded into counting cassettes and counted in a Wallac MicroBeta TriLux scintillation counter.

Binding Constant (K_i) Determination

Eleven serial dilutions of test compounds were distributed to assay plates using the PE/Cetus Pro/Pette pipettor. These dilutions were, followed by radioligand and the bead-membrane mixture prepared as described above. The specifically bound cpm obtained were fit to a one-site binding model using GraphPad Prism ver 2.0. Estimated IC₅₀ values were converted to K_i values using the Cheng-Prusoff equation (Cheng, Y. C. et al. Biochem Pharmacol, 22, 3099-108, 1973). The K_i values obtained from the assay are shown in Table 1.

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TABLE 1
5-HT₆ receptor Binding Assay Data

EXAMPLE NO	K _i (nM)
1	24
2	6
3	22
4	18
5	38
6	69
7	2 6
8	398
9	62
10	20
11	23
12	184
13	43
14	40
15	394
16	148
17	164
18	356
19	311
20	37
21	72
22	81
23	32
24	85
25	40
26	47
27	138
28	72

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29	11
30	12
31	21
32	--
33	211
34	5 7
35	23
36	16
37	11
38	6 9
39	12
40	88
41	2 4
42	20
43	182
44	180
45	6 6
46	6 1
47	2 2
48	123
49	4 5
50	138
51	113

The compounds and their preparations of the present invention will be better understood in connection with the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

EXAMPLES OF PREFERRED EMBODIMENTS

Preparation 1 1,2,3,9-Tetrahydro-4H-carbazol-4-one

To a solution of 1,3-cyclohexane dione (1.99 g, 17.7 mmol) in water (55 mL) is added phenylhydrazine (1.92 g, 17.7 mmol) in 10 mL of water. A gummy solid quickly formed, which after completion of the addition is scrapped with a spatula to give a solid. The solid is collected, washed with water and dried in a vacuum oven to give 3.0 g of a tan solid. After drying, the tan solid is stirred at reflux in TFA (25 mL) overnight. Upon cooling, TFA is removed in vacuo and water is added to the residue. The resulting solid is collected, washed with water, and dried to give 1.82 g (55%) of the title compound, mp 218-220 °C, IR (drift) 3150, 3130, 3104, 3093, 3056, 2976, 2954, 2944, 1607, 1577, 1466, 1413, 1251, 1178, 755 cm^{-1} . ^1H NMR (CDCl_3) δ 2.26, 2.64, 3.00, 7.26, 7.35, 8.21, 8.74. Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{NO}$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.82; H, 6.15; N, 7.54.

Preparation 2 9-Benzyl-1,2,3,9-tetrahydro-4H-carbazol-4-one

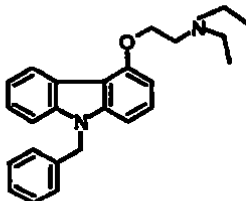
Sodium hydride (60% in oil, 0.207 g, 5.18 mmol) is washed three times with hexane. DMF (3 mL) is added, followed by 36B added in portions. A moderate exotherm ensued, THF (3 mL) is added. After ten minutes benzyl bromide (1.047 g, 6.12 mmol) is added. After stirring for 4 h, an additional 0.1 g of benzyl bromide is added. The mixture is stirred overnight and then the solvents are removed, the residue is partitioned between CH_2Cl_2 and aq. sodium bicarbonate. The organic layers are dried over sodium sulfate. Chromatography on silica gel (150 mL) using $\text{CH}_3\text{OH}:\text{CH}_2\text{Cl}_2$ (1/99) as eluent, followed by re-chromatography of mixed fractions using EtOAc-hexane (30/70) gave 1.023 g (79%) of the title compound, mp 157.0-157.5 °C, IR (drift) 2940, 1636, 1610, 1530, 1484, 1464, 1445, 1399, 1357, 1187, 1133, 749, 742, 731, 698 cm^{-1} . ^1H NMR (CDCl_3) δ 2.23, 2.60, 2.88, 5.34, 7.03, 7.2-7.3, 8.30. Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{NO}$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.51; H, 6.21; N, 5.13.

Preparation 3 9-Benzyl-9H-carbazol-4-ol

To a mixture of 9-Benzyl-1,2,3,9-tetrahydro-4H-carbazol-4-one (3.89 g, 14.13 mmol) in THF (20 mL) and DMF (15 mL) is added pyridinium hydrobromide perbromide (5.42 g, 16.96 mmol) as a solution in DMF (5 mL). After stirring for 5 h at room temperature, TLC (EtOAc-hexane, 20/80) showed little or no reaction had occurred, so the mixture is stirred at 70 °C for 4 h and then allowed to cool (and stir the remainder of

the night) The solvents then are removed and the residue is partitioned between Et₂O and brine, dil Na₂S₂O₃ and brine. The aqueous layer is removed and CH₂Cl₂ is added to the organic layer (from which solids had begun to precipitate). The organic layers are dried over MgSO₄ and taken to dryness. Without further purification the crude product is stirred with LiBr (2.67 g, 31 mmol) and Li₂CO₃ (2.07 g, 28 mmol) in DMF (50 mL) at 100 °C for 45 min, and then at reflux for 3 h. After cooling the solvent is removed and the residue is partitioned between CH₂Cl₂ and water. The organic layers are dried over sodium sulfate and concentrated to dryness. The residue is chromatographed on silica gel (250 mL) using EtOAc-heptane (15/85)/CH₂Cl₂ (6/1) as eluent to give 2.78 g of solid, mp 119-121.5 °C, IR (drift) 3353, 1602, 1485, 1458, 1337, 1328, 1279, 1230, 1138, 1104, 780, 748, 735, 714, 700 cm⁻¹, ¹H NMR (CDCl₃) δ 5.32, 5.50, 6.60, 6.97, 7.14, 7.26, 7.3-7.4, 8.33. Anal. Calcd for C₁₉H₁₅NO: C, 83.49, H, 5.53, N, 5.12. Found: C, 82.35, H, 5.51, N, 5.06.

Example 1 N-(2-[(9-Benzyl-9H-carbazol-4-yl)oxy]ethyl)-N,N-diethylamine



A mixture of 9-benzyl-9H-carbazol-4-ol (0.0305 g, 0.1116 mmol), potassium carbonate (0.0308 g, 0.2232 mmol) and DMF (1.0 mL) is stirred at 100 °C. Diethylaminoethyl chloride hydrochloride (0.0230 g, 0.1339 mmol) is added in aliquots over 40 min. After 2.3 h, an additional 0.032 g of potassium carbonate and 0.023 g of diethylaminoethyl chloride hydrochloride are added. The mixture is stirred overnight and then the solvent is removed and the residue partitioned between CH₂Cl₂ and aq. sodium bicarbonate. The organic layers are dried over sodium sulfate. Chromatography on silica gel (15 mL) using acetone-hexane (20/80) gave 0.0382 g of the title compound as a solid, mp 79-80.5 °C, IR (drift) 2965, 1581, 1457, 1439, 1356, 1342, 1333, 1268, 1147, 1112, 1053, 782, 750, 729, 713 cm⁻¹, ¹H NMR (CDCl₃) δ 1.14, 2.75, 3.13, 4.36, 5.50, 6.71, 6.98, 7.12, 7.2-7.4, 8.38. Anal. Calcd for C₂₅H₂₈N₂O: C, 80.61, H, 7.58, N, 7.52. Found: C, 79.90, H, 7.52, N, 7.43.

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Preparation 4 8-Chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one

2-Chlorophenylhydrazine hydrochloride (1.6885 g, 0.0094 mol) is added portion-wise to a solution of 1,3-cyclohexanedione (1.0316 g, 0.0092 mol) in water (17.4 mL). The mixture is allowed to stir for three days at room temperature. The solids are collected by filtration, washed with water and vacuum dried at 50 °C for 30 min and then overnight at room temperature to give the hydrazone. The hydrazone is then heated at reflux in trifluoroacetic acid (9 mL). After stirring overnight, the mixture is cooled and then partitioned between ice water and dichloromethane. The organic layer is washed with aqueous sodium bicarbonate and the aqueous layer is backwashed with dichloromethane. The combined organic layers are then dried over sodium sulfate and concentrated to a foam. Product is precipitated from the foam by adding dichloromethane, methanol and acetone. After filtering the solids, the filtrate is concentrated to a foam and again more product is precipitated using acetone/dichloromethane (2/98). The solids are collected by filtration and the filtrate is chromatographed on silica gel (150 mL) using acetone/dichloromethane (2/98 and 4/96) to give product. All of the solids are combined and recrystallized from dichloromethane/methanol/hexane to give 0.3724 g (18%) of a first crop and 0.1092 g (5%) of a second crop of the title compound, mp > 247 °C, MS (ESI⁺) for C₁₂H₁₀ClNO *m/z* 217.9 (M-H). IR (drift) 3155, 3142, 3105, 3080, 2943, 1633, 1613, 1473, 1174, 1139, 1071, 1015, 858, 791, 744 cm⁻¹; ¹H NMR (CDCl₃) δ 2.28, 2.61, 3.03, 7.22, 8.11, 8.60. Anal. Calcd for C₁₂H₁₀ClNO: C, 65.61, H, 4.59, N, 6.38. Found: C, 65.48, H, 4.62, N, 6.38.

Preparation 5 9-Benzyl-8-chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one

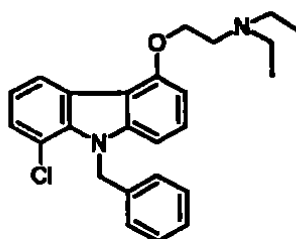
8-Chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.2019 g, 0.92 mmol) is added to a slurry of pentane-washed NaH (0.0275 g, 0.68 mmol) in DMF (1 mL) and after stirring 22 min benzyl bromide (0.13 mL, 0.0011 mol) is added. Starting material remained after 30 min, so additional NaH (0.0140 g, 0.35 mmol) and DMF (1 mL) are added and the mixture is allowed to stir overnight. The mixture is then partitioned between aqueous sodium bicarbonate and ethyl acetate and the organic layer is dried over sodium sulfate and concentrated to dryness. The resulting solids are recrystallized from 30% ethyl acetate/hexane and dichloromethane to give 0.1942 g (68%) of the title compound, mp 161-162 °C, MS (ESI⁺) for C₁₉H₁₆ClNO *m/z* 310.1 (M+H)⁺, IR (drift) 1644, 1605, 1538, 1484, 1462, 1447, 1425, 1357, 1188, 1106, 793, 784, 737, 725, 699 cm⁻¹; ¹H NMR (CDCl₃) δ 2.22, 2.59, 2.85, 5.82.

6 95, 7 18 7 28 8 28 Anal. Calcd for $C_{19}H_{16}ClNO$ C 73 66 H 5 20 N 4 52 Found
C 73 41 H 5 17 N 4 57

Preparation 6 9-Benzyl-8-chloro-9H-carbazol-4-ol

- 5 Pyridinium bromide perbromide (0 1856 g, 0 58 mmol) is added to a solution of 9-benzyl-8-chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one in THF (0 7 mL) and DMF (0 5 mL) and the mixture is heated to 75 °C After stirring for 5 5 h, THF is removed under reduced pressure and the residue is partitioned between dichloromethane and brine. The combined organic layers are washed with dilute sodium sulfate/brine and the aqueous layer is
- 10 backwashed with dichloromethane The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to give a residue. A mixture of the resulting residue, lithium bromide (0 0940 g, 0 0011 mol), lithium carbonate (0 0772 g, 0 0010 mol) and DMF (2 mL) is heated at 120 °C for two hours. The DMF is then removed under high vacuum and the residue is partitioned between dichloromethane and water The
- 15 combined organic layers are dried over sodium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (80 mL) using 15% ethyl acetate in heptane/dichloromethane (6 1) to give 0 1060 g (72%) of the title compound mp 163-165 5 °C, MS (ESI-) for $C_{19}H_{14}ClNO$ m/z 306 1 (M-H), IR (drift) 3537, 1632, 1587 1452, 1417, 1351 1339 1311 1268, 1208, 1112, 1073 789, 734 729 cm^{-1} , ^1H NMR ($CDCl_3$) δ 5 42, 5 98 6 59, 6 93
- 20 7 09 7 15-7 28, 7 36, 8 29 Anal. Calcd for $C_{19}H_{14}ClNO$ C 74 15, H, 4 59, N, 4 55 Found C 73 22 H 4 53, N, 4 62

Example 2 N-{2-[(9-Benzyl-8-chloro-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine



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9-Benzyl-8-chloro-9H-carbazol-4-ol (0 0826 g 0 27mmol), 2-diethylaminoethylchloride hydrochloride (0 0719 g 0 42 mmol), potassium carbonate (0 1157 g 0 84 mmol), sodium iodide (0 0031 g 0 021 mmol) and DMF (1 mL) are heated at 85 °C for 4 h After the mixture had cooled it is partitioned between water and ether

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The combined organic layers are dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (30 mL) using methanol/dichloromethane (1/99 to 2/98 to 4/96) to give 0.0675 g (62%) of the title compound mp 73.5-75 °C, MS (ESI+) for $C_{25}H_{27}ClN_2O$ m/z 407.3 (M+H)⁺, IR (drift) 2966, 1588, 1499, 1454, 1413, 1355, 1337, 1266, 1124, 1027, 789, 732, 727, 717, 697 cm^{-1} , ¹H NMR (CDCl₃) δ 1.13, 2.72, 3.10, 4.33, 5.99, 6.71, 6.96, 7.10, 7.15-7.26, 7.33, 8.33. Anal. Calcd for $C_{25}H_{27}ClN_2O$ C 73.79, H 6.69, N 6.88. Found C, 73.47, H 6.81, N 6.76.

Preparation 7 8-Chloro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydro-4H-carbazol-4-one

8-Chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.1973 g, 0.90 mmol) is added to a slurry of pentane-washed NaH (0.0286 g, 0.72 mmol) in DMF (1 mL) and, after stirring for 22 min, p-fluorobenzyl bromide (0.14 mL, 0.0011 mol) is added. Starting material remained after 30 min, so additional NaH (0.0166 g, 0.42 mmol) and DMF (1.8 mL) are added. The mixture is stirred for 1 h, at which time the mixture is partitioned between aq. sodium bicarbonate and ethyl acetate. The organic layer is dried over sodium sulfate and concentrated to dryness. The resulting solids are recrystallized from 30% ethyl acetate/hexane and dichloromethane to give 0.2088 g (71%) of the title compound, mp 166-166.5 °C, MS (ESI+) for $C_{19}H_{15}ClFNO$ m/z 328.1 (M+H)⁺, IR (drift) 1639, 1607, 1510, 1485, 1449, 1426, 1413, 1226, 1189, 1157, 1108, 1095, 830, 790, 734 cm^{-1} , ¹H NMR (CDCl₃) δ 2.22, 2.59, 2.84, 5.78, 6.97, 7.19, 8.27. Anal. Calcd for $C_{19}H_{15}ClFNO$ C 69.62, H 4.61, N 4.27. Found C, 69.44, H 4.55, N 4.34.

Preparation 8 8-Chloro-9-(4-fluorobenzyl)-9H-carbazol-4-ol

Pyridinium bromide perbromide (0.1988 g, 0.62 mmol) is added to a solution of 8-chloro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydro-4H-carbazol-4-one in THF (0.7 mL) and DMF (0.5 mL) and the mixture is heated to 75 °C. After stirring for 5.5 h, THF is removed under reduced pressure and the residue is partitioned between dichloromethane and brine. The combined organic layers are washed with dilute sodium sulfate/brine and the aqueous layer is backwashed with dichloromethane. The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to give a residue. A mixture of the resulting residue, lithium bromide (0.0976 g, 0.0011 mol), lithium carbonate (0.0762 g, 0.0010 mol) and DMF (2 mL) is heated at 120 °C for two hours. The DMF is then removed under high vacuum and the residue is partitioned between dichloromethane and water. The

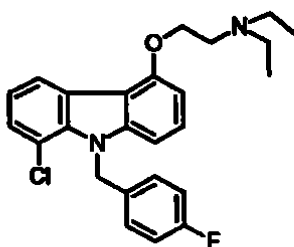
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combined organic layers are dried over sodium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (80 mL) using 15% ethyl acetate in heptane/dichloromethane (6/1) to give 0.1199 g (72%) of the title compound, mp 142-145 °C. MS (ESI⁺) for

$C_{19}H_{13}ClFNO$ m/z 324.1 (M-H), IR (drift) 3521, 1591, 1508, 1457, 1416, 1351, 1337

5 1311, 1269, 1226, 1218, 1110, 852, 791, 736 cm^{-1} , ^1H NMR ($CDCl_3$) δ 5.38, 5.94, 6.60, 6.93, 7.06, 7.18, 7.26, 7.36, 8.29. Anal. Calcd for $C_{19}H_{13}ClFNO$: C, 70.05; H, 4.02; N, 4.30. Found: C, 69.26; H, 4.05; N, 4.20.

Example 3 N-(2-[[8-chloro-9-(4-fluorobenzyl)-9H-carbazol-4-yl]oxy]ethyl)-N,N-diethylamine



8-chloro-9-(4-fluorobenzyl)-9H-carbazol-4-ol (0.1038 g, 0.32 mmol), 2-

diethylaminoethylchloride hydrochloride (0.0831 g, 0.48 mmol), potassium carbonate

(0.1248 g, 0.90 mmol), sodium iodide (0.0037 g, 0.025 mmol) and DMF (1 mL) are heated

15 at 85 °C for 5.5 h. After the mixture had cooled, it is partitioned between water and ether.

The combined organic layers are dried over magnesium sulfate and concentrated to an oil.

The oil is chromatographed on silica gel (50 mL) using methanol/dichloromethane (1/99

2/98 and 4/96) to give 0.0741 g (55%) of the title compound, mp 104.5-105.5 °C, MS

(ESI⁺) for $C_{23}H_{26}ClFN_2O$ m/z 425.1 (M+H)⁺, IR (drift) 2966, 2932, 1590, 1506, 1455

20 1414, 1354, 1334, 1270, 1221, 1157, 1124, 822, 791, 734 cm^{-1} , ^1H NMR ($CDCl_3$) δ 1.19,

2.82, 3.20, 4.43, 5.95, 6.73, 6.94, 7.04, 7.16, 7.36, 8.30. Anal. Calcd for $C_{23}H_{26}ClFN_2O$:

C, 70.66; H, 6.17; N, 6.59; Cl, 8.34. Found: C, 70.30; H, 6.13; N, 6.54.

Preparation 9 8-Methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one

25 O-Tolylhydrazine hydrochloride (1.3957 g, 0.0091 mol) is added in portions to a solution of 1,3-cyclohexanedione (1.0113 g, 0.0090 mol) in water (17.5 mL). The mixture is allowed to stir overnight at room temperature. The resulting slurry is filtered, washed with water and vacuum dried at 50 °C for 30 min and then overnight at room temperature to give the hydrazone. The hydrazone is then heated at reflux in trifluoroacetic acid (9 mL).

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After stirring for 3 h, the mixture is cooled and then partitioned between ice water and dichloromethane. The organic layer is washed with aq. sodium bicarbonate and the aqueous layer is backwashed with dichloromethane. The combined organic layers are then dried over sodium sulfate and concentrated to a foam. Product is precipitated from the foam by adding methanol/dichloromethane (2/98). After collecting the solids by filtration, the filtrate is concentrated and again more product is precipitated using methanol/dichloromethane (2/98). These solids are collected by filtration and the filtrate is chromatographed on silica gel (150 mL) using acetone/dichloromethane (2/98, 4/96 and 8/92) to give product. All of the solids are combined and recrystallized from dichloromethane, methanol and hexane to give 0.3550 g (20%) for a first crop and 0.1261 g (7%) for a second crop of the title compound, mp >247 °C, MS (ESI-) for $C_{13}H_{13}NO$ m/z 198.0 (M-H), IR (drift) 3187, 3159, 3088, 2940, 1612, 1475, 1454, 1410, 1216, 1183, 1140, 1068, 1013, 791, 756 cm^{-1} , ^1H NMR ($CDCl_3$) δ 2.26, 2.50, 2.60, 3.00, 7.04, 7.17, 8.06, 8.39. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36, H, 6.58, N, 7.03. Found: C, 78.05, H, 6.61, N, 7.05.

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Preparation 10 9-Benzyl-8-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one

8-Methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.1967 g, 0.99 mmol) is added to a slurry of pentane-washed NaH (0.0485 g, 0.0012 mol) in DMF (2 mL) and after stirring for 30 min, benzyl bromide (0.14 mL, 0.0012 mol) is added. After 3 h starting material still remained, so additional benzyl bromide (0.015 mL, 0.013 mmol) is added and the mixture is stirred overnight at room temperature. The mixture is then partitioned between aq. sodium bicarbonate and ethyl acetate and the organic layer is dried over sodium sulfate and concentrated to dryness. The resulting solids are recrystallized from ethyl acetate/hexane/dichloromethane to give 0.2076 g (73%) of the title compound, mp 165-166 °C. MS (ESI+) for $C_{20}H_{19}NO$ m/z 290.2 (M+H)⁺, IR (drift) 2940, 1637, 1599, 1538, 1494, 1462, 1447, 1416, 1357, 1322, 1121, 787, 752, 727, 697 cm^{-1} , ^1H NMR ($CDCl_3$) δ 2.21, 2.51, 2.59, 2.82, 5.58, 6.89, 6.95, 7.16, 7.29, 8.23. Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01, H, 6.62, N, 4.84. Found: C, 82.53, H, 6.62, N, 4.86.

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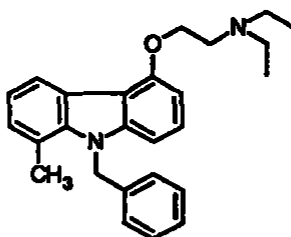
Preparation 11 9-Benzyl-8-methyl-9H-carbazol-4-ol

Pyridinium bromide perbromide (0.2032 g, 0.64 mmol) is added to a mixture of 9-benzyl-8-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one in THF (0.7 mL) and DMF (0.5 mL) and the mixture is heated to 75 °C. After stirring for 8 h THF is removed under reduced

pressure and the residue is partitioned between dichloromethane and brine. The combined organic layers are washed with dilute sodium thiosulfate/brine and the aqueous layer is backwashed with dichloromethane. The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to give a residue. A mixture of the
 5 resulting residue, lithium bromide (0.1005 g, 0.0012 mol), lithium carbonate (0.0768 g, 0.0010 mol) and DMF (2 mL) is heated at 120 °C for two hours. The DMF is removed under high vacuum and the residue is partitioned between dichloromethane and water. The combined organic layers are dried over sodium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (75 mL) using ethyl acetate/heptane (10/90) to give 0.0888 g
 10 (59%) of the title compound. The product is then recrystallized from ethyl acetate/hexane, MS (ESI+) for $C_{20}H_{17}NO$ m/z 288.1 (M+H)⁺, IR (drift) 3537, 1587, 1492, 1451, 1351, 1338, 1315, 1271, 1236, 1205, 963, 792, 745, 729, 720 cm^{-1} . ¹H NMR (CDCl₃) δ 2.64, 5.32, 5.76, 6.58, 6.88, 7.02, 7.15-7.26, 8.24. Anal. Calcd for $C_{20}H_{17}NO$: C, 83.59, H 5.96, N, 4.87. Found: C, 80.86, H, 5.73, N, 4.72.

15

Example 4 N-(2-[(9-Benzyl-8-methyl-9H-carbazol-4-yl)oxy]ethyl)-N,N-diethylamine



9-Benzyl-8-methyl-9H-carbazol-4-ol (0.0566 g, 0.20 mmol), 2-diethylaminoethylchloride
 20 hydrochloride (0.0505 g, 0.29 mmol), potassium carbonate (0.0922 g, 0.67 mmol), sodium iodide (0.0029 g, 0.019 mmol) and DMF (1 mL) are heated at 85 °C for 4 h. After the mixture had cooled, it is partitioned between water and ether. The combined organic layers are dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (15 mL) using methanol/dichloromethane (1/99 to 2/98 to 4/96) to give 0.0248 g
 25 (32%) of the title compound, MS (ESI+) for $C_{26}H_{30}N_2O$ m/z 387.2 (M+H)⁺, IR (drift) 2966, 1585, 1497, 1449, 1353, 1336, 1268, 1251, 1140, 1106, 1069, 791, 743, 725 cm^{-1} . ¹H NMR (CDCl₃) δ 1.18, 2.64, 2.81, 3.20, 4.41, 5.77, 6.69, 6.91, 6.99, 7.13, 7.22-7.33, 8.28. Anal. Calcd for $C_{26}H_{30}N_2O$: C, 80.79, H, 7.82, N, 7.25. Found: C, 79.00, H 7.76, N, 7.10.

275 280

Preparation 12 9-(4-Fluorobenzyl)-8-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one

8-Methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.1967 g, 0.99 mmol) is added to a slurry of pentane washed NaH (0.0449 g, 0.0011 mol) in DMF (2 mL). After stirring for 5 30 min, p-fluorobenzyl bromide (0.15 mL, 0.0012 mol) is added. Starting material is still present after 3 h, so additional p-fluorobenzyl bromide (0.015 mL, 0.12 mmol) is added and the mixture is stirred overnight. The mixture is then partitioned between aq. sodium bicarbonate and ethyl acetate and the organic layer is dried over sodium sulfate and concentrated to dryness. The resulting solids are chromatographed on silica gel (75 mL) 10 using methanol/dichloromethane (2/98). The impure fractions are rechromatographed on silica gel (60 mL) using methanol/dichloromethane (2/98). The pure fractions are combined and recrystallized from ethyl acetate/hexane/dichloromethane to give 0.1021 g (34%) of the title compound, mp 154-155 °C, MS (ESI+) for $C_{20}H_{18}FNO$ m/z 308.2 (M+H)⁺, IR (drift) 1635, 1602, 1539, 1510, 1462, 1449, 1414, 1226, 1159, 835, 826, 801, 786, 756, 747 cm^{-1} . 15 ¹H NMR (CDCl₃) δ 2.21, 2.51, 2.59, 2.81, 5.55, 6.87, 6.98, 7.17, 8.23. Anal. Calcd for $C_{20}H_{18}FNO$: C, 78.15, H, 5.90, N, 4.56. Found: C, 77.72, H, 5.95, N, 4.64.

Preparation 13 9-(4-Fluorobenzyl)-8-methyl-9H-carbazol-4-ol

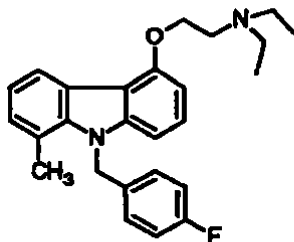
Pyridinium perbromide (0.0800 g, 0.25 mmol) is added to a solution of 9-(4-fluorobenzyl)-8-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one in THF (0.4 mL) and DMF 20 (0.3 mL) and the mixture is heated to 75 °C. After stirring for 8 h, THF is removed under reduced pressure and the residue is partitioned between dichloromethane and brine. The combined organic layers are washed with dilute sodium sulfate/brine and the aqueous layer is backwashed with dichloromethane. The combined organic layers are dried over magnesium 25 sulfate and concentrated under reduced pressure to give a residue. A mixture of the resulting residue, lithium bromide (0.0391 g, 0.45 mmol), lithium carbonate (0.0358 g, 0.48 mmol) and DMF (1.2 mL) is heated at 120 °C for two hours. The DMF is then removed under high vacuum and the residue is partitioned between dichloromethane and water. The combined organic layers are dried over sodium sulfate and concentrated to an oil. The oil is 30 chromatographed on silica gel (30 mL) using ethyl acetate/heptane (10/90) to give 0.0321 g (52%) of the title compound, MS (ESI+) for $C_{20}H_{18}FNO$ m/z 306.1 (M+H)⁺. IR (drift) 3545, 1588, 1508, 1453, 1408, 1336, 1316, 1269, 1234, 1227, 1203, 819, 791, 743, 720.

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246 281

cm⁻¹, ¹H NMR (CDCl₃) δ 2.63, 5.36, 5.72, 6.58, 6.85, 6.96, 7.15-7.22, 8.25 Anal. Calcd for C₂₀H₁₆FN O C, 78.67, H, 5.28, N, 4.59 Found C, 74.98, H, 5.05, N, 4.37

Example 5 N,N-Diethyl-N-(2-([9-(4-fluorobenzyl)-8-methyl-9H-carbazol-4-yl]oxy)ethyl)amine



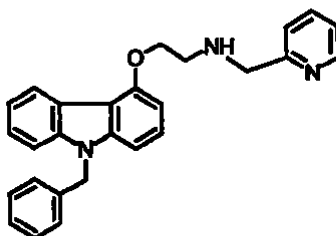
9-(4-Fluorobenzyl)-8-methyl-9H-carbazol-4-ol (0.0176 g, 0.058 mmol), 2-diethylaminoethylchloride hydrochloride (0.0144 g, 0.084 mmol) potassium carbonate (0.0332 g, 0.24 mmol) sodium iodide (0.0008 g, 0.0053 mmol) and DMF (1 mL) are heated at 85 °C for 4 h. After the mixture had cooled, it is partitioned between water and ethyl acetate. The aqueous layer is also washed with dichloromethane. The combined organic layers are dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (10 mL) using methanol/dichloromethane (1/99 and 2/98) to give 0.0148 g (55%) of the title compound. MS (ESI+) for C₂₆H₂₉FN₂O m/z 405.2 (M+H)⁺ ¹H NMR (CDCl₃) δ 1.23, 2.65, 2.88, 3.26, 4.47, 5.75, 6.73, 6.95, 7.15, 7.33, 8.29 Anal. Calcd for C₂₆H₂₉FN₂O C, 77.20, H, 7.22, N, 6.93 Found C, 73.47, H, 7.06, N, 6.53

Preparation 14 9-Benzyl-4-(2-bromoethoxy)-9H-carbazole

To a mixture of 9-benzyl-9H-Carbazol-4-ol (2.46 g, 9.00 mmol), potassium carbonate (5.11 g, 27.0 mmol), and DMF (10 mL) is added dibromoethane (3.90 mL, 45.0 mmol). The mixture is stirred at 80 °C for 4.5 h and then allowed to cool and stir the remainder of the night. The mixture is then stirred at 85 °C after about 2 h an additional 1.0 mL of dibromoethane is added. After 5.5 h the mixture is cooled and the solvent and excess dibromochthane are removed in vacuo. The residue is partitioned between Et₂O, water and brine. The organic layers are dried over MgSO₄ and taken to dryness. Chromatography on silica gel (250 mL) using EtOAc/heptane (10/90 to 20/80) to give 1.80 g (53%) after crystallization from CH₂Cl₂-hexane, IR (neat) 1583, 1458, 1446, 1342, 1333, 1281, 1270, 1245, 1154, 1147, 1114, 783, 753, 734, 719 cm⁻¹, ¹H NMR (CDCl₃) δ 3.87, 4.58, 5.51,

6 66 7 02 7 12 7 2-7 4 8 43 Anal Calcd for $C_{21}H_{18}BrNO$ C 66 33 H 4 77 N 3 68, Br, 21 01 Found C 66 30 H, 4 76 N 3 62

Example 6 N-{2-[(9-Benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-(2-pyridinylmethyl)amine



5

A mixture of 9-benzyl-4-(2-bromoethoxy)-9H-carbazole (0 0622 g, 0 1635 mmol) diisopropylethylamine (0 0211 g, 0 1635 mmol) 2-(2-aminomethylpyridine) (0 0531 g, 0 4907 mmol) and DMF (0 5 mL) is stirred at 100 °C for 30 min. After cooling, the solvent is removed and the residue partitioned between CH_2Cl_2 and aq sodium bicarbonate. The organic layers are dried over sodium sulfate, chromatography on silica gel (40 mL) using $CH_3OH-CH_2Cl_2$ (2/98) gave 0 0539 g (81%) of the title compound, IR (drift) 1586, 1457 1342 1269, 1237, 1153, 1145, 1118 1047, 782, 776, 753, 745 718, 710 cm^{-1} , ^1H NMR ($CDCl_3$) δ 3 32, 4 13, 4 44, 5 51, 6 70, 6 99, 7 12, 7 2-7 4, 7 66 8 39, 8 60 Anal. Calcd for $C_{27}H_{25}N_3O$ C, 79 58, H, 6 18, N 10 31 Found C, 79 66 H, 6 41, N, 10 28

15

Preparation 15 8-Fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one

2-Fluorophenylhydrazine hydrochloride (4 74 g 0 0291 mol) is added in portions to a solution of 1,3-cyclohexanedione (3 20 g, 0 0285 mol) in water (60 mL). The mixture is allowed to stir overnight at room temperature. The resulting solids are collected by filtration, washed with water followed by a small hexane wash and vacuum dried at 50 °C for 40 min and then overnight at room temperature to give the hydrazone. The hydrazone, p-toluene sulfonic acid monohydrate (5 8557 g, 0,031 mol) and trimethylbenzene (43 mL) are heated at 160 °C for 52 min. After cooling, the mixture is partitioned between water and dichloromethane. The aqueous layer is also washed once with chloroform. The combined organic layers are washed with aq sodium bicarbonate, dried over sodium sulfate and concentrated to a residue. The resulting residue is chromatographed on silica gel (400 mL) using ethyl acetate/hexane (20/80, 40/60 and 60/40 to give 0 8221 g (15%) of the title compound, mp 225-226 °C, MS (ESI-) for $C_{12}H_{10}FNO$ 202 0 (M-H), IR (drift) 3117, 3078 3049 3015 2952 2867 1615 1475 1235 1219, 1184 1143 864 786 735 cm^{-1} ^1H NMR

(CDCl₃) δ 2.27, 2.61, 3.02, 6.95, 7.16, 7.97, 8.82. Anal. Calcd for C₁₂H₁₀FNO: C, 70.93, H, 4.96, N, 6.89. Found: C, 71.40, H, 5.00, N, 6.92.

Preparation 16 9-Benzyl-8-fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one

5 8-Fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one (2.23 g, 0.011 mol) is added to a slurry of pentane-washed NaH (0.59 g, 0.015 mol) in DMF (18 mL) and after stirring for 20 min, benzyl bromide (1.7 mL, 0.014 mol) is added. The mixture is stirred for 1 h at which time the mixture is partitioned between water and ethyl acetate. The combined organic layers are dried over sodium sulfate and concentrated to dryness. The resulting residue is
10 chromatographed on silica gel (200 mL) using methanol/dichloromethane (1/99). The solids are then recrystallized from ethyl acetate/dichloromethane/hexane to give 2.25 g (70%) of the title compound, mp 183-184 °C, MS (ESI-) for C₁₉H₁₆FNO *m/z* 292.1 (M-H), IR (drift) 1639, 1631, 1495, 1459, 1434, 1359, 1246, 1219, 1193, 1125, 798, 789, 736, 730, 698 cm⁻¹. ¹H NMR (CDCl₃) δ 2.23, 2.58, 2.87, 5.51, 6.92, 7.03, 7.16, 7.29, 8.07. Anal. Calcd for
15 C₁₉H₁₆FNO: C, 77.80, H, 5.50, N, 4.78. Found: C, 77.58, H, 5.59, N, 4.79.

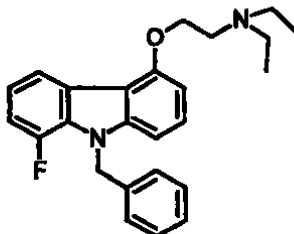
Preparation 17 9-Benzyl-8-fluoro-9H-carbazol-4-ol

Pyridinium bromide perbromide (2.9945 g, 0.0094 mol) is added to a mixture of 9-benzyl-8-fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one (2.1145 g, 0.0072 mol) in THF (22
20 mL) and DMF (16 mL) and the mixture is heated to 75 °C. After stirring for 5.5 h, THF is removed under reduced pressure and the residue is partitioned between ethyl acetate and brine. The combined organic layers are washed with dilute sodium thiosulfate/brine and the aqueous layer is backwashed with ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue
25 is recrystallized from ethyl acetate/heptane and the resulting solids are combined with lithium bromide (1.1338 g, 0.013 mol), lithium carbonate (0.8831 g, 0.012 mol), and DMF (24 mL) and heated to 120 °C. After 1.5 h, the mixture is partitioned between ethyl acetate and brine. The combined organic layers are washed with dilute brine and then dried over sodium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (150 mL) using
30 dichloromethane (100) to give 1.0857 g (52%) of the title compound, mp 155-156 °C, MS (ESI-) for C₁₉H₁₄FNO *m/z* 290.1 (M-H), IR (drift) 3524, 1581, 1498, 1456, 1432, 1343, 1318, 1272, 1239, 1134, 966, 790, 731, 714, 698 cm⁻¹. ¹H NMR (CDCl₃) δ 5.33, 5.69.

6 59 6 98 7 14, 7 25, 8 10 Anal. Calcd for $C_{19}H_{14}FNO$ C 78 33, H 4 84 N 4 81
 Found C 77 67 H 4 90, N, 4 71

Example 7 N-{2-[(9-Benzyl-8-fluoro-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine

5



9-Benzyl-8-fluoro-9H-carbazol-4-ol (0 0273 g, 0 0940 mmol), 2-diethylaminoethylchloride hydrochloride (0 0237 g, 0 14 mmol) potassium carbonate (0 0396 g 0 29 mmol), sodium iodide (0 0013 g, 0 0087 mmol) and DMF (1 mL) are heated
 10 at 80 °C for 3 h After the mixture had cooled, it is partitioned between water and ethyl acetate. The organic layer is dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (20 mL) using methanol/dichloromethane (1/99 to 2/98 to 3/97) to give 0 0206 g (56%) of the title compound mp 60-60 5 °C, MS (ESI+) for $C_{25}H_{27}FN_2O$ m/z 391 3 ($M+H$)⁺, ¹H NMR ($CDCl_3$) δ 1 17, 2 79 3 17 4 39 5 53 6 73
 15 7 02, 7 13, 7 25, 7 38, 8 15 Anal. Calcd for $C_{25}H_{27}FN_2O$ C 76 89, H, 6 97, N, 7 17
 Found C 76 33, H, 7 18 N, 7 13

Preparation 18 2-[(9-Benzyl-8-fluoro-9H-carbazol-4-yl)oxy]acetonitrile

A mixture of 9-benzyl-8-fluoro-9H-carbazol-4-ol (1 0775 g, 0 0037 mol), potassium
 20 carbonate (0 6284 g, 0 0046 mol), bromoacetonitrile (0 6 mL, 0 0086 mol) and DMF (12 mL) is stirred at room temperature for 4 h. The mixture is then partitioned between water and dichloromethane. The aqueous layer is also washed with ethyl acetate. The combined organic layers are dried over sodium sulfate and concentrated to a residue, which is then partitioned between water and ethyl acetate. The combined organic layers are dried over
 25 magnesium sulfate and concentrated to a residue. The resulting residue is chromatographed on silica gel (100 mL) using ethyl acetate/hexane (20/80) followed by dichloromethane (100 %). The solids are recrystallized from ethyl acetate/heptane to give 0 8869 g (73%) of the title compound, mp 134-134 25 °C, MS (ESI+) for $C_{21}H_{15}FN_2O$ m/z 353 1 ($M+Na$)⁺, IR(draft) 1578 1500 1458 1439 1369 1344 1335 1323 1278 1235, 1144, 1080 793

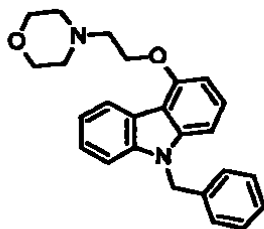
739 695 cm^{-1} , $^1\text{H NMR}$ (CDCl_3) δ 5.05, 5.71, 6.75, 7.16, 7.24, 7.41, 8.07. Anal. Calcd for $\text{C}_{21}\text{H}_{13}\text{FN}_2\text{O}$: C, 76.35; H, 4.58; N, 8.48. Found: C, 76.15; H, 4.63; N, 8.35.

Examples 8-32

- 5 A mixture of 9-benzyl-4-(2-bromoethoxy)-9H-carbazole (0.020 g, 0.0526 mmol) and an appropriate amine (0.0631 mmol), diisopropylethylamine (0.0631 mmol), and DMF (0.2 or 0.4 mL) is stirred in 7 mL capped glass vials (at room temperature for volatile amines and at 70 °C for the remainder). When TLC showed most of the starting material had been consumed (3-4 days for room temperature reactions and overnight for heated reactions), the
- 10 vials (minus caps) are placed in a vacuum oven for removal of solvent. The residues are chromatographed on silica gel (using disposable glass Pasteur pipettes as columns) eluting with $\text{CH}_3\text{OH}-\text{CH}_2\text{Cl}_2$ (2/98 to 8/92, depending on the polarity of the product). Product fractions are combined and the eluent is allowed to evaporate.

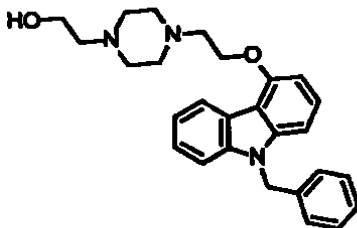
Example 8 9-benzyl-4-[2-(4-morpholinyl)ethoxy]-9H-carbazole

- 15 ms (m + H) at 387



Example 9 2-(4-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-1-piperazinyl)-1-ethanol

ms (m + H) at 430



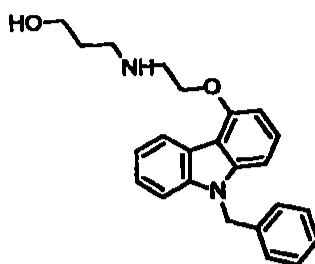
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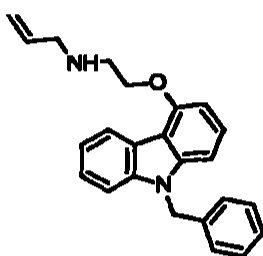
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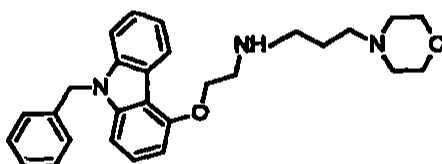
Example 10 3-((2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)amino)-1-propanol
ms (m + H) at 375



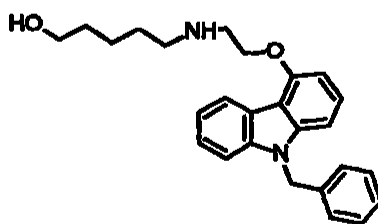
5 Example 11 N-(2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)-2-propen-1-amine
ms (m + H) at 357



Example 12 N-(2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)-3-(4-morpholinyl)-1-
10 propanamine ms (m + H) at 444

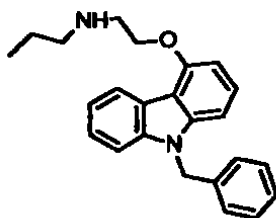


Example 13 5-((2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)amino)-1-pentanol
15 ms (m + H) at 403



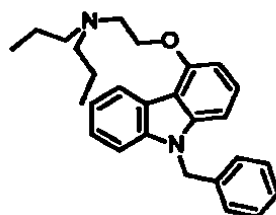
Example 14 N-(2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl) 1-propanamine

ms (m + H) at 359



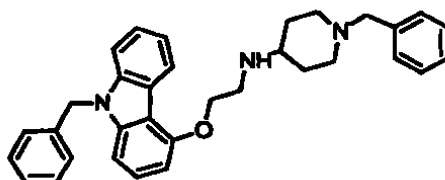
Example 15 N-(2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)-N-propyl-1-propanamine

5 ms (m + H) at 401



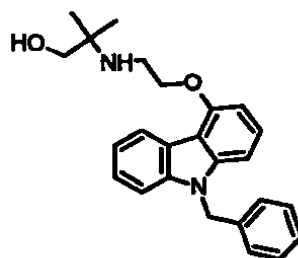
Example 16 1-benzyl-N-(2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)-4-piperidamine

ms (m + H) at 490



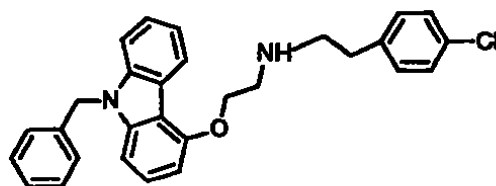
10 Example 17 2-({2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}amino)-2-methyl-1-propanol

ms (m + H) at 389

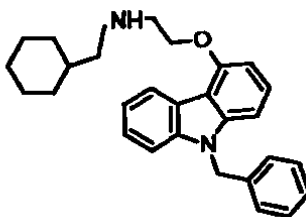


Example 18 2-[(9-benzyl-9H-carbazol-4-yl)oxy]-N-(4-chlorophenethyl)-1-ethanamine

ms (m + H) at 455

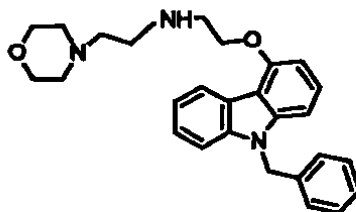


Example 19 2-[(9-benzyl-9H-carbazol-4-yl)oxy]-N-(cyclohexylmethyl)-1-ethanamine
ms (m + H) at 413

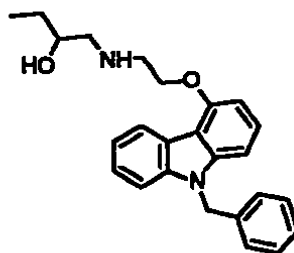


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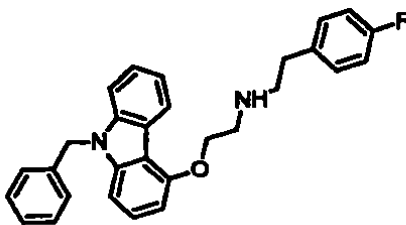
Example 20 2-[(9-benzyl-9H-carbazol-4-yl)oxy]-N-[2-(4-morpholinyl)ethyl]-1-ethanamine
ms (m + H) at 430



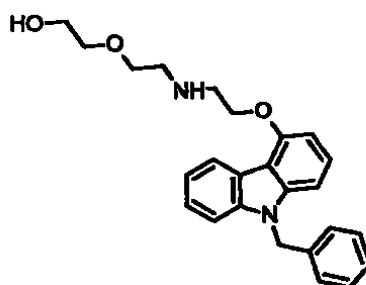
10 Example 21 1-[(2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)amino]-2-butanol
ms (m + H) at 389



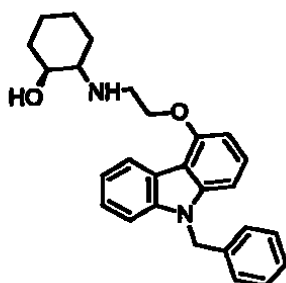
Example 22 2-[(9-benzyl-9H-carbazol-4-yl)oxy]-N-(4-fluorophenethyl)-1-ethanamine
15 ms (m + H) at 439



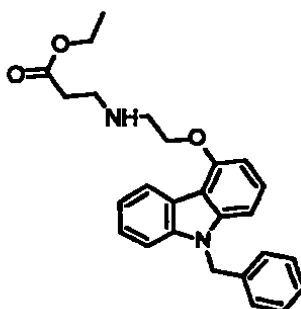
Example 23 2-[2-((2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)amino)ethoxy]-1-ethanol
ms (m + H) at 405



Example 24 (1S,2S)-2-((2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)amino)cyclohexanol
ms (m + H) at 415

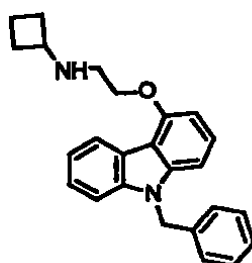


Example 25 ethyl 3-((2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)amino)propanoate
ms (m + H) at 417



10

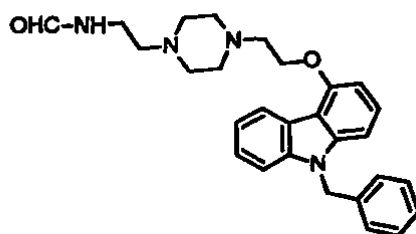
Example 26 N-(2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)cyclobutanamine
ms (m + H) at 371



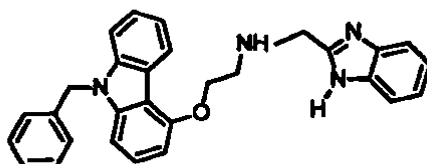
285

6219 1

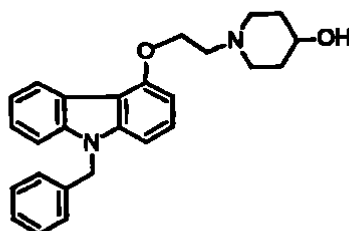
Example 27 2-(4-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-1-piperazinyl)ethylformamide
 ethylformamide ms (m + H) at 457



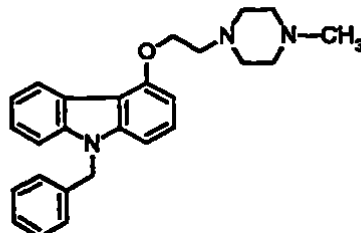
Example 28 N-(1H-benzimidazol-2-ylmethyl)-2-[(9-benzyl-9H-carbazol-4-yl)oxy]-1-ethanamine
 5 ethanamine ms (m + H) at 447



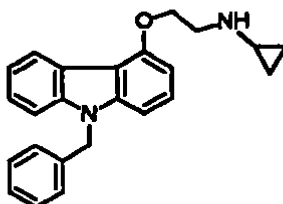
Example 29 1-(2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)-4-piperidinol
 10 H) at 401 ms (m +



Example 30 9-benzyl-4-[2-(4-methyl-1-piperazinyl)ethoxy]-9H-carbazole
 10 H) at 400 ms (m +

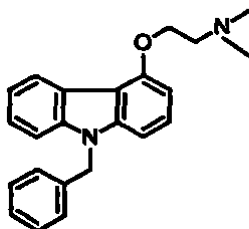


Example 31 N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-cyclopropylamine
 ms (m + H) at 357

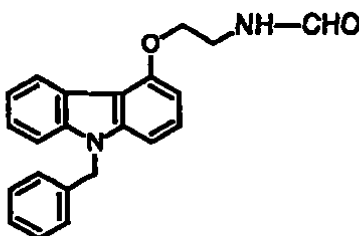


15

Example 32 N-(2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)-N,N-dimethylamine
ms (m + H) at 345

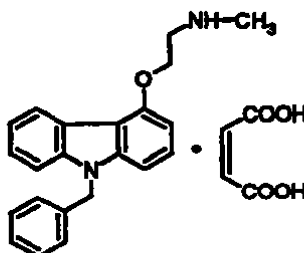


5 Example 33 N-(2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)formamide



A mixture of 2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethylamine (0.0714 g, 0.226 mmol) and ethyl formate (3 mL) is stirred at 65-70 °C for 45 min. After cooling, excess ethyl formate is removed in vacuo and the residue is partitioned between CH₂Cl₂ and aq. sodium sulfate. The organic layers are dried over sodium sulfate and concentrated, the residue is crystallized from CH₂Cl₂-EtOAc-hexane to give 0.0585 g (75%) of the title compound as a white, crystalline solid, mp 161-162 °C, MS (ESI+) for *m/z* 345 (M+H)⁺, 367 (M+Na). ¹H NMR (CDCl₃) δ 3.95, 4.38, 5.52, 6.13, 6.68, 7.03, 7.10, 7.2-7.4, 8.27, 8.29, IR (drift) 3297, 1659, 1459, 1385, 1341, 1332, 1269, 1255, 1145, 1116, 780, 747, 737, 717, 700 cm⁻¹.
10
15 Anal. Calcd for C₂₂H₂₀N₂O₂: C, 76.72, H, 5.85, N, 8.13. Found: C, 76.53, H, 5.99, N, 8.09.

Example 34 N-(2-[(9-Benzyl-9H-carbazol-4-yl)oxy]ethyl)-N-methylamine, maleic acid salt

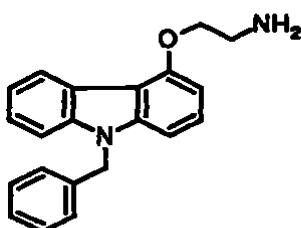


20 A mixture of 9-benzyl-4-(2-bromoethoxy)-9H-carbazole (0.165 g, 0.434 mmol) and methylamine (40% in H₂O, 0.4 mL) in acetonitrile (3 mL) is stirred in a glass pressure vessel

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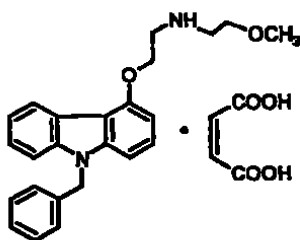
with a screw top cap at 95 °C for 3.5 h, after which it is allowed to cool and stir at room temperature overnight. The solvent is then removed and the residue is chromatographed on silica gel using CH₃OH-CH₂Cl₂ (4/96 to 8/92) to give 0.125 g (87%) of product as the free base. The free base and maleic acid (0.0439 g) are dissolved in CH₂Cl₂ and CH₃OH concentrated and crystallized from CH₂Cl₂/hexane to give 0.119 g of the title compound mp 182.5-184.5 °C, ¹H NMR (free base) (CDCl₃) δ 2.61, 3.21, 4.40, 5.51, 6.71, 6.99, 7.12, 7.2-7.4, 8.30. Anal. Calcd for C₂₂H₂₂N₂O•C₄H₄O₄: C 69.94, H 5.87, N 6.27. Found: C 69.71, H 5.79, N 6.21.

10 Example 35 2-[(9-Benzyl-9H-carbazol-4-yl)oxy]ethylamine



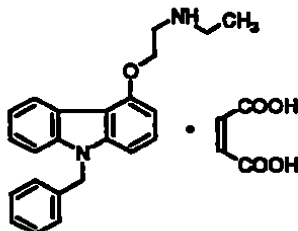
Sodium hydride (60% in oil, 0.934 g, 23.36 mmol) is washed three times with pentane. DMF (5 mL) is added followed by 9-benzyl-9H-carbazol-4-ol (1.52 g, 5.56 mmol) dissolved in DMF (10 mL) added over 10 min. The mixture is stirred an additional 5 min and then cooled in an ice-water bath. A solution of 2-chloroethylamine hydrochloride (1.29 g, 11.12 mmol) dissolved in DMF (5 mL) is added dropwise over about 5 min. The cooling bath is removed and the mixture is allowed to stir at room temperature over the weekend. Aq. sodium bicarbonate is added and the mixture partitioned between EtOAc, brine, and aq. sodium bicarbonate. The organic layers are dried over MgSO₄ and taken to dryness. The residue is chromatographed on silica gel (120 mL) using CH₃OH-CH₂Cl₂ (4/96) to give 1.26 g (72%) of the title compound as a white solid. An aliquot is crystallized from CH₂Cl₂-EtOAc-hexane. IR (drift) 1597, 1587, 1458, 1441, 1342, 1329, 1269, 1156, 1145, 1110, 1045, 860, 785, 749, 726 cm⁻¹; ¹H NMR (CDCl₃) δ 3.30, 4.29, 5.51, 6.70, 7.00, 7.12, 7.2-7.4, 8.34. Anal. Calcd for C₂₁H₂₀N₂O: C 79.72, H 6.37, N 8.85. Found: C, 78.70, H 6.41, N, 8.70.

Example 36 N-(2-[(9-Benzyl-9H-carbazol-4-yl)oxy]ethyl)-N (2-methoxyethyl)amine



A mixture of 2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethylamine (0.103 g, 0.327 mmol)
 5 2-bromoethylmethyl ether (0.050 g, 0.359 mmol), diisopropylethylamine (0.0464 g, 0.359 mmol), acetonitrile (1 mL), and THF (1 mL) is stirred at room temperature for 40 min and then at 70 °C for 43 h. After cooling, the solvents are removed and the residue is chromatographed on silica gel (15 mL) using CH₃OH/CH₂Cl₂ (4/96). The pure product fractions are concentrated to dryness to give 0.044 g (36%) of an oil. Maleic acid (0.013 g)
 10 is added and the salt is crystallized from CH₂Cl₂/CH₃OH/hexane to give the title compound mp 175.0-175.5 °C. ¹H NMR (CDCl₃) δ 2.98, 3.26, 3.39, 3.57, 4.38, 5.51, 6.70, 6.99, 7.12, 7.2-7.4, 8.33. Anal. Calcd for C₂₄H₂₆N₂O₂•C₄H₄O₄: C, 68.56, H, 6.16, N, 5.71. Found C, 68.54, H, 6.22, N, 5.81.

15 Example 37 N-Ethyl-N-([(1-phenyl-1,2-dihydro[1,4]oxazino[2,3-4-jk]carbazol-7-yl)oxy]ethyl)amine, maleic acid salt

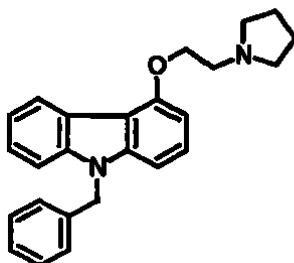


To a mixture of N-(2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)acetamide (0.3043 g, 0.849 mmol) and dry THF (7 mL) is added borane-methylsulfide complex (0.24 mL, 2.55 mmol) while under argon atmosphere. The mixture is refluxed at 85 °C for 18 h. Methanol is slowly added to consume unreacted borane complex. The mixture is stripped of solvent, then MeOH (5.0 mL) is added then stripped. The oil is dissolved in methanol/CH₂Cl₂ (10/1), to which is added concentrated hydrochloric acid (1.0 mL). The mixture is heated at 65 °C
 25 for 0.5 h. Water (5.0 mL) is added and the mixture neutralized with potassium carbonate,

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289

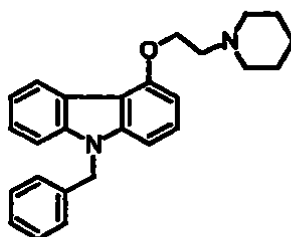
then partitioned between CH_2Cl_2 and water. The organic layer is washed with water and dried over magnesium sulfate. Column chromatography (50g silica gel) using methanol/ CH_2Cl_2 (5/95) gave an oil which is converted to the maleic acid salt to give 0.1445 g (60%) of the title compound. ^1H NMR (300 MHz, DMSO-d_6) δ 1.24, 3.16, 3.55, 4.47, 5.64, 5.99, 6.78, 7.09, 7.24, 7.37, 7.57, 8.30, 8.61. Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O} \cdot \text{C}_4\text{H}_4\text{O}_4$: C, 70.42, H, 6.13, N, 6.08. Found: C, 70.27, H, 6.22, N, 6.03.

Example 38 9-Benzyl-4-[2-(1-pyrrolidinyloxy)]-9H-carbazole



A mixture of 9-benzyl-4-(2-bromoethoxy)-9H-carbazole (0.020 g, 0.0526 mmol) pyrrolidine (0.040 g, 0.562 mmol) and acetonitrile (1.0 mL) is stirred over the weekend at room temperature. Much starting material remained so the mixture is heated at 75°C in a capped vial for 24 h. After cooling and removal of the solvent, the residue is partitioned between CH_2Cl_2 and aq. sodium bicarbonate. The organic layers are dried over sodium sulfate, chromatography on silica gel eluting with $\text{CH}_3\text{OH}-\text{CH}_2\text{Cl}_2$ (4/96) gave 0.0165 g (85%) of the title compound as a waxy solid. ^1H NMR (CDCl_3) δ 1.97, 3.04, 3.36, 4.59, 5.30, 6.71, 7.02, 7.12, 7.2-7.4, 8.32. Anal. Calcd for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}$: C, 81.05, H, 7.07, N, 7.56. Found: C, 79.84, H, 7.02, N, 7.44.

Example 39 9-Benzyl-4-[2-(1-piperidinyloxy)]-9H-carbazole



In the same manner as for 9-Benzyl-4-[2-(1-pyrrolidinyloxy)]-9H-carbazole, 80 (0.020 g) and piperidine (0.040 g) gave 0.0196 g (97%) of the title compound. mp $113.5-114.5^\circ\text{C}$. ^1H NMR (CDCl_3) δ 1.52, 1.73, 2.78, 3.14, 4.50, 5.51, 6.70, 7.00, 7.12, 7.2-7.4,

8 35 Anal Calcd for $C_{26}H_{28}N_2O$ C, 81.21 H 7.34 N 7.28 Found C, 80.59 H, 7.31, N 7.22 CH CH

Preparation 19 tert-Butyl 4-{2-[(9-Benzyl-9H-carbazol-4-yl)oxy]ethyl}-1-

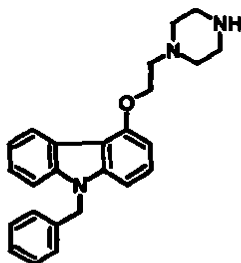
5 piperazinecarboxylate

A mixture of 9-benzyl-4-(2-bromoethoxy)-9H-carbazole (0.0647 g, 0.170 mmol), Boc-piperazine (0.0380 g, 0.204 mmol), triethylamine (0.0206 g 0.204 mmol), and acetonitrile (2 mL) is heated at reflux for 24 h. After cooling the mixture is partitioned between CH_2Cl_2 and aq sodium bicarbonate. The organic layers are dried over sodium sulfate, chromatography on silica gel eluting with $CH_3OH-CH_2Cl_2$ (2/98) gave poor separation of product and impurities. Re-chromatography (silica gel, 20 mL) using acetone-hexane (10/90 to 20/80) gave 0.0650 g (83%) of the title compound, IR (drift) 1693, 1457, 1420 1365, 1341 1332 1291 1266, 1243 1174 1154 1145 1129 1112, 752 cm^{-1} ^1H NMR ($CDCl_3$) δ 1.46, 2.65, 3.06, 3.48, 4.41, 5.51, 6.69, 6.99, 7.12, 7.2-7.4, 8.37. Anal.

10 Calcd for $C_{30}H_{33}N_3O_3$ C 74.20 H, 7.26, N 8.65 Found C, 73.82, H, 7.41, N, 8.52

15

Example 40 9-Benzyl-4-[2-(1-piperazyl)ethoxy]-9H-carbazole



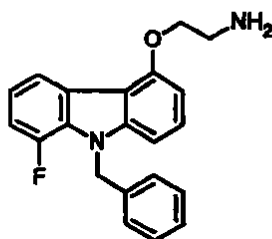
A mixture of tert-Butyl 4-{2-[(9-Benzyl-9H-carbazol-4-yl)oxy]ethyl}-1-

20 piperazinecarboxylate (0.0450 g, 0.0927 mmol), trifluoroacetic acid (2.5 mL), and CH_2Cl_2 (2.5 mL) is stirred at room temperature for 1 h. Trifluoroacetic acid and CH_2Cl_2 are then removed in vacuo and the residue is partitioned between CH_2Cl_2 and aq sodium bicarbonate. The organic layers are dried over sodium sulfate and taken to dryness to give 0.0326 g (91%) of the title compound, IR (drift) 2935, 2821, 1584, 1456 1353, 1342,

25 1332 1271, 1245 1154, 1145, 1112 783, 750, 715 cm^{-1} , ^1H NMR ($CDCl_3$) δ 2.70 2.95 3.04 4.41, 5.50 6.69 6.99, 7.12 7.2-7.4 8.39. Anal. Calcd for $C_{25}H_{27}N_3O$ C, 77.89 H, 7.06 N 10.90 Found C, 76.35, H 7.20, N 10.30

7/6
29/1

Example 41 2-[(9-Benzyl-8-fluoro-9H-carbazol-4-yl)oxy]ethylamine



5

A mixture of 2-[(9-benzyl-8-fluoro-9H-carbazol-4-yl)oxy]acetonitrile (0.7685 g, 0.0023 mol), dry THF (20 mL) and borane-methyl sulfide (0.71 mL, 0.0075 mol) is stirred at room temperature for 3.5 h. Additional borane-methyl sulfide (0.20 mL, 0.0021 mol) is added and the mixture is stirred overnight. The excess borane is cautiously quenched with methanol and the mixture is concentrated under reduced pressure. Methanol and dichloromethane are added to the residue and the solution is again concentrated under reduced pressure (repeated twice). The solids are then dissolved in methanol/dichloromethane and conc. HCl (3 mL) is added. After the mixture is stirred for 50 min, the solvent is removed under reduced pressure and the residue is partitioned between dichloromethane and aq. sodium bicarbonate. The combined organic layers are dried over sodium sulfate and concentrated to dryness. The residue is chromatographed on silica gel (100 mL) using methanol/dichloromethane (2/98 and 4/96) and recrystallized from ethyl acetate/dichloromethane/heptane to give 0.333 g (43%) of the title compound. mp 122-123 °C, MS (ESI+) for $C_{21}H_{19}FN_2O$ m/z 335.2 ($M+H$)⁺, IR (drift) 1602, 1577, 1498, 1456, 1443, 1352, 1337, 1325, 1269, 1254, 1242, 1228, 1141, 792, 736 cm^{-1} , ¹H NMR (CDCl₃) δ 3.30, 4.28, 5.30, 6.70, 7.01, 7.11, 7.22, 7.36, 8.10, NH₂ not seen. Anal. Calcd for $C_{21}H_{19}FN_2O$: C, 75.43, H, 5.73, N, 8.38. Found: C, 75.25, H, 5.79, N, 8.28.

Preparation 20 8-Fluoro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydro-4H-carbazol-4-one

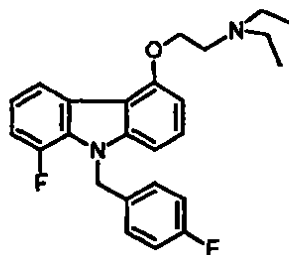
8-Fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.1416 g, 0.70 mmol) is added to a slurry of pentane-washed NaH (0.0400 g, 0.0010 mol) in DMF (2 mL) and after stirring for 30 min, p-fluorobenzyl bromide (0.11 mL, 0.88 mmol) is added. After the mixture had stirred for 2.3 h, it is partitioned between aq. sodium bicarbonate and ethyl acetate. The organic layer is dried over sodium sulfate and concentrated to dryness. The resulting solids

are chromatographed on silica gel (100 mL) using first dichloromethane (100%) and then methanol/dichloromethane (2/98). The product fractions are combined and rechromatographed on silica gel (50 mL) using acetone/heptane/ NH_4OH (15/85/0.25) and then recrystallized using ethyl acetate/hexane to give 0.0932 g (43%) of the title compound, mp 177-178 °C, MS (ESI-) for $\text{C}_{19}\text{H}_{13}\text{F}_2\text{NO}$ m/z 310.1 (M-H), IR (drift) 1638, 1630, 1509, 1496, 1459, 1436, 1413, 1361, 1249, 1222, 1194, 1158, 1125, 830, 790 cm^{-1} , ^1H NMR (CDCl_3) δ 2.24, 2.58, 2.86, 5.47, 6.89-7.02, 7.16, 8.06. Anal. Calcd for $\text{C}_{19}\text{H}_{13}\text{F}_2\text{NO}$: C, 73.30; H, 4.86; N, 4.50. Found: C, 73.40; H, 4.83; N, 4.50.

10 Preparation 21 8-Fluoro-9-(4-fluorobenzyl)-9H-carbazol-4-ol

Pyridinium bromide perbromide (0.0860 g, 0.27 mmol) is added to a solution of 8-fluoro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydro-4H-carbazol-4-one in THF (0.5 mL) and DMF (0.5 mL) and the mixture is heated to 75 °C. After stirring for 4.5 h, THF is removed under reduced pressure and the residue is partitioned between ethyl acetate and dilute brine. The combined organic layers are washed with dilute sodium sulfate/brine and the aqueous layer is backwashed with ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to give a residue. A mixture of the resulting residue, lithium bromide (0.0428 g, 0.49 mmol), lithium carbonate (0.0311 g, 0.42 mmol) and DMF (1 mL) is heated at 120 °C for two hours. The mixture is partitioned between ethyl acetate and brine. The combined organic layers are dried over sodium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (20 mL) using ethyl acetate/heptane (5/95 and 10/90) to give 0.0460 g (71%) of the title compound, MS (ESI-) for $\text{C}_{19}\text{H}_{13}\text{F}_2\text{NO}$ m/z 308.1 (M-H), IR (drift) 1580, 1508, 1461, 1434, 1329, 1274, 1242, 1235, 1221, 1157, 1129, 907, 788, 755, 732 cm^{-1} , ^1H NMR (CDCl_3) δ 5.37, 5.64, 6.60, 6.94, 7.14, 7.28, 8.10. Anal. Calcd for $\text{C}_{19}\text{H}_{13}\text{F}_2\text{NO}$: C, 73.78; H, 4.24; N, 4.53. Found: C, 72.52; H, 4.18; N, 4.37.

Example 42 N,N-Diethyl-N-(2-([8-fluoro-9-(4-fluorobenzyl)-9H-carbazol-4-yl]oxy)ethyl)amine



8-Fluoro-9-(4-fluorobenzyl)-9H-carbazol-4-ol (0.0226 g, 0.073 mmol), 2-diethylaminoethylchloride hydrochloride (0.0202 g, 0.12 mmol), potassium carbonate (0.0330 g, 0.24 mmol), sodium iodide (0.0018 g, 0.012 mmol) and DMF (1 mL) are heated at 80 °C for 3 h. After the mixture had cooled it is partitioned between water and ethyl acetate. The organic layer is dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (20 mL) using methanol/dichloromethane (2/98 and 4/96) to give 0.0222 g (74%) of the title compound, mp 59-60 °C, MS (ESI+) for $C_{25}H_{27}F_2N_2O$ m/z 409.3 (M+H)⁺, ¹H NMR (CDCl₃) δ 1.21, 2.87, 3.22, 4.45, 5.67, 6.74, 6.94, 7.02, 7.14, 7.39, 8.11. Anal. Calcd for $C_{25}H_{26}F_2N_2O$ C, 73.51, H, 6.41, N, 6.86. Found C 73.05, H, 6.61, N, 6.83.

15 Preparation 22 6-Chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one

4-Chlorophenylhydrazine hydrochloride (5.3766 g, 0.0300 mol) is added portionwise to a solution of 1,3-cyclohexanedione (3.29 g, 0.029 mol) in water (58 mL) and the mixture is allowed to stir over night at room temperature. The resulting solids are collected by filtration, washed with water, and vacuum dried at 50 °C overnight to give the hydrazone. The hydrazone (0.5249 g, 0.0022 mol) is then heated at reflux in trifluoroacetic acid (3 mL) for 7 h, at which time the heat is turned off and the mixture is allowed to stir overnight at room temperature. Additional trifluoroacetic acid (1 mL) then is added and the mixture is stirred at reflux another 7h and stored in the refrigerator overnight. The mixture is partitioned between water and dichloromethane. The organic layer is washed with aq sodium bicarbonate and the aqueous layer is backwashed with dichloromethane. The combined organic layers are then dried over magnesium sulfate and concentrated to solids. The solids are chromatographed on silica gel (100 mL) using ethyl acetate/dichloromethane and then recrystallized from ethyl acetate/dichloromethane/methanol to give 0.0872 g (15%) of the title compound, MS (ESI-) for $C_{12}H_{10}ClNO$ m/z 218.0 (M-H), IR (drift) 3201, 3172

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294

3137 3109, 3063 2954 2933 1631 1578 1472 1373 1013 879, 811 623 cm^{-1} ^1H NMR
(CD_3OD) δ 2.22, 2.54 3.00 7.16 7.32, 7.97, NH not seen Anal. Calcd for $\text{C}_{12}\text{H}_{10}\text{ClNO}$
C, 65.61, H, 4.59 N, 6.38 Found C, 65.49 H, 4.51, N, 6.32

5 Preparation 23 9-Benzyl-6-chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one

6-Chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.4010 g, 0.0018 mol) is added to a
slurry of pentane-washed NaH (0.0902 g, 0.0023 mol) in DMF (2 mL) and after stirring for
27 min, benzyl bromide (0.26 mL, 0.0022 mol) is added. After stirring for 2.5 h at room
temperature, the mixture is partitioned between aq. sodium bicarbonate and ethyl acetate.

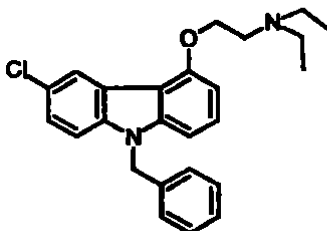
- 10 The combined organic layers are dried over sodium sulfate and concentrated to dryness.
The resulting solids are chromatographed on silica gel (200 mL) using
dichloromethane/heptane (60/40 and 100/0) to give 0.5158 g (91%) of the title compound.
An aliquot (0.0625 g) is recrystallized from ethyl acetate/heptane to give 0.0415 g of
product, mp 196.5-197 °C, MS (ESI+) for $\text{C}_{19}\text{H}_{16}\text{ClNO}$ m/z 310.1 ($\text{M}+\text{H}$) $^+$, ^1H NMR
15 (CDCl_3) δ 2.24, 2.58, 2.87, 5.31, 6.99, 7.16, 7.29, 8.28 Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{ClNO}$ C,
73.66 H, 5.20, N, 4.52 Found C 73.18, H 5.19, N, 4.58

Preparation 24 9-Benzyl-6-chloro-9H-carbazol-4-ol

- Pyridinium bromide perbromide (0.5495 g, 0.0017 mol) is added to a solution of 9-
20 benzyl-6-chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.4406 g, 0.0014 mol) in THF (2.8
mL) and DMF (1.5 mL) and the mixture is heated to 75 °C. After stirring for 5 h, THF is
removed under reduced pressure and the residue is partitioned between dichloromethane and
brine. The combined organic layers are washed with dilute sodium thiosulfate/brine and the
aqueous layer is backwashed with dichloromethane. The combined organic layers are dried
25 over magnesium sulfate and concentrated under reduced pressure to give a residue. A
mixture of the resulting residue, lithium bromide (0.2799 g, 0.0032 mol), lithium carbonate
(0.2286 g, 0.0031 mol) and DMF (6 mL) is heated at 120 °C for two hours. The DMF is
removed under high vacuum and the residue is partitioned between dichloromethane and
water. The combined organic layers are dried over sodium sulfate and concentrated to an
30 oil. The oil is chromatographed on silica gel (100 mL) using dichloromethane (100%) to
give 0.3139 g (72%) of the title compound. An aliquot (0.0391) is recrystallized from
dichloromethane/methanol/hexane to give 0.0272 g of product, MS (ESI-) for $\text{C}_{19}\text{H}_{14}\text{ClNO}$
 m/z 306.0 ($\text{M}-\text{H}$), IR (neat) 1470, 1452, 1334, 1293, 1284, 1266, 1231, 1146, 1112, 885,

796, 777, 746, 717 702 cm^{-1} , $^1\text{H NMR}$ (CDCl_3) δ 5.41, 5.49, 6.60, 6.97, 7.13, 7.28, 7.35, 8.33. Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{ClNO}$: C, 74.15, H, 4.59, N, 4.55, Cl, 11.52. Found: C, 73.07, H, 4.63, N, 4.59.

- 5 Example 43 N-{2-[(9-Benzyl-6-chloro-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine



- 9-Benzyl-6-chloro-9H-carbazol-4-ol (0.0616 g, 0.20 mmol), 2-diethylaminoethylchloride hydrochloride (0.0517 g, 0.30 mmol), potassium carbonate (0.0863 g, 0.62 mmol), sodium iodide (0.0027 g, 0.018 mmol) and DMF (1 mL) are heated at 85 °C for 3.5 h. After the mixture had cooled, it is partitioned between water and ether. The combined organic layers are dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (60 mL) using methanol/dichloromethane (1/99 to 2/98 to 4/96) to give 0.0665 g (82%) of the title compound, mp 96-97.5 °C. MS (ESI+) for $\text{C}_{25}\text{H}_{27}\text{ClN}_2\text{O}$ m/z 407.3 ($\text{M}+\text{H}^+$), IR (drift) 2966, 1583, 1466, 1453, 1340, 1268, 1242, 1149, 1124, 1069, 795, 780, 745, 718, 708 cm^{-1} , $^1\text{H NMR}$ (CDCl_3) δ 1.16, 2.75, 3.12, 4.34, 5.47, 6.69, 6.97, 7.08, 7.21-7.38, 8.34. Anal. Calcd for $\text{C}_{25}\text{H}_{27}\text{ClN}_2\text{O}$: C, 73.79, H, 6.69, N, 6.88. Found: C, 73.39, H, 6.73, N, 6.78.
- 20 Preparation 25 6-Chloro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydro-4H-carbazol-4-one
- 6-Chloro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.4042 g, 0.0018 mol) is added to a slurry of pentane-washed NaH (0.091 g, 0.0023 mol) in DMF (2 mL) and after stirring for 20 min, p-fluorobenzyl bromide (0.28 mL, 0.0023 mol) is added. Additional DMF (1 mL) is added and the mixture is stirred for 4 h, at which time the mixture is partitioned between aq. sodium bicarbonate and ethyl acetate. The combined organic layers are washed with water, dried over sodium sulfate and concentrated to dryness. The resulting solids are chromatographed on silica gel (200 mL) using dichloromethane/heptane (60/40 and 80/20) to give 0.5519 g (92%) of the title compound, mp 207-207.75 °C, MS (ESI+) for $\text{C}_{19}\text{H}_{15}\text{ClFNO}$ m/z 328.1 ($\text{M}+\text{H}^+$), IR (drift) 1628, 1511, 1467, 1448, 1360, 1226, 1218

1145 1096 878 849 840 804 764 649 cm^{-1} ^1H NMR (CDCl_3) δ 2.23, 2.58 2.86 5.27
6.99 7.16, 8.27 Anal. Calcd for $\text{C}_{19}\text{H}_{13}\text{ClFNO}$ C 69.62, H, 4.61, N 4.27 Found (av)
C 69.08, H, 4.50, N, 4.26

5 Preparation 26 6-Chloro-9-(4-fluorobenzyl)-9H-carbazol-4-ol

Pyridinium bromide perbromide (0.6155 g, 0.0019 mol) is added to a solution of 6-chloro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydro 4H-carbazol-4-one in THF (2.2 mL) and DMF (1.5 mL) and the mixture is heated to 75 °C. After stirring for 3.5 h, the THF is removed under reduced pressure and the residue is partitioned between dichloromethane and brine.

- 10 The combined organic layers are washed with dilute sodium thiosulfate/brine and the aqueous layer is backwashed with dichloromethane. The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to give a residue. A mixture of the resulting residue, lithium bromide (0.3077 g, 0.0036 mol), lithium carbonate (0.2376 g, 0.0032 mol) and DMF (6 mL) is heated at 120 °C for two hours. The DMF is
15 removed under high vacuum and the residue is partitioned between dichloromethane and water. The combined organic layers are dried over sodium sulfate and concentrated to dryness. The residue is chromatographed on silica gel (125 mL) using dichloromethane (100%) to give 0.3773 g (73%) of the title compound. An aliquot is recrystallized from dichloromethane/hexane. MS (ESI-) for $\text{C}_{19}\text{H}_{13}\text{ClFNO}$ m/z 324.1 (M-H), IR (drift) 1510,
20 1468, 1444 1335, 1297, 1263, 1232, 1218 1147, 1116, 832 822, 791, 778, 745 cm^{-1} , ^1H NMR (CDCl_3) δ 5.37 5.43, 6.59 6.94 7.07 7.23, 7.33 8.31 Anal. Calcd for $\text{C}_{19}\text{H}_{13}\text{ClFNO}$ C, 70.05, H, 4.02, N 4.30, Cl, 10.88 Found C 68.51, H, 3.96, N, 4.27

25 Preparation 27 N-(2-([6-Chloro-9-(4-fluorobenzyl)-9H-carbazol-4-yl]oxy)ethyl)-N,N-diethylamine

- 6-Chloro-9-(4-fluorobenzyl)-9H-carbazol-4-ol (0.0619 g, 0.19 mmol) 2-diethylaminoethylchloride hydrochloride (0.0494 g, 0.29 mmol) potassium carbonate (0.0750 g, 0.54 mmol) sodium iodide (0.0021 g, 0.014 mmol) and DMF (1 mL) are heated at 85 °C for 4 h. After the mixture had cooled, it is partitioned between water and ether.
30 The aqueous layer is also extracted with ethyl acetate several times. The combined organic layers are dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (75 mL) using methanol/dichloromethane (1/99 to 2/98 to 4/96) to give 0.0591 g (73%) of the title compound mp 99-99.5 °C, MS (ESI+) for

$C_{23}H_{26}ClFN_2O$ m/z 425 2 (M+H)⁺, IR (drift) 2972, 1588, 1507, 1467, 1454 1342, 1270 1221, 1151 1123 817, 799 778 740 714 cm^{-1} , ^1H NMR ($CDCl_3$) δ 1 15 2 75, 3 12, 4 33 5 44 6 71, 6 93, 7 04, 7 20, 7 34, 8 33 Anal Calcd for $C_{23}H_{26}ClFN_2O$ C, 70 66, H 6 17, N 6 59 Found C 70 23 H, 6 05 N 6 61

5

Preparation 28 6-Fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one

4-Fluorophenylhydrazine hydrochloride (4 5697 g, 0 0281 mol) is added in portions to a solution of 1,3-cyclohexanedione (3 11 g 0 0277 mol) in water (55 mL) The mixture is allowed to shake overnight at room temperature. Additional 4-fluorophenylhydrazine hydrochloride (0 1052 g 0 65 mmol) is added and the mixture is shaken another 6 h. After sitting at room temperature overnight the mixture is extracted with ethyl acetate. The organic layer is washed with water and the aqueous layer is backwashed with ethyl acetate. The combined organic layers are dried over sodium sulfate and concentrated to give the hydrazone The hydrazone and trifluoroacetic acid (37 mL) are heated at 85 °C for 3 5h. After cooling the mixture is partitioned between water and dichloromethane. The combined organic layers are washed with aq sodium bicarbonate and the aqueous layer is washed with dichloromethane. The combined organic layers are dried over magnesium sulfate and concentrated to a foam. The foam is chromatographed on silica gel (200 mL) using ethyl acetate/dichloromethane (5/95 to 10/90 to 20/80) and recrystallized from ethyl acetate/methanol/hexane to give 0 6197 g (11%) for a first crop and 0 3281 g (6%) for a second crop of the title compound, MS (ESI-) for $C_{12}H_{10}FNO$ m/z 202 0 (M-H), IR (drift) 3231, 3183, 2942, 1638, 1623, 1482, 1468, 1377, 1203 1173, 1131, 914, 856, 804, 793 cm^{-1} , ^1H NMR (CD_3OD) δ 2 22 2 54 3 00 6 95, 7 32 7 66 NH not seen. Anal Calcd for $C_{12}H_{10}FNO$ C, 70 93 H, 4 96, N, 6 89 Found C, 70 76, H, 5 05, N, 6 85

25

Preparation 29 9-Benzyl-6-fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one

6-Fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0 3938 g 0 0019 mol) is added to a slurry of pentane-washed NaH (0 0970 g 0 0024 mol) in DMF (3 mL) and after stirring for 10 min, benzyl bromide (0 28 mL, 0 0024 mol) is added After stirring for 4 h at room temperature the mixture is partitioned between water and ethyl acetate. The combined organic layers are dried over sodium sulfate and concentrated to dryness The resulting solids are chromatographed on silica gel (200 mL) using dichloromethane/heptane (60/40 to 80/20 to 100/0) to give 0 3681 g (65%) of the title compound An aliquot is recrystallized

from ethyl acetate/heptane MS (ESI+) for $C_{19}H_{16}FNO$ m/z 294.2 ($M+H$)⁺, IR (drift) 1634, 1523, 1483, 1466, 1447, 1357, 1254, 1138, 900, 868, 803, 799, 759, 729, 700 cm^{-1} , ¹H NMR (CDCl₃) δ 2.22, 2.59, 2.88, 5.32, 6.95, 7.01, 7.15, 7.30, 7.96. Anal. Calcd for $C_{19}H_{16}FNO$: C, 77.80; H, 5.50; N, 4.78. Found: C, 77.65; H, 5.39; N, 4.69.

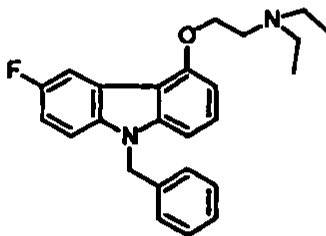
5

Preparation 30 9-Benzyl-6-fluoro-9H-carbazol-4-ol

Pyridinium bromide perbromide (0.4620 g, 0.0014 mol) is added to a mixture of 9-benzyl-6-fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.3271 g, 0.0011 mol) in THF (3.4 mL) and DMF (2.4 mL) and the mixture is heated to 75 °C. After stirring for 6.5 h, the mixture is stored in the freezer overnight. Heating is resumed for an additional 2.5 h, at which time THF is removed under reduced pressure and the residue is partitioned between dichloromethane and brine. The combined organic layers are washed with dilute sodium thiosulfate/brine and the aqueous layer is backwashed with dichloromethane. The combined organic layers are dried over sodium sulfate and concentrated under reduced pressure to give a residue. The residue is heated to 120 °C in DMF (5 mL) with lithium bromide (0.2348 g, 0.0027 mol) and lithium carbonate (0.1813 g, 0.0025 mol). After 2 h, DMF is removed under high vacuum and the mixture is partitioned between dichloromethane and water. The combined organic layers are washed with water and the aqueous layer is backwashed with dichloromethane. The combined organic layers are dried over sodium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (100 mL) using dichloromethane/hexane (30/70 and 50/50) to give 0.1893 g (58%) of the title compound. An aliquot is precipitated from hexane/ether; MS (ESI+) for $C_{19}H_{14}FNO$ m/z 292.2 ($M+H$)⁺, IR (drift) 1483, 1466, 1451, 1337, 1304, 1174, 1157, 1138, 884, 859, 794, 777, 745, 713, 700 cm^{-1} , ¹H NMR (CDCl₃) δ 5.34, 5.47, 6.56, 6.95, 7.13, 7.20, 7.30, 8.01. Anal. Calcd for $C_{19}H_{14}FNO$: C, 78.33; H, 4.84; N, 4.81. Found: C, 78.17; H, 4.83; N, 4.78.

25

Example 44 N-{2-[(9-Benzyl-6-fluoro-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine



304
299

9-Benzyl-6-fluoro-9H-carbazol-4-ol (0 0587 g 0 20 mmol) 2-diethylaminoethylchloride hydrochloride (0 0524 g 0 30 mmol) potassium carbonate (0 0872 g 0 63 mmol) sodium iodide (0 0062 g, 0 041 mmol) and DMF (2 mL) are heated at 85 °C for 3 h. After the mixture had cooled, it is partitioned between water and ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (50 mL) using methanol/dichloromethane (1/99 to 3/97) to give 0 0485 g (62%) of the title compound, mp 68-69 °C, MS (ESI+) for $C_{23}H_{27}FN_2O$ m/z 391 3 (M+H)⁺, IR (drift) 2966 1584, 1483 1463 1345 1268 1185 1162, 1145, 1052, 799, 778, 741, 726, 713 cm^{-1} , ¹H NMR (CDCl₃) δ 1 14, 2 73, 3 10, 4 33, 5 48, 6 68 6 97 7 11, 7 21, 7 35, 8 03. Anal. Calcd for $C_{23}H_{27}FN_2O$ C, 76 89, H 6 97, N 7 17. Found C, 77 16 H, 7 28, N 7 16.

Preparation 31 6-Fluoro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydro-4H-carbazol-4-one

6-Fluoro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0 3940 g 0 0019 mol) is added to a slurry of pentane-washed NaH (0 0966 g 0 0024 mol) in DMF (3 mL) and after stirring for 10 min, p-fluorobenzyl bromide (0 29 mL, 0 0023 mol) is added. After stirring for 4 h at room temperature the mixture is partitioned between water and ethyl acetate. The combined organic layers are dried over sodium sulfate and concentrated to dryness. The resulting solids are chromatographed on silica gel (100 mL) using methanol/dichloromethane (0 5/99 5) to give 0 5678 g (94%) of the title compound. An aliquot is recrystallized from ethyl acetate/heptane mp 182 5-183 °C MS (ESI+) for $C_{19}H_{15}F_2NO$ m/z 312 2 (M+H)⁺, IR (drift) 1631 1511, 1483 1466, 1449, 1256 1228, 1218 1137 1094, 867, 836, 813 808, 802 cm^{-1} ¹H NMR (CDCl₃) δ 2 24 2 58 2 86 5 28 6 94 7 13 7 96. Anal. Calcd for $C_{19}H_{15}F_2NO$ C, 73 30, H, 4 86, N, 4 50. Found C, 73 27, H, 4 92, N 4 54.

Preparation 32 6-Fluoro-9-(4-fluorobenzyl)-9H-carbazol-4-ol

Pyridinium bromide perbromide (0 7068 g 0 0022 mol) is added to a mixture of 6-fluoro-9-(4-fluorobenzyl)-1,2,3,9-tetrahydro-4H-carbazol-4-one (0 5245 g, 0 0017 mol) in THF (4 mL) and DMF (4 mL) and the mixture is heated to 75 °C. After stirring for 6 5 h, the mixture is stored in the freezer overnight. Heating is resumed for an additional 2 5 h, at which time THF is removed under reduced pressure and the residue is partitioned between dichloromethane and brine. The combined organic layers are washed with dilute sodium thiosulfate/brine and the aqueous layer is backwashed with dichloromethane. The combined

organic layers are dried over sodium sulfate and concentrated under reduced pressure to give a residue. The residue is heated to 120 °C in DMF (8 mL) with lithium bromide (0.3412 g, 0.0039 mol) and lithium carbonate (0.2548 g, 0.0035 mol). After 2 h, DMF is removed under high vacuum and the mixture is partitioned between dichloromethane and water. The combined organic layers are washed with water, dried over sodium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (100 mL) using dichloromethane/hexane (30/70 to 50/50) to give 0.2706 g (52%) of the title compound, MS (ESI-) for $C_{19}H_{13}F_2NO$ m/z 308.0 (M-H), IR (drift) 1511, 1483, 1465, 1450, 1336, 1222, 1215, 1172, 1157, 1138, 883, 858, 791, 777, 744 cm^{-1} , ^1H NMR ($CDCl_3$) δ 5.35, 5.44, 6.57, 6.95, 7.06-7.30, 8.01. Anal. Calcd for $C_{19}H_{13}F_2NO$: C, 73.78, H, 4.24, N, 4.53. Found: C, 72.65, H, 4.20, N, 4.45.

Preparation 33 N,N-Diethyl-N-(2-([6-fluoro-9-(4-fluorobenzyl)-9H-carbazol-4-yl]oxy)ethyl)amine

6-Fluoro-9-(4-fluorobenzyl)-9H-carbazol-4-ol (0.0584 g, 0.19 mmol), 2-diethylaminoethylchloride hydrochloride (0.0593 g, 0.35 mmol), potassium carbonate (0.0926 g, 0.63 mmol), sodium iodide (0.0061 g, 0.041 mmol) and DMF (2 mL) are heated at 85 °C for 3 h. After the mixture had cooled, it is partitioned between water and ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (50 mL) using methanol/dichloromethane (1/99) to give 0.0471 g (61%) of the title compound, mp 75-76 °C, MS (ESI+) for $C_{25}H_{26}F_2N_2O$ m/z 409.3 (M+H)⁺, IR (drift) 1585, 1507, 1481, 1461, 1343, 1269, 1221, 1159, 1145, 871, 820, 799, 776, 739, 712 cm^{-1} , ^1H NMR ($CDCl_3$) δ 1.14, 2.73, 3.10, 4.33, 5.44, 6.69, 6.93, 7.04-7.18, 7.36, 8.03. Anal. Calcd for $C_{25}H_{26}F_2N_2O$: C, 73.51, H, 6.41, N, 6.86. Found: C, 73.30, H, 6.59, N, 6.77.

Preparation 34 6-Methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one

p-Tolylhydrazine hydrochloride (8.6693 g, 0.0547 mol) is added in portions to a solution of 1,3-cyclohexanedione (6.00 g, 0.053 mol) in water (100 mL). The mixture is allowed to stir for three days at room temperature. The resulting solids are collected by filtration, washed with water and vacuum dried at 56 °C for 30 min and then overnight at room temperature to give the hydrazone. The hydrazone, p-toluene sulfonic acid monohydrate (8.31 g, 0.044 mol) and toluene (350 mL) are heated at 120 °C for 2.5 h.

After cooling the toluene layer is decanted and washed with water and aq sodium bicarbonate then dried over sodium sulfate and concentrated to dryness. The residue left behind in the round bottom flask is dissolved in dichloromethane and washed with water and aq sodium bicarbonate (emulsion observed) and the organic layer is dried over sodium sulfate and concentrated to dryness. The solids in the emulsion are collected and washed with water followed by ether and vacuum dried at room temperature to give 3.2168 g (39%) of the title compound. The solids obtained from the extractions are combined and chromatographed on silica gel (250 mL) using methanol/dichloromethane (0/100 to 2/98 to 4/96) and then triturated in ethyl acetate/dichloromethane/methanol/heptane to give 0.4377 g (5%) of the title compound. An aliquot is chromatographed on silica gel (15 mL) using dichloromethane (100 %) and then precipitated from dichloromethane/methanol/hexane, mp > 255 °C. MS (ESI-) for $C_{13}H_{13}NO$ m/z 198.0 (M-H), IR (drift) 3182, 3155, 3121, 3079, 3062, 3027, 2936, 1615, 1586, 1471, 1377, 1215, 1185, 1123, 798 cm^{-1} , ^1H NMR (CD_3OD) δ 2.21, 2.41, 2.53, 2.98, 7.02, 7.23, 7.83. NH not seen. Anal. Calcd for $C_{13}H_{13}NO$ C, 78.36, H, 6.58, N, 7.03. Found (av) C, 77.70, H, 6.55, N, 6.96.

Preparation 35 9-Benzyl-6-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one

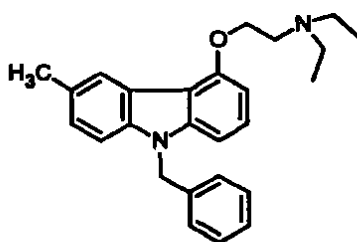
6-Methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one (7.6342 g, 0.038 mol) is added to a slurry of pentane-washed NaH (1.9563 g, 0.049 mol) in DMF (43 mL) and, after stirring for 20 min, benzyl bromide (0.58 mL, 0.0011 mol) is added. The mixture is cooled with a cold water bath and additional DMF (9 mL) is added to thin the slurry. After the slurry is stirred for 34 min, it is partitioned between water and ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated to dryness. The resulting solids are recrystallized from ethyl acetate/dichloromethane/heptane to give 9.23 g (83%) of the title compound. The filtrate from the recrystallization is chromatographed on silica gel (225 mL) using methanol/dichloromethane (1/99) to give 1.14 g (10%) of the title compound, mp 179-179.5 °C, MS (ESI+) for $C_{20}H_{19}NO$ m/z 290.1 (M+H)⁺, IR (drift) 2938, 1631, 1521, 1468, 1447, 1386, 1360, 1189, 1105, 953, 795, 757, 731, 702, 654 cm^{-1} , ^1H NMR ($CDCl_3$) δ 2.21, 2.46, 2.58, 2.86, 5.30, 7.03, 7.14, 7.28, 8.11. Anal. Calcd for $C_{20}H_{19}NO$ C, 83.01, H, 6.62, N, 4.84. Found C, 82.61, H, 6.75, N, 4.76.

Preparation 36 9-Benzyl-6-methyl-9H-carbazol-4-ol

Pyridinium bromide perbromide (11.9436 g, 0.0373 mol) is added to a mixture of 9-benzyl 6-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one (8.93 g, 0.0309 mol) in dry THF (42 mL) and dry DMF (30 mL) and the mixture is heated to 75 °C. After stirring for 6 h, THF is removed under reduced pressure and the residue is partitioned between dichloromethane and brine. The combined organic layers are washed with dilute sodium thiosulfate/brine and the combined organic layers are dried over magnesium sulfate and concentrated under high vacuum to give an oil. Hexane is added to the oil and solids precipitated. These solids are upgraded by precipitation from dichloromethane/ethyl acetate/hexane and vacuum dried at room temperature. The solids are combined with lithium bromide (3.5386 g, 0.041 mol) lithium carbonate (2.7427 g, 0.037 mol) and dry DMF (72 mL) and heated at 120 °C for 1.5 h. DMF then is removed under high vacuum and the mixture is partitioned between dichloromethane and water. The combined organic layers are washed with water and the aqueous layer is backwashed with dichloromethane. The combined organic layers are dried over sodium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (300 mL) using ethyl acetate/heptane (30/70). The product fractions are rechromatographed on silica gel (200 mL) using ethyl acetate/heptane (10/90) to give 3.75 g (42%) of 9-benzyl-6-methyl-9H-carbazol-4-ol containing a significant amount of 9-benzyl-3-bromo-6-methyl-9H-carbazol-4-ol as an impurity. The material is purified by reduction of the bromide 9-Benzyl-6-methyl-9H-carbazol-4-ol. The mixture (2.25 g, 0.0078 mol) is dissolved in dry THF (8 mL) is added to a slurry of lithium aluminum hydride (0.7604 g, 0.020 mol) in dry THF (42 mL). The mixture is stirred overnight at 75-80 °C. The mixture then is cooled and water (0.8 mL) is added followed by 15% NaOH (0.8 mL) and then water (2.4 mL). The solids are removed by filtration and washed with THF. The filtrate is concentrated to dryness and the residue is chromatographed on silica gel (50 mL) using dichloromethane (100 %). Recrystallization from dichloromethane/hexane gave 1.48 g (52%) of the title compound, mp 160-161 °C, MS (ESI+) for $C_{20}H_{17}NO$ m/z 288.2 (M+H)⁺, IR (drift) 3294, 1468, 1450, 1338, 1302, 1281, 1238, 1147, 1117, 790, 779, 746, 720, 714, 703 cm^{-1} , ¹H NMR (CDCl₃) δ 2.54, 5.29, 5.47, 6.57, 6.93, 7.12, 7.23, 8.12. Anal. Calcd for $C_{20}H_{17}NO$ C, 83.59; H, 5.96; N, 4.87. Found C, 83.51; H, 6.03; N, 4.94.

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Example 45 N-{2-[(9-Benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethyl} N,N-diethylamine



9-Benzyl-6-methyl-9H-carbazol-4-ol (0.0597 g, 0.21 mmol) 2-

5 diethylaminoethylchloride hydrochloride (0.0565 g, 0.33 mmol), potassium carbonate (0.1007 g, 0.73 mmol) sodium iodide (0.0054 g, 0.036 mmol) and DMF (1 mL) are heated at 85 °C for 4.5 h. After the mixture had cooled, it is partitioned between water and ether. The aqueous layer is also washed twice with ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated to dryness. The residue is chromatographed on silica gel (60 mL) using methanol/dichloromethane (1/99 to 3/97 to 5/95) to give 0.0605 g (75%) of the title compound containing N-(2-[(9-benzyl-3-bromo-6-methyl-9H-carbazol-4-yl)oxy]ethyl)-N,N-diethylamine as an impurity. Attempts at purifying this material through recrystallization are unsuccessful, MS (ESI+) for $C_{26}H_{30}N_2O$ m/z 387.3 (M+H)⁺ ¹H NMR (CDCl₃) δ 1.17, 2.53, 2.78, 3.17, 4.37, 5.47, 6.68, 6.96, 7.11, 7.21, 7.34, 8.17.

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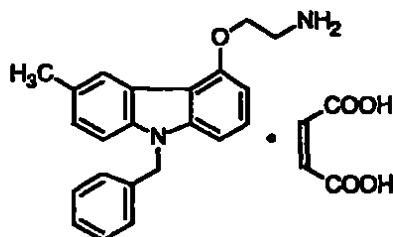
Preparation 37 2-[(9-Benzyl-6-methyl-9H-carbazol-4-yl)oxy]acetonitrile

A mixture 9-benzyl-6-methyl-9H-carbazol-4-ol (1.4172 g, 0.0049 mol), potassium carbonate (0.8184 g, 0.0059 mol), bromoacetonitrile (0.75 mL, 0.011 mol) and DMF (18 mL) is stirred at room temperature for 3 h. The mixture is then partitioned between water and dichloromethane and the combined organic layers are dried over sodium sulfate and concentrated to a residue. Water is added to the residue and solids precipitated. The solids are collected by filtration and washed with water, followed by a little hexane, and then vacuum dried at room temperature. The solids are chromatographed on silica gel (150 mL) using dichloromethane (100 %) to give 1.4723 g (91%) of the title compound. An aliquot is recrystallized from ethyl acetate/hexane, chromatographed on silica gel (50 mL) using ethyl acetate/hexane (20/80) and then recrystallized again from ethyl acetate/dichloromethane/hexane, mp 188-188.25 °C MS (ESI+) for $C_{22}H_{18}N_2O$ m/z 327.2 (M+H)⁺, IR (drift) 1497, 1467, 1447, 1365, 1340, 1305, 1264, 1237, 1152, 1126, 1053, 799, 781, 754, 711 cm⁻¹, ¹H NMR (CDCl₃) δ 2.54, 5.06, 5.49, 6.73, 7.10, 7.25, 7.36, 8.10.

Anal. Calcd for $C_{22}H_{18}N_2O$ C 80.96, H 5.56, N 8.58 Found C, 80.62, H 5.68, N, 8.55

Example 46 2-[(9-Benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethylamine

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Borane-methyl sulfide (1.2 mL, 0.013 mol) is added to a mixture of 2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]acetonitrile (1.3337 g, 0.0041 mol) in dry THF (35 mL) and the mixture is allowed to stir at room temperature for 5.5 h. The excess borane then is cautiously quenched with methanol and the mixture is concentrated under reduced pressure. Methanol and dichloromethane are added to the residue and the solution is again concentrated under reduced pressure (repeated twice). The solids are then dissolved in methanol/dichloromethane with heating and 4N HCl (10 mL) is added. The mixture is stirred for 15 min while being warmed slightly. The solvent is then removed under reduced pressure and the residue is partitioned between dichloromethane and aq. sodium bicarbonate. The combined organic layers are dried over sodium sulfate and concentrated to dryness. The residue is chromatographed on silica gel (300 mL) using methanol/dichloromethane (2/98 and 6/94) to give 0.89 g (66%) of the title compound. The salt of 2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethylamine (0.2310 g, 0.70 mmol) is formed with maleic acid in dichloromethane and recrystallized from methanol/dichloromethane/hexane to give 0.2051 g (66%) of the maleic acid salt, mp 187.5-188 °C, MS (ESI+) for $C_{22}H_{22}N_2O$ m/z 331.3 ($M+H$)⁺, IR (drift) 3027, 2984, 2926, 2887, 1601, 1579, 1497, 1483, 1465, 1364, 1344, 1267, 1150, 865, 747 cm^{-1} . ¹H NMR (CD_3OD) δ 2.52, 3.59, 4.52, 5.54, 6.23, 6.77, 7.09, 7.22, 7.33, 8.16. NH_2 not seen. Anal. Calcd for $C_{22}H_{22}N_2O \cdot C_4H_4O_4$ C, 69.94, H, 5.87, N, 6.27 Found C 69.93, H, 5.90, N, 6.29

Preparation 38 2-[(9-Benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethylformamide

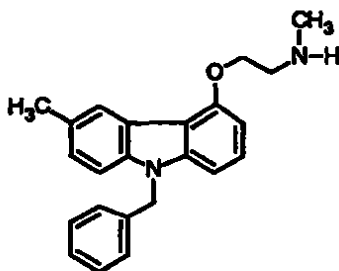
A mixture of 2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethylamine (0.2974 g, 0.90 mmol), dichloromethane (4 mL) and ethyl formate (4 mL) is heated at 62 °C

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Additional dichloromethane (6 mL) and ethyl formate (6 mL) are added. After 4 h, the mixture is concentrated to dryness and the residue is chromatographed on silica gel (100 mL) using methanol/dichloromethane (4/96). The resulting solids are recrystallized from ethyl acetate/dichloromethane/hexane to give 0.2716 g (84%) of the title compound, ¹H NMR (CDCl₃) δ 2.55, 3.94, 4.36, 5.48, 6.11, 6.64, 6.99, 7.11, 7.24, 7.32, 8.06, 8.28.

Example 47 N-{2-[(9-Benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethyl}-N-methylamine



Borane-methyl sulfide (0.12 mL, 0.0013 mol) is added to a mixture of 2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethylformamide (0.1565 g, 0.0013 mol) in dry THF (3 mL) and the mixture is stirred overnight at room temperature. The excess borane is cautiously quenched with methanol and the mixture is concentrated under reduced pressure. Methanol and dichloromethane are added to the residue and the solution is again concentrated under reduced pressure (repeated twice). The solids are then dissolved in methanol/dichloromethane and conc. HCl (27 drops) is added. After the mixture had stirred for 1.3 h, the solvent is removed under reduced pressure and the residue is partitioned between dichloromethane and aq. sodium bicarbonate. The combined organic layers are dried over sodium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (40 mL) using acetone/dichloromethane/0.25% NH₄OH (10/90, 20/80 and 50/50) to give 0.1300 g (86%) of the title compound, mp 96-96.75 °C, MS (ESI+) for C₂₃H₂₄N₂O m/z 345.2 (M+H)⁺, IR (drift) 1600, 1580, 1467, 1449, 1341, 1307, 1268, 1242, 1151, 1128, 794, 779, 744, 718, 708 cm⁻¹, ¹H NMR (CDCl₃) δ 2.54, 2.61, 3.22, 4.39, 5.48, 6.68, 6.96, 7.11, 7.24, 7.31, 8.09. Anal. Calcd for C₂₃H₂₄N₂O: C, 80.20, H, 7.02, N, 8.13. Found: C, 79.88, H, 7.15, N, 8.12.

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Preparation 39 9-(4-Fluorobenzyl)-6-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one

6-Methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.5457 g, 0.0027 mol) is added to a slurry of pentane-washed NaH (0.1369 g, 0.0034 mol) in DMF (3 mL) and after stirring for 20 min, p-fluorobenzyl bromide (0.42 mL, 0.0034 mol) is added, followed by additional DMF (2 mL). After the slurry had stirred for 2.5 h it is partitioned between water and ethyl acetate. The combined organic layers are washed with water, dried over sodium sulfate and concentrated to dryness. The resulting solids are chromatographed on silica gel (200 mL) using dichloromethane (100%) to give 0.6929 g (82%) of the title compound. An aliquot is recrystallized from ethyl acetate/heptane, mp 209.5–210 °C; MS (ESI+) for $C_{20}H_{18}FNO$ m/z 308.2 (M+H)⁺ IR (drift) 2939, 1629, 1510, 1467, 1449, 1413, 1362, 1225, 1219, 1190, 1158, 1107, 1094, 832, 797 cm^{-1} , ¹H NMR (CDCl₃) δ 2.23, 2.47, 2.59, 2.85, 5.27, 6.99, 7.05, 7.12, 8.11. Anal. Calcd for $C_{20}H_{18}FNO$ C 78.15, H 5.90, N 4.56. Found C, 77.64, H, 5.87, N 4.44.

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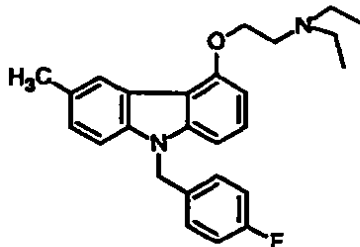
Preparation 40 9-(4-Fluorobenzyl)-6-methyl-9H-carbazol-4-ol

Pyridinium bromide perbromide (0.8153 g, 0.0026 mol) is added to a mixture of 9-(4-fluorobenzyl)-6-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.6351 g, 0.0021 mol) in dry THF (4.2 mL) and dry DMF (3 mL) and the mixture is heated to 75 °C. After stirring for 6 h, additional pyridinium bromide perbromide (0.0951 g, 0.30 mmol) is added and the mixture is stirred another hour. After storing in the freezer overnight, the mixture is again heated for another 40 min. THF is removed under reduced pressure and the residue is partitioned between dichloromethane and brine. The combined organic layers are washed with dilute sodium thiosulfate/brine and the aqueous layer is backwashed with dichloromethane. The combined organic layers are dried over magnesium sulfate and concentrated to dryness. The residue is combined with lithium bromide (0.4092 g, 0.0047 mol), lithium carbonate (0.3652 g, 0.0049 mol) and dry DMF (12 mL) and heated at 120 °C for 1.5 h. DMF is removed under high vacuum and the mixture is partitioned between dichloromethane and water. The combined organic layers are dried over sodium sulfate and concentrated to dryness. The residue is chromatographed on silica gel (100 mL) using hexane (100% to remove oil from sample) followed by ethyl acetate (100%). The residue is chromatographed again on silica gel (125 mL) using ethyl acetate/heptane (10/90) to give

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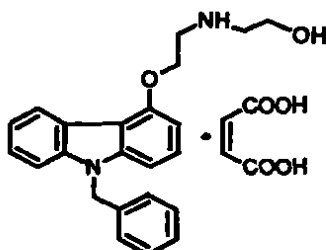
0.0505 g (8%) of the title compound, MS (ESI-) for $C_{20}H_{16}FNO$ m/z 304.1 (M-H), ^1H NMR ($CDCl_3$) δ 2.54, 5.33, 5.43, 6.57, 6.93, 7.08, 7.24, 8.12

Example 48 N,N-Diethyl-N-(2-([9-(4-fluorobenzyl)-6-methyl-9H-carbazol-4-yl]oxy)ethyl)amine



9-(4-Fluorobenzyl)-6-methyl-9H-carbazol-4-ol (0.0505 g, 0.17 mmol), 2-diethylaminoethylchloride hydrochloride (0.0411 g, 0.24 mmol), potassium carbonate (0.1018 g, 0.74 mmol), sodium iodide (0.0046 g, 0.031 mmol) and DMF (3 mL) are heated at 85 °C for 3 h. After the mixture had cooled, it is partitioned between water and ethyl acetate. The combined organic layers are dried over magnesium sulfate and concentrated to dryness. The residue is chromatographed on silica gel (60 mL) using methanol/dichloromethane (1/99 to 2/98 to 4/96) to give 0.0332 g (50%) of the title compound. MS (ESI+) for $C_{26}H_{29}FN_2O$ m/z 405.3 (M+H)⁺, IR (neat) 2966, 1601, 1506, 1460, 1339, 1269, 1242, 1218, 1150, 1127, 1054, 790, 781, 746, 717 cm^{-1} , ^1H NMR ($CDCl_3$) δ 1.90, 2.55, 2.80, 3.18, 4.39, 5.46, 6.71, 6.94, 7.07, 7.22, 7.33, 8.19. Anal. Calcd for $C_{26}H_{29}FN_2O$: C, 77.20, H, 7.22, N, 6.93. Found: C, 75.79, H, 7.61, N, 6.55.

Example 49 2-([2-([9-benzyl-9H-carbazol-4-yl]oxy)ethyl]amino)-1-ethanol and its maleic acid salt



To a mixture of 9-benzyl-4-(2-bromoethoxy)-9H-carbazole (0.2350 g, 0.618 mmol), ethanolamine (0.41 mL, 0.68 mmol) and acetonitrile (10 mL) is added diisopropylethylamine (0.118 mL, 0.68 mmol). The mixture is refluxed at 85 °C for 24 h. The mixture is then concentrated, partitioned between CH_2Cl_2 and brine. The organic layer is washed with

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water and dried over magnesium sulfate. Column chromatography (30 ml silica gel) using methanol/ CH_2Cl_2 (5/95) gave an oil, which is converted to the maleic acid salt to give 0.108 g (37 %) of the title compound. mp 160 °C, IR (neat) 1580, 1532, 1499, 1487, 1458, 1380, 1356, 1343, 1334, 1268, 1146, 1113, 748, 714, 705 cm^{-1} , ^1H NMR (300 MHz, DMSO- d_6) δ 3.18, 3.30, 3.69, 4.50, 5.27, 5.64, 5.99, 6.78, 7.09, 7.19, 7.36, 7.57, 8.30, 8.66. Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_2 \cdot \text{C}_4\text{H}_4\text{O}_4 \cdot 0.5 \text{H}_2\text{O}$: C, 66.79, H, 6.02, N, 5.77. Found: C, 66.58, H, 5.89, N, 5.69.

Preparation 41 9H-Carbazol-4-ol

1,2,3,9-Tetrahydro-4H-carbazol-4-one (11.59, 0.063 mol), anhydrous lithium chloride (10.76 g, 0.255 mol), anhydrous copper (II) chloride (17.73 g, 0.132 mol) and DMF (70 mL) are combined and heated at 62 °C for 28 h. The mixture is cooled and the resulting solids are collected and washed with water followed by hexane. The solids are triturated four times in ethyl acetate at 80 °C. Each time the filtrate is washed with water and the organic layer is dried over sodium sulfate and concentrated to dryness. The solids collected by filtration are then dissolved in dichloromethane/methanol, dried over sodium sulfate and concentrated to dryness. The combined solids gave 12.29 g of the chloro intermediate. A mixture of the chloro intermediate (6.52 g, 0.030 mol), lithium bromide (5.464 g, 0.063), lithium carbonate (4.530, 0.061 mol) and dry DMF (80 mL) is heated at 120 °C for 7.5 h and then stirred for two days at room temperature. The mixture is partitioned between water and dichloromethane and the combined organic layers are washed with brine, dried over sodium sulfate and concentrated to dryness. The resulting residue is chromatographed on silica gel (300 mL) using ethyl acetate/hexane (20/80) to give 2.543 g (42%) of the title compound, MS (ESI+) for $\text{C}_{12}\text{H}_9\text{NO}$ m/z 184.1 ($\text{M}+\text{H}$) $^+$. ^1H NMR (CDCl_3) δ 5.32, 6.60, 7.04, 7.27, 7.43, 8.07, 8.29.

Preparation 42 2-(9H-Carbazol-4-yloxy)acetonitrile

A mixture of 9H-carbazol-4-ol (2.543 g, 0.014 mol), potassium carbonate (0.2386 g, 0.017 mol), bromoacetonitrile (2.5 mL, 0.036 mol) and DMF (42 mL) is stirred at room temperature for 4 h. The mixture is then partitioned between water and ethyl acetate. The combined organic layers are dried over sodium sulfate and concentrated to a residue. The resulting residue is chromatographed on silica gel (200 mL) using ethyl acetate/hexane (20/80) to give 0.703 g (23%) of the title compound, mp 120-120.5 °C, MS (ESI-) for

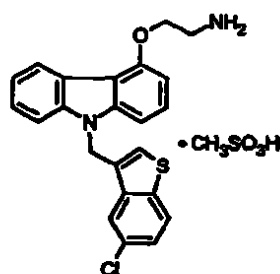
$C_{14}H_{10}N_2O$ m/z 221.0 (M⁺) IR (drift) 3399, 1605, 1585, 1508, 1452, 1346, 1336, 1269, 1242, 1212, 1106, 785, 757, 750, 723 cm^{-1} , ^1H NMR ($CDCl_3$) δ 5.07, 6.76, 7.21, 7.29, 7.38-7.47, 8.18, 8.28. Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.53; N, 12.60. Found: C, 75.41; H, 4.52; N, 12.48.

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Preparation 43 2-((9-[(5-chloro-1-benzothiophen-3-yl)methyl]-9H-carbazol-4-yl)oxy)acetonitrile

2-(9H-Carbazol-4-yloxy)acetonitrile (0.146 g, 0.66 mmol) is added to a slurry of pentane-washed NaH (0.0441 g, 0.0011 mol) in DMF (1 mL) and allowed to stir for 20 min at room temperature. 3-(Bromomethyl)-5-chlorobenzothiophene (0.229 g, 0.88 mmol) is added and after stirring for 1 h the mixture is partitioned between ethyl acetate and water. The combined organic layers are dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (75 mL) using ethyl acetate/hexane (20/80) and solids are precipitated using dichloromethane/hexane to give 0.148 g (56%) of the title compound. MS (ESI⁺) for $C_{23}H_{15}ClN_2OS$ m/z 425.2 (M+Na). IR (drift) 1581, 1460, 1439, 1332, 1279, 1232, 1221, 1155, 1148, 1115, 1079, 833, 780, 752, 717 cm^{-1} , ^1H NMR ($CDCl_3$) δ 5.10, 5.70, 6.72, 6.80, 7.12, 7.28-7.47, 7.80, 7.87, 8.36. Anal. Calcd for $C_{23}H_{15}ClN_2OS$: C, 68.57; H, 3.75; N, 6.95. Found: C, 68.87; H, 4.22; N, 6.56.

20 Example 50 2-((9-[(5-chloro-1-benzothiophen-3-yl)methyl]-9H-carbazol-4-yl)oxy)ethylamine, methane sulfonate salt



A mixture of 2-((9-[(5-chloro-1-benzothiophen-3-yl)methyl]-9H-carbazol-4-yl)oxy)acetonitrile (0.0915 g, 0.23 mmol), dry THF (2 mL) and borane-methyl sulfide (0.07 mL, 0.77 mmol) is stirred at 83 °C for 1.5 h. The mixture is then cooled, the excess borane is cautiously quenched with methanol and the mixture is concentrated under reduced pressure. Twice more methanol and dichloromethane are added to the residue and the solution is again concentrated under reduced pressure. The solids are slurried in

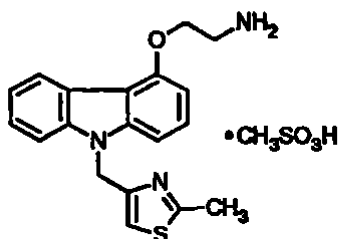
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methanol/dichloromethane and conc HCl (approx 1.5 mL) is added and the mixture is heated at 64 °C for 40 min. After cooling, the mixture is concentrated to dryness under reduced pressure and the residue is partitioned between dichloromethane and aq sodium bicarbonate. The combined organic layers are dried over sodium sulfate and concentrated to dryness. The residue is chromatographed on silica gel (50 mL) using methanol/dichloromethane (2/98 and 4/96 and 6/94) to give the desired free base. The methane sulfonate salt is formed by dissolving the free base (0.0547 g, 0.13 mmol) in dichloromethane/methanol and adding methanesulfonic acid (0.0013 g, 0.14 mmol) to the solution. Solids crystallized and are collected, washed with dichloromethane and vacuum dried at room temperature to give 0.0481 g (42%) of the title compound, mp >256 °C, MS (ESI+) for $C_{23}H_{19}ClN_2OS$ m/z 407.2 (M+H)⁺, IR (drift) 1585, 1457, 1328, 1269, 1240, 1221, 1197, 1180, 1165, 1149, 1044, 783, 772, 750, 717 cm^{-1} , ¹H NMR (CD₃OD) δ 2.71, 3.61, 4.55, 5.82, 6.85, 7.00, 7.20-7.53, 7.86, 8.43. Anal. Calcd for $C_{23}H_{19}ClN_2OS \cdot CH_4O_3S$: C, 57.30; H, 4.61; N, 5.57. Found: C, 56.90; H, 4.68; N, 5.49.

Preparation 44 2-((9-[(2-methyl-1,3-thiazol-4-yl)methyl]-9H-carbazol-4-yl)oxy)acetonitrile

2-(9H-Carbazol-4-yloxy)acetonitrile (0.143 g, 0.64 mmol) is added to a slurry of pentane-washed NaH (0.0825 g, 0.0021 mol) in DMF (1 mL) and allowed to stir for 20 min at room temperature. 4-Chloromethyl-2-methylthiazole hydrochloride (0.163 g, 0.89 mmol) is added and after stirring for 2 h the mixture is partitioned between ethyl acetate and water. The combined organic layers are dried over magnesium sulfate and concentrated to an oil. The oil is chromatographed on silica gel (75 mL) using ethyl acetate/hexane (20/80 and 40/60) and solids are crystallized from dichloromethane/ether to give 0.162 g (76%) of the title compound, MS (ESI+) for $C_{19}H_{15}N_3OS$ m/z 334.2 (M+H)⁺, IR (drift) 1581, 1459, 1440, 1341, 1333, 1275, 1228, 1215, 1182, 1157, 1151, 1113, 782, 754, 718 cm^{-1} , ¹H NMR (CDCl₃) δ 2.74, 5.09, 5.62, 6.38, 6.78, 7.19, 7.31, 7.44, 8.32. Anal. Calcd for $C_{19}H_{15}N_3OS$: C, 68.45; H, 4.53; N, 12.60. Found: C, 68.27; H, 4.53; N, 12.33.

Example 51 2-((9-[(2-Methyl-1,3-thiazol-4-yl)methyl]-9H-carbazol-4-yl)oxy)ethylamine, methane sulfonate salt



- 5 A mixture of 2-((9-[(2-methyl-1,3-thiazol-4-yl)methyl]-9H-carbazol-4-yl)oxy)acetonitrile (0.1229 g, 0.37 mmol), dry THF (3 mL) and borane-methyl sulfide (0.11 mL, 0.0012 mol) is stirred at 83 °C for 3 h. The mixture is then cooled, the excess borane is cautiously quenched with methanol and the mixture is concentrated under reduced pressure. Methanol and dichloromethane are added to the residue and the solution is again,
- 10 concentrated under reduced pressure (repeated twice). The solids are heated at 60 °C in methanol/dichloromethane and conc. HCl (2 mL) for 1 h. After cooling, the mixture is concentrated to dryness under reduced pressure and partitioned between dichloromethane and aq. sodium bicarbonate. The combined organic layers are dried over sodium sulfate and concentrated to dryness. The oil is chromatographed on silica gel (30 mL) using
- 15 methanol/dichloromethane (2/98 and 4/96) to give 0.0754 g (61%) of the desired free base. The methane sulfonate salt is formed by dissolving the free base (0.0696 g, 0.21 mmol) in dichloromethane and adding methanesulfonic acid (0.0201 g, 0.21 mmol) to the solution. The solution is concentrated and the solids are recrystallized from ethyl
- 20 acetate/dichloromethane/methanol to give 0.0400 g (45%) of the title compound, mp 228.5-229.0 °C, MS (ESI+) for $C_{19}H_{19}N_3OS$ m/z 338.2 ($M+H$)⁺, IR (drift) 1458, 1343, 1335, 1269, 1239, 1223, 1182, 1165, 1155, 1119, 1043, 782, 770, 751, 713 cm^{-1} , ¹H NMR (CD₃OD) δ 2.65, 2.69, 3.58, 4.52, 5.60, 6.75, 6.81, 7.23, 7.39, 7.51, 8.38. Anal. Calcd for $C_{19}H_{19}N_3OS \cdot CH_4O_3S$: C, 55.41; H, 5.35; N, 9.69. Found: C, 55.08; H, 5.39; N, 9.54.

25 Preparation 45 9-Benzyl-1,2,3,9-tetrahydro-4H-carbazol-4-one

A mixture of 9-benzyl-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.491 g, 1.78 mmol), copper (II) chloride (1.60 g, 8.92 mmol), LiCl (0.225 g, 5.34 mmol), and DMF (5 mL) is stirred at 105 °C for 2.5 h and then at 140 °C for an additional 1 h. After cooling, the mixture is stored overnight in the refrigerator and then partitioned between ethyl acetate and

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brine/aq sodium bicarbonate and brine. The organic layer is dried over magnesium sulfate and concentrated to dryness. The resulting solid is used without further purification in the next step (to prepare 9-benzyl-3-chloro 9H-carbazol-4-ol

^1H NMR (CDCl_3) δ 3.03-3.10, 5.35-5.37, 7.03-7.30, 8.31

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Preparation 46 9-Benzyl-3-chloro-9H-carbazol-4-ol

A mixture of 9-benzyl-3,3-dichloro-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.225 g, 1.78 mmol), LiCl (0.225 g, 5.34 mmol), Li_2CO_3 (0.395 g, 5.34 mmol), and DMF (6 mL) is heated at 135 °C for 45 min. After cooling, the mixture is partitioned between ethyl ether and aq ammonium chloride/brine and brine. The organic layer is dried over magnesium sulfate and concentrated to dryness. Chromatography on silica gel (40 mL) using ethyl acetate/hexane (10/90) gave 0.382 g of 9-benzyl-3-chloro-9H-carbazol-4-ol.

^1H NMR (CDCl_3) δ 5.48, 6.14, 6.88-7.11, 7.12, 7.24-7.36, 7.43, 8.37

15 Preparation 47 [(9-Benzyl-3-chloro-9H-carbazol-4-yl)oxy]acetonitrile

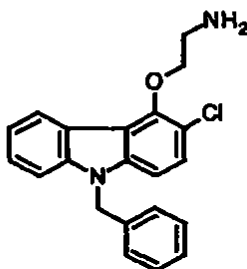
A mixture of 9-benzyl-3-chloro-9H-carbazol-4-ol (0.227 g, 0.739 mmol) bromoacetonitrile (0.177 g, 1.48 mmol), potassium carbonate (0.204 g, 1.48 mmol), and DMF (2 mL) is heated at 85 °C for 4 h, then allowed to cool and stir at room temperature for 12 h. Additional bromoacetonitrile (0.177 g) and potassium carbonate (0.204 g) are added and the mixture is heated again at 85 °C for 2 h. After cooling, the mixture is combined with that from another experiment run in the same manner (starting with 0.15 g of 9-benzyl-3-chloro-9H-carbazol-4-ol) and the combined mixtures are partitioned between ethyl acetate-aq ammonium chloride/brine and brine. The organic layer is dried over magnesium sulfate and concentrated to dryness. Chromatography on silica gel (55 mL) using ethyl acetate-hexane (10/90) gave 0.292 g of [(9-benzyl-3-chloro-9H-carbazol-4-yl)oxy]acetonitrile as a clear liquid.

^1H NMR (CDCl_3) δ 5.07-5.50, 7.11-7.15, 7.25-7.47, 7.50, 8.34

30

60203771.051200

Example 52 2-[(9-Benzyl-3-chloro-9H-carbazol-4-yl)oxy]ethylamine,
methanesulfonate salt



To [(9-benzyl-3-chloro-9H-carbazol-4-yl)oxy]acetonitrile (0.292 g, 0.842 mmol) in
5 THF (6 mL) is added borane-methyl sulfide complex (0.24 mL, 2.53 mmol). The mixture is
stirred at 80°C for 2.5 h and then allowed to cool. MeOH is carefully added to the residue
until gas evolution ceased and then the mixture is concentrated under vacuum. MeOH
addition/removal is repeated two more times and then MeOH-dichloromethane (about 2 mL
each) is added followed by several drops of conc. HCl. The mixture is stirred for about 15
10 min and then taken to dryness under vacuum. After partitioning with dichloromethane and
aq. sodium bicarbonate and drying, the residue is chromatographed on silica gel (50 mL)
using MeOH-dichloromethane (2/98 to 4/96) to give 0.206 g (70%) of 2-[(9-benzyl-3-
chloro-9H-carbazol-4-yl)oxy]ethylamine. The methanesulfonate salt is prepared by
dissolving 2-[(9-benzyl-3-chloro-9H-carbazol-4-yl)oxy]ethylamine in MeOH and
15 dichloromethane and adding methanesulfonic acid (0.0581 g). The mixture is concentrated
to dryness under vacuum and the residue is crystallized from dichloromethane-hexane to
give 0.206 g of 2-[(9-benzyl-3-chloro-9H-carbazol-4-yl)oxy]ethylamine, methanesulfonate
salt as a white crystalline solid.

¹H NMR (CDCl₃) δ 1.9, 3.29, 4.31, 5.49, 7.07, 7.12, 7.27, 7.35-7.49, 8.32

20

Preparation 48 9H-Carbazol-4-ol

To a mixture of 1,2,3,9-tetrahydro-4H-carbazol-4-one (6.02 g, 32.5 mmol) in 1:1
ethylene glycol-p-dioxane (100 mL) at 80 °C is added copper (II) chloride (21 g, 156.2
mmol). The mixture is heated for 20 minutes. The mixture is then partitioned between
25 water and ethyl acetate. The layers are separated and the organic layer is washed three times
with water (200 mL). The organic layer is dried over anhydrous sodium sulfate, filtered and
concentrated. The residue is dissolved in DMF (100 mL) to which is added lithium bromide
(7.04 g, 81.25 mmol) and lithium carbonate (6.0 g, 81.25 mmol). The mixture is heated at
120 °C for 4.5 hours. The mixture is then partitioned between water and ether. The ether

319
314

layer is washed three times with water (200 mL). The ether layer is dried over anhydrous sodium sulfate, filtered and concentrated. Column chromatography, silica gel (800 mL) using CH_2Cl_2 as eluent gave 1.1 g (18%) of the title compound,

^1H NMR (CDCl_3) δ 5.26, 6.57, 7.01, 7.26, 7.41, 8.05, 8.26. Anal. Calcd for $\text{C}_{12}\text{H}_9\text{NO}$: C

5 78.67, H, 4.95, N, 7.64. Found: C, 78.04, H, 4.94, N, 7.58.

Preparation 49 (9H-Carbazol-4-yloxy)acetonitrile

To a mixture of 9H-carbazol-4-ol (1.1 g, 6.0 mmol) in acetonitrile (100 mL) is added potassium carbonate (1.66 g, 12 mmol) and bromoacetonitrile (0.42 mL, 6.0 mmol). The mixture is stirred at room temperature for 20 h. The mixture is partitioned between water and CH_2Cl_2 . The layers are separated and the organic layer dried over anhydrous sodium sulfate, filtered and concentrated. Column chromatography, silica gel (100 mL), using CH_2Cl_2 as eluent gave 1.13 g (85%) of the title compound, ^1H NMR ($\text{DMSO}-d_6$) δ 5.4, 6.81, 7.18, 7.36, 7.46, 8.09. Anal. Calcd for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}$: C, 75.66, H, 4.53, N, 12.60.

10 mixture is stirred at room temperature for 20 h. The mixture is partitioned between water and CH_2Cl_2 . The layers are separated and the organic layer dried over anhydrous sodium sulfate, filtered and concentrated. Column chromatography, silica gel (100 mL), using CH_2Cl_2 as eluent gave 1.13 g (85%) of the title compound, ^1H NMR ($\text{DMSO}-d_6$) δ 5.4, 6.81, 7.18, 7.36, 7.46, 8.09. Anal. Calcd for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}$: C, 75.66, H, 4.53, N, 12.60.

15 Found: C, 75.18, H, 4.56, N, 12.54.

Preparation 50 2-(9H-Carbazol-4-yloxy)ethylamine

To a mixture of (9H-carbazol-4-yloxy)acetonitrile (1.13 g, 5.1 mmol) in dry THF (50 mL) is added borane-methyl sulfide complex (1.4 mL, 15.3 mmol). The mixture is heated at 85 °C for 6 h. Methanol is added slowly until gas evolution ceased. The solvents are removed under reduced pressure. Methanol (20 mL) is added then removed under reduced pressure. Methanol (50 mL) and concentrated hydrochloric acid are added and the mixture heated at 65 °C overnight. The mixture is neutralized with saturated potassium carbonate and partitioned between water and CH_2Cl_2 . The layers are separated and the organic layer washed twice with water (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated. Column chromatography, silica gel (200 mL) using $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ (4/96) gave 0.61 g (53%) of the title compound, IR (drift) 3082, 1608, 1585, 1456, 1443, 1346, 1336, 1303, 1252, 1222, 1098, 911, 782, 750, 719 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$) δ 3.05, 4.13, 6.65, 7.03, 7.12, 7.24, 7.31, 7.41, 8.12. Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}$: C, 74.31, H, 6.24, N, 12.38. Found: C, 73.90, H, 6.32, N, 12.14.

20 85 °C for 6 h. Methanol is added slowly until gas evolution ceased. The solvents are removed under reduced pressure. Methanol (20 mL) is added then removed under reduced pressure. Methanol (50 mL) and concentrated hydrochloric acid are added and the mixture heated at 65 °C overnight. The mixture is neutralized with saturated potassium carbonate and partitioned between water and CH_2Cl_2 . The layers are separated and the organic layer washed twice with water (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated. Column chromatography, silica gel (200 mL) using $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ (4/96) gave 0.61 g (53%) of the title compound, IR (drift) 3082, 1608, 1585, 1456, 1443, 1346, 1336, 1303, 1252, 1222, 1098, 911, 782, 750, 719 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$) δ 3.05, 4.13, 6.65, 7.03, 7.12, 7.24, 7.31, 7.41, 8.12. Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}$: C, 74.31, H, 6.24, N, 12.38. Found: C, 73.90, H, 6.32, N, 12.14.

25 washed twice with water (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated. Column chromatography, silica gel (200 mL) using $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ (4/96) gave 0.61 g (53%) of the title compound, IR (drift) 3082, 1608, 1585, 1456, 1443, 1346, 1336, 1303, 1252, 1222, 1098, 911, 782, 750, 719 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$) δ 3.05, 4.13, 6.65, 7.03, 7.12, 7.24, 7.31, 7.41, 8.12. Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}$: C, 74.31, H, 6.24, N, 12.38. Found: C, 73.90, H, 6.32, N, 12.14.

30 6.24, N, 12.38. Found: C, 73.90, H, 6.32, N, 12.14.

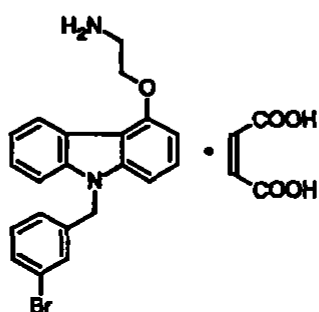
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Preparation 51 tert-Butyl 2-(9H-carbazol-4-yloxy)ethylcarbamate

To a mixture of sodium hydroxide (0.1 g, 2.6 mmol) in water (60 mL) is added 2-(9H-carbazol-4-yloxy)ethylamine (0.59 g, 2.6 mmol) in THF (10 mL). Boc anhydride (0.567 g, 2.6 mmol) is slowly added and the mixture stirred at room temperature for 2 h. The mixture is partitioned between water and CH₂Cl₂. The layers are separated and the organic layer washed with water (50 mL). The organic layer is dried over anhydrous sodium sulfate, filtered and concentrated to give 0.84 g (100 %) of the title compound, ¹H NMR (CDCl₃) δ 1.46, 3.75, 4.3, 5.1, 6.6, 7.05, 7.3, 7.32, 7.4, 8.12, 8.25. Anal. Calcd for C₁₉H₂₂N₂O₃: C, 69.92, H, 6.79, N, 8.58. Found: C, 66.47, H, 6.60, N, 7.94.

10

Example 53 2-([9-(3-Bromobenzyl)-9H-carbazol-4-yloxy]ethylamine, maleic acid salt



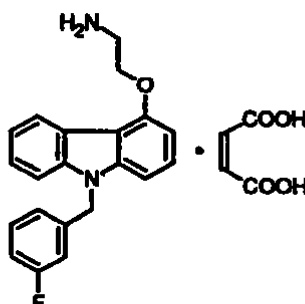
To a solution of sodium hydride (0.0059 g, 0.375 mmol) in dry DMF (2 mL) is added tert-butyl 2-(9H-carbazol-4-yloxy)ethylcarbamate (0.08 g, 0.245 mmol). The mixture is stirred for ½ h at room temperature. 1-Bromo-3-(bromomethyl)benzene (0.062 g, 0.248 mmol) is added and the mixture stirred at room temperature for 2 h. The mixture is partitioned between water and CH₂Cl₂. The layers are separated and the organic layer washed three times with water (5 mL). The organic layer is dried over anhydrous sodium sulfate, filtered and TFA (2 mL) is added. The mixture is stirred at room temperature for 30 minutes. The mixture is neutralized with saturated potassium carbonate. The layers are separated and the organic layer washed twice with water (5 mL). Column chromatography silica gel (100 mL) using CH₂Cl₂:CH₃OH:NH₄OH (95:4:1) gave an oil. The oil is converted to the maleic acid salt to give 0.0731 g (58%) of the title compound. IR (drift)

1623, 1581, 1499, 1482, 1460, 1353, 1332, 1273, 1113, 1019, 999, 861, 782, 749, 717 cm⁻¹.

1

^1H NMR (DMSO- d_6) δ 3.4, 4.4, 5.7, 6.0, 6.8, 7.04, 7.25, 7.37, 8.0, 8.36. Anal. Calcd for $\text{C}_{21}\text{H}_{19}\text{BrN}_2\text{O} \cdot \text{C}_4\text{H}_4\text{O}_4$: C, 58.72, H, 4.53, N, 5.48, Br, 15.63. Found: C, 58.37, H, 4.66, N, 5.37.

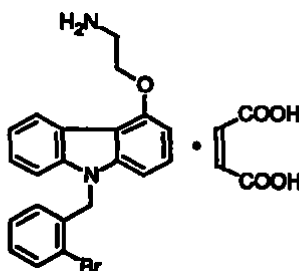
5 **Example 54** 2-([9-(3-Fluorobenzyl)-9H-carbazol-4-yl]oxy)ethylamine, maleic acid salt



Following the procedure of Example 53, the title compound is prepared.

IR (drift) 3051, 2938, 1618, 1586, 1500, 1485, 1460, 1360, 1335, 1271, 1247, 862, 781, 750, 715 cm^{-1} . MS (ESI+) for $\text{C}_{21}\text{H}_{19}\text{N}_2\text{O} \cdot \text{C}_4\text{H}_4\text{O}_4$ m/z 335.3 ($\text{M}+\text{H}^+$). ^1H NMR (DMSO- d_6) δ 3.43, 4.4, 5.7, 6.0, 6.8, 6.9, 7.0, 7.3, 7.4, 7.6, 8.0, 8.4. Anal. Calcd for $\text{C}_{21}\text{H}_{19}\text{FN}_2\text{O} \cdot \text{C}_4\text{H}_4\text{O}_4$: C, 66.66, H, 5.15, N, 6.22. Found: C, 65.62, H, 5.21, N, 6.01.

15 **Example 55** 2-([9-(2-Bromobenzyl)-9H-carbazol-4-yl]oxy)ethylamine, maleic acid salt

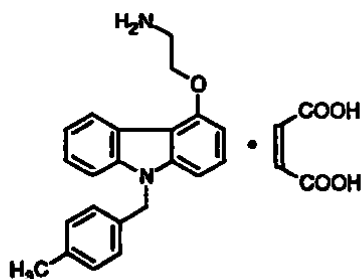


Following the procedure of Example 53, the title compound is prepared.

IR (drift) 1585, 1570, 1517, 1499, 1482, 1461, 1443, 1352, 1341, 1271, 1021, 997, 863, 749, 716 cm^{-1} . MS (ESI+) for $\text{C}_{21}\text{H}_{19}\text{N}_2\text{O} \cdot \text{C}_4\text{H}_4\text{O}_4$ m/z 395.2 ($\text{M}+\text{H}^+$). ^1H NMR (DMSO- d_6) δ 3.4, 4.4, 5.7, 6.0, 6.2, 6.8, 7.2, 7.4, 7.4, 7.7, 8.0, 8.4. Anal. Calcd for $\text{C}_{21}\text{H}_{19}\text{BrN}_2\text{O} \cdot \text{C}_4\text{H}_4\text{O}_4$: C, 58.72, H, 4.53, N, 5.48, Br, 15.63. Found: C, 58.24, H, 4.61, N, 5.27.

3/17

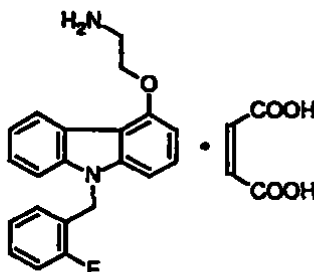
Example 56 2-([9-(4-Methylbenzyl)-9H-carbazol-4-yl]oxy)ethylamine maleic acid salt



Following the procedure of Example 53, the title compound is prepared

- 5 IR (drift) 1581 1531 1499, 1483, 1461 1353 1343, 1333 1112 1019, 998 861, 782, 750, 715 cm^{-1} MS (ESI+) for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_4$ m/z 331 3 ($\text{M}+\text{H}^+$) ^1H NMR ($\text{DMSO}-d_6$) δ 2.19, 3.4, 4.4, 5.6, 6.0, 6.7, 7.0, 7.18, 7.24, 7.4, 8.0, 8.3 Anal Calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_4$ C, 69.94, H, 5.87, N, 6.27 Found C, 68.73, H, 5.95, N, 5.93

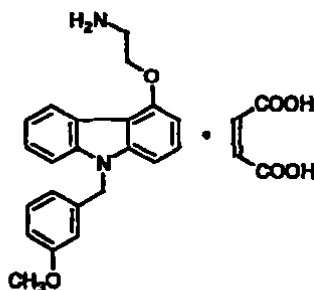
- 10 Example 57 2-([9-(2-Fluorobenzyl)-9H-carbazol-4-yl]oxy)ethylamine, maleic acid salt



Following the procedure of Example 53, the title compound is prepared

- 15 IR (drift) 3046, 1623, 1585, 1488 1460 1352 1334 1275 1177 1145, 1113 861 782, 749 714 cm^{-1} MS (ESI+) for $\text{C}_{21}\text{H}_{19}\text{FN}_2\text{O}_4$ m/z 335 3 ($\text{M}+\text{H}^+$) ^1H NMR ($\text{DMSO}-d_6$) δ 3.4, 4.4, 5.69, 6.02, 6.7, 6.78, 6.98, 7.26, 7.37, 7.56, 8.04, 8.35, Calcd for $\text{C}_{21}\text{H}_{19}\text{FN}_2\text{O}_4$ C, 66.66, H, 5.15, N, 6.22 Found C, 66.10, H, 5.20, N, 6.06

Example 58 2-([9-(3-Methoxybenzyl)-9H-carbazol-4-yl]oxy)ethylamine maleic acid salt



Following the procedure of Example 53, the title compound is prepared.

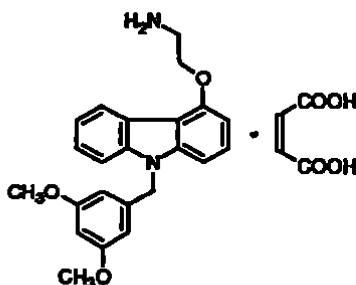
IR (drift) 3045, 3005, 2947, 1622, 1598, 1531, 1488, 1459, 1353, 1336, 1271, 864, 752,

5 748, 718 cm^{-1} MS (ESI+) for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2 \cdot \text{C}_4\text{H}_4\text{O}_4$ Anal m/z 346.5 ($\text{M}+\text{H}^+$) ^1H NMR ($\text{DMSO}-d_6$)

δ 3.43, 3.63, 4.41, 5.6, 6.0, 6.5, 6.69, 6.78, 7.2, 7.4, 7.6, 8.0, 8.34, Calcd for

$\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2 \cdot \text{C}_4\text{H}_4\text{O}_4$ C, 67.52, H, 5.67, N, 6.06 Found. C, 66.81, H, 5.73, N, 5.87

Example 59 2-([9-(3,5-Dimethoxybenzyl)-9H-carbazol-4-yl]oxy)ethylamine, maleic acid
10 salt



Following the procedure of Example 53, the title compound is prepared.

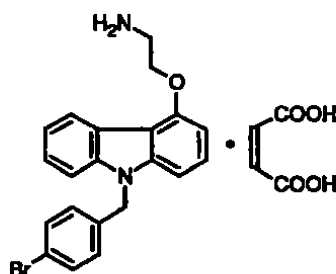
IR (drift) 3046, 3001, 2958, 2837 1596, 1551, 1532, 1499, 1482, 1459, 1351, 1205, 1157

748 711 cm^{-1} MS (ESI+) for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_3 \cdot \text{C}_4\text{H}_4\text{O}_4$ Anal m/z 377.4 ($\text{M}+\text{H}^+$) ^1H NMR ($\text{DMSO}-d_6$) δ

15 3.42, 3.61, 4.41, 5.6, 6.0, 6.2, 6.3, 6.8, 7.2, 7.4, 7.6, 8.0, 8.3 Anal Calcd for

$\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_3 \cdot \text{C}_4\text{H}_4\text{O}_4$ C, 65.84, H, 5.73, N, 5.69 Found C, 65.21, H, 5.89, N, 5.42

Example 60 2-([9-(4-Bromobenzyl)-9H-carbazol-4-yl]oxy)ethylamine, maleic acid salt



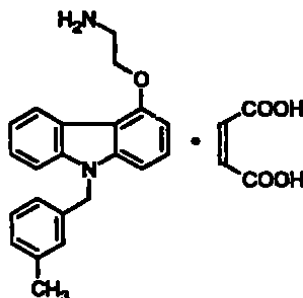
Following the procedure of Example 53 the title compound is prepared

IR (drift) 3047 3030 1622, 1582 1551 1531 1499 1484 1460 1359 1334 1270 861

749, 715 cm^{-1} ^1H NMR (DMSO- d_6) δ 3.43 4.41 5.63 6.01 6.78 7.02 7.23 7.37 7.42

5 7.56, 8.06, 8.34, Anal Calcd for $\text{C}_{21}\text{H}_{19}\text{BrN}_2\text{O}$ $\text{C}_4\text{H}_4\text{O}_4$ C 58.72 H 4.53 N 5.48 Br 15.63 Found C, 58.35, H, 4.57 N, 5.34

Example 61 2-([9-(3-Methylbenzyl)-9H-carbazol-4-yl]oxy)ethylamine, maleic acid salt



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Following the procedure of Example 53, the title compound is prepared

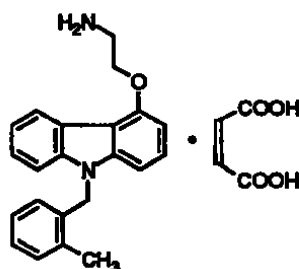
IR (drift) 3053, 3026 2958, 1579 1535 1525 1517 1499, 1483 1460 1355 1334 1271

751, 716 cm^{-1} MS (ESI+) for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}$ m/z 331.34 ($\text{M}+\text{H}$) $^+$ ^1H NMR (DMSO- d_6) δ

3.43, 4.41, 5.59, 6.04, 6.77, 7.02, 6.99, 7.2, 7.37, 7.55, 8.0, 8.34, Anal Calcd for

15 $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}$ $\text{C}_4\text{H}_4\text{O}_4$ C, 69.94, H, 5.87, N, 6.27 Found C, 67.42, H, 5.80, N 5.75

Example 62 2-([9-(2-Methylbenzyl)-9H-carbazol-4-yl]oxy)ethylamine, maleic acid salt



Following the procedure of Example 53, the title compound is prepared

IR (drift) 1627, 1595 1580, 1531, 1517 1498 1483 1460 1352 1343 1272, 861 749
739 716 cm^{-1} MS (ESI+) for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}$ m/z 331 35 (M+H)⁺ ¹H NMR (DMSO- d_6) δ
2.4 3.5, 4.4, 5.6, 6.0, 6.04, 6.78 6.86, 7.1, 7.23, 7.33 7.42, 8.06, 8.38, Anal Calcd for
 $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}$ C, 69.94, H, 5.87, N, 6.27 Found C, 69.08, H, 6.04, N 5.97

Preparation 52 6-Methoxy-1,2,3,9-tetrahydro-4H-carbazol-4-one

To a mixture of 4-methoxyphenyl hydrazine (0.359 g, 2.06 mmol) in toluene (30
mL) is added 1,3-cyclohexanedione (0.231 g, 2.06 mmol). The mixture is refluxed for 30
minutes. The toluene is removed under reduced pressure and the residue triturated in
 CH_2Cl_2 CH_3OH (95:5). A white solid is filtered to give 0.2903 g (65%) of the title
compound,
IR (drift) 3160, 3141 3114, 3064, 1619, 1588, 1474, 1434 1277, 1215, 1140, 1015 844,
802, 791 cm^{-1} MS (ESI+) for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_2$ m/z 216 (M+H)⁺ ¹H NMR (DMSO- d_6) δ
2.08, 2.39, 2.3 7.4 6.74 7.25, 7.43 Anal Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_2$ C, 72.54, H, 6.09, N,
6.51 Found C, 71.48, H 6.06, N, 6.45

Preparation 53 9-Benzyl-6-methoxy-1,2,3,9-tetrahydro-4H-carbazol-4-one

To a slurry of 60 % sodium hydride (0.76 g 19.6 mmol) in DMF (20 mL) is added
6-methoxy-1,2,3,9-tetrahydro-4H-carbazol-4-one (3.84 g, 17.8 mmol) over a period of 5
minutes and benzyl bromide (2.4 mL, 19.6 mmol). The mixture is heated to 50 °C for 1
hour then room temperature overnight. The mixture is partitioned between water and
 CH_2Cl_2 . The layers are separated and the organic layer washed with water (200 mL) and
concentrated. The residue is triturated in hexanes and filtered to give 4.45 g (80%) of the
title compound, mp 174 – 175 °C, IR (drift) 2939, 1633, 1484 1467, 1448, 1349, 1276,
1242 1159, 1130, 1099, 854, 791, 762 710 cm^{-1} ¹H NMR (DMSO- d_6) δ 2.1, 2.2, 2.93
3.75, 5.44, 6.77, 7.09, 7.28, 7.39, 7.51, Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_2$ C, 78.66, H, 6.27, N,
4.59 Found C, 78.45 H 6.31, N, 4.58

Preparation 54 9-Benzyl-6-methoxy-9H-carbazol-4-one

To a mixture of 9-benzyl-6-methoxy-1,2,3,9-tetrahydro-4H-carbazol-4-one (4.23 g
13.85 mmol) in ethylene glycol p-dioxane ((1:1) 150 mL) is added copper (II) chloride

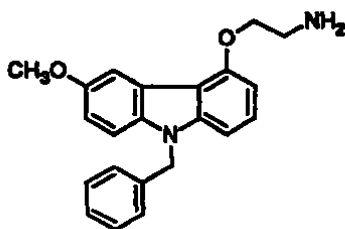
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(9.31 g, 69.26 mmol) The mixture is heated at 80 °C for 30 minutes. The mixture is partitioned between water and Et₂O. The layers are separated and the organic layer washed with water (100 mL). The ether layer is dried over anhydrous sodium sulfate, filtered and concentrated. The residue is dissolved in DMF (50 mL) to which is added lithium bromide (2.45 g, 28.3 mmol) and lithium carbonate (2.09 g, 28.3 mmol). The mixture is heated at 120 °C for 5 h. The mixture is partitioned between water and ethyl acetate. The layers are separated and the organic layer washed twice with water (200 mL). Column chromatography (250 mL) silica gel using ethyl acetate/ hexanes (20/80) gave 2.5 g (73 %) of the title compound, IR (drift) 3471, 1482, 1469, 1450, 1328, 1198, 1171, 1144, 805, 799, 780, 745, 724, 717, 701 cm⁻¹. ¹H NMR (DMSO-d₆) δ 3.82, 5.54, 6.56, 6.97, 7.14, 7.23, 7.43, 7.72. Anal. Calcd for C₂₀H₁₇NO₂: C, 79.18, H, 5.65, N, 4.62. Found: C, 78.99, H, 5.75, N, 4.63.

Preparation 55 [(9-Benzyl-6-methoxy-9H-carbazol-4-yl)oxy]acetonitrile

To a mixture of 9-benzyl-6-methoxy-9H-carbazol-4-ol (1.21 g, 4.0 mmol) in DMF (25 mL) is added potassium carbonate (2.07 g, 15 mmol) and bromoacetonitrile (0.7 mL, 10 mmol). The mixture is heated at 120 °C overnight. The mixture is partitioned between water and Et₂O. The organic layer is washed twice with water (100 mL) and dried over anhydrous sodium sulfate. The residue is dissolved in CH₂Cl₂ and passed through a silica gel plug. The filtrates are concentrated to dryness to give 0.43 g (31%) of the title compound, IR (drift) 1487, 1469, 1449, 1439, 1291, 1275, 1211, 1181, 1170, 1147, 1120, 775, 745, 705, 697 cm⁻¹. ¹H NMR (CDCl₃) δ 3.94, 5.06, 5.48, 6.7, 7.09, 7.24, 7.36, 7.81. Anal. Calcd for C₂₂H₁₆N₂O₂: C, 77.17, H, 5.30, N, 8.18. Found: C, 76.68, H, 5.31, N, 8.08.

Example 63 2-[(9-Benzyl-6-methoxy-9H-carbazol-4-yl)oxy]ethylamine



To a mixture of [(9-benzyl-6-methoxy 9H-carbazol-4-yl)oxy]acetonitrile (0.43 g, 1.26 mmol) in dry THF (20 mL) is added borane-methylsulfide complex (0.36 mL, 3.8 mmol). The mixture is heated at 85°C overnight. Methanol is slowly added to the mixture until gas evolution ceased. The solvents are removed under reduced pressure. Methanol (20 mL) is added then removed under reduced pressure. Methanol (50 mL) and concentrated hydrochloric acid (10 mL) is added to the mixture and heated at 65°C overnight. The mixture is neutralized with saturated potassium carbonate and partitioned between water and CH₂Cl₂. The layers are separated and the organic layer washed twice with water (100 mL). The CH₂Cl₂ is dried over anhydrous sodium sulfate and concentrated. Column chromatography with silica gel (60 mL) using 4% CH₃OH in CH₂Cl₂ gave 0.371 g (85 %) of the title compound, IR (drift) 1581, 1488, 1467, 1452, 1440, 1343, 1323, 1289, 1271, 1211, 1167, 1150, 1031, 742, 727 cm⁻¹. HRMS (FAB) calcd for C₂₂H₂₂N₂O₂ + H⁺ 347.1759, found 347.1761. % Water (KF) 0.17. ¹H NMR (CDCl₃) δ 3.28, 3.92, 4.28, 5.47, 6.65, 6.95, 7.02, 7.09, 7.21, 7.32, 7.87. Anal. Calcd for C₂₂H₂₂N₂O₂: C 76.15, H 6.41, N 8.07. Found C, 75.90, H, 6.38, N, 7.99.

Preparation 56 7-Methoxy-1,2,3,9-tetrahydro-4H-carbazol-4-one

To a chilled mixture of m-anisidine (10 g, 81 mmol) in water (200 mL) and concentrated hydrochloric acid (25 mL) is added sodium nitrite (5.6 g, 81 mmol) dissolved in water (30 mL). The mixture is stirred at 5°C for one h. To this is added tin (II) chloride dihydrate (36.6 g, 162 mmol) dissolved in concentrated hydrochloric acid (75 mL). The mixture is allowed to warm to room temperature and stirred for 1 h. 1,3-cyclohexanedione (9.1 g, 81 mmol) is added and the mixture stirred for 2 h. The mixture is slowly neutralized with 10% NaOH. Filtered solids and washed with water (500 mL). The solids are then slurried in acetonitrile (600 mL), filtered and washed with acetonitrile (200 mL). The filtrates are dried over anhydrous sodium sulfate, filtered and concentrated. The residue is refluxed in TFA (70 mL) for 18 h. The mixture is partitioned between water and CH₂Cl₂. The organic layer is separated and washed twice with water (200 mL). The organic layer is dried over anhydrous sodium sulfate, filtered, and concentrated. Ethyl acetate (100 mL) is added to the residue and the solids filtered to give 2.29 g (13%) of the title compound. IR (drift) 3156, 3118, 3073, 1620, 1583, 1501, 1470, 1451, 1288, 1196, 1178, 1153, 1142, 1107, 830 cm⁻¹. ¹H NMR (DMSO-d₆) δ 2.08, 2.7, 2.9, 3.8, 6.7, 6.9, 7.8. Anal. Calcd for C₁₃H₁₃NO₂: C 72.54, H 6.09, N 6.51. Found C 60.95, H 5.18, N 5.61.

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323

Preparation 57 9-Benzyl-7-methoxy-1,2,3,9-tetrahydro-4H-carbazol-4-one

To a slurry of sodium hydride (0.26 g, 11 mmol) in dry DMF (50 mL) is added 7-methoxy-1,2,3,9-tetrahydro-4H-carbazol-4-one (2.2 g, 10.2 mmol). The mixture is stirred at room temperature for 30 min. To this is added benzyl bromide (1.3 mL, 11 mmol). The mixture is stirred at room temperature overnight. The mixture is partitioned between water and Et₂O. The layers are separated and the organic layer washed twice with water (200 mL). The organic layer is dried over anhydrous sodium sulfate, filtered and concentrated. Column chromatography (200 mL) silica gel using CH₃OH/CH₂Cl₂ (2/98) gave 1.7 g (55%) of the title compound, IR (drift) 1638, 1628, 1578, 1535, 1497, 1461, 1449, 1357, 1266, 1200, 1149, 1105, 834, 807, 700 cm⁻¹. ¹H NMR (CDCl₃) δ 2.2, 2.6, 2.8, 3.8, 6.7, 6.9, 7.0, 7.3, 8.1, Anal. Calcd for C₂₀H₁₉NO₂: C, 78.66, H, 6.27, N, 4.59. Found: C, 78.29, H, 6.39, N, 4.53.

15 Preparation 58 9-Benzyl-7-methoxy-9H-carbazol-4-ol

To a mixture of 9-benzyl-7-methoxy-1,2,3,9-tetrahydro-4H-carbazol-4-one (1.65 g, 5.4 mmol) in 1,1-p-dioxane-ethylene glycol (50 mL) at 80 °C is added copper (II) chloride (3.6 g, 27 mmol). The mixture is heated for 17 minutes. The mixture is partitioned between water and ethyl acetate. The layers are separated and the ethyl acetate layer washed twice with water (200 mL). The ethyl acetate is dried over anhydrous sodium sulfate, filtered, and concentrated. The residue is dissolved in DMF (50 mL). Lithium bromide (0.94 g, 10.8 mmol) and lithium carbonate (0.8 g, 10.8 mmol) is added and the mixture heated to 120 °C for 6 hours. The mixture is partitioned between water and ethyl acetate. The layers are separated and the ethyl acetate layer washed twice with water (200 mL). The ethyl acetate is dried over anhydrous sodium sulfate, filtered and concentrated. Column chromatography silica gel (100 mL) using CH₂Cl₂/CH₃OH (96/4) gave 1.0 gm (61%) of the title compound, IR (drift) 1607, 1465, 1334, 1330, 1320, 1276, 1251, 1207, 1102, 809, 745, 740, 722, 711, 696 cm⁻¹. ¹H NMR (CDCl₃) δ 3.9, 5.4, 6.6, 6.8, 6.9, 7.2, 7.2, 8.2. Anal. Calcd for C₂₀H₁₇NO₂: C, 79.18, H, 5.65, N, 4.62. Found: C, 78.35, H, 5.66, N, 4.55.

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Preparation 59 [(9-Benzyl-7-methoxy-9H-carbazol-4-yl)oxy]acetonitrile

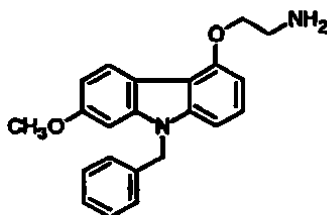
To a mixture of 9-benzyl-7-methoxy-9H-carbazol-4-ol (0.86 g, 2.8 mmol) in DMF (30 mL) is added potassium carbonate (1.17 g, 8.5 mmol) and bromoacetonitrile (0.56 mL,

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8.0 mmol) The mixture is stirred at room temperature for 18 h. The mixture is partitioned between water and CH_2Cl_2 . The layers are separated and the organic layer washed twice with water (100 mL). The organic layer is dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (100 mL) silica gel using CH_2Cl_2 as eluent gave 0.9 g (94%) of the title compound, ^1H NMR (CDCl_3) δ 3.86, 5.04, 5.46, 6.73, 6.82, 6.87, 7.05, 7.14, 7.28, 8.15, Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_2$: C, 77.17, H, 5.30, N, 8.18. Found: C, 76.00, H, 5.32, N, 8.43.

Example 64

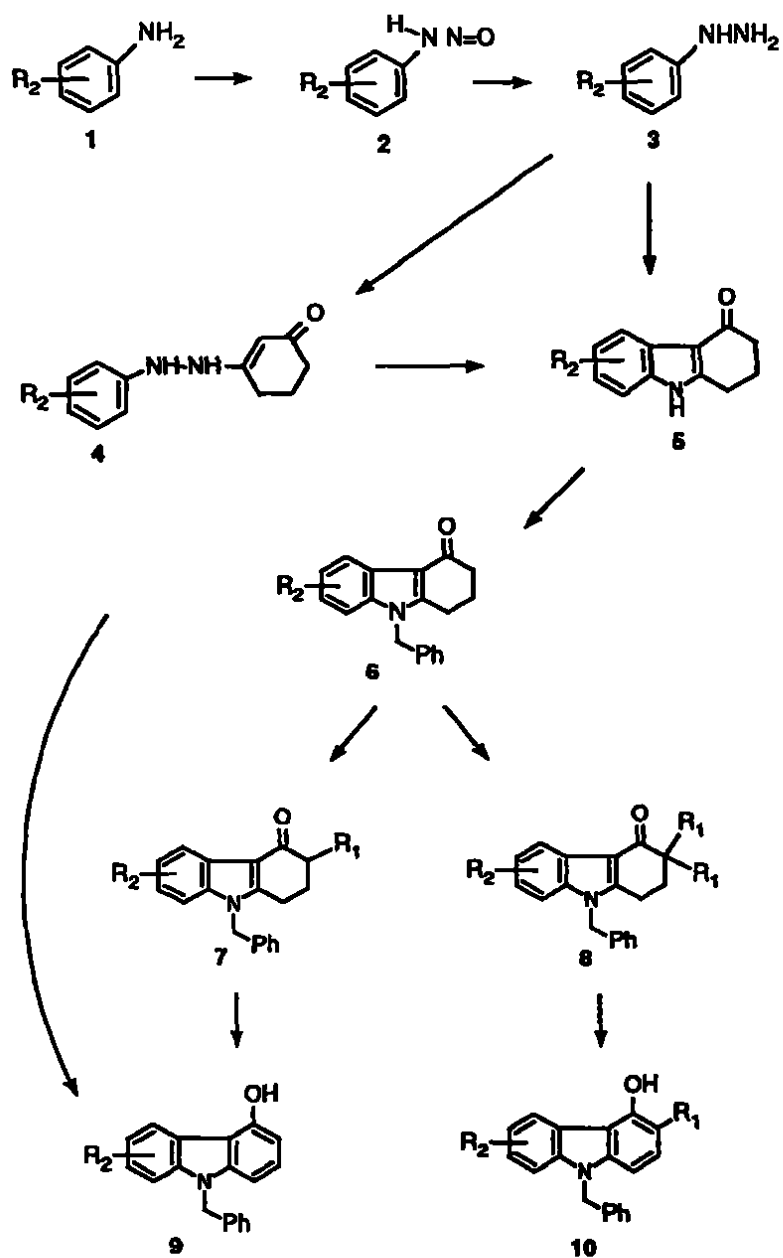
2-[(9-Benzyl-7-methoxy-9H-carbazol-4-yl)oxy]ethylamine



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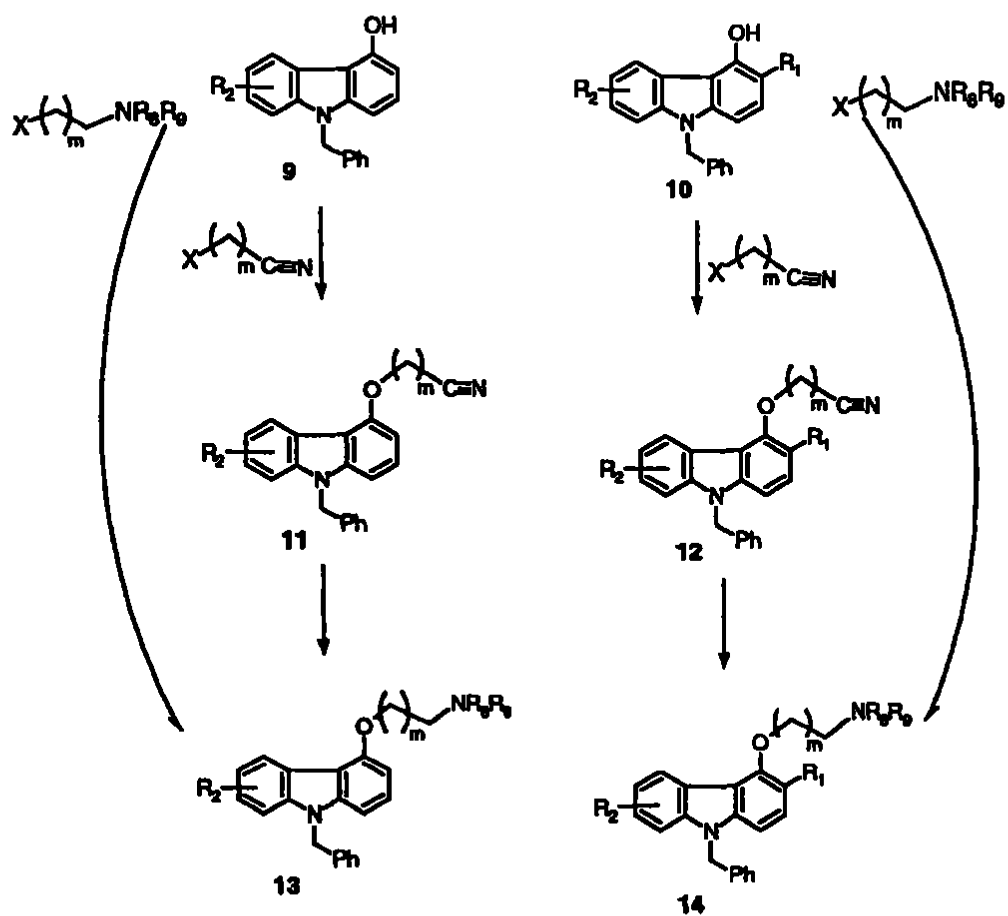
To a mixture of [(9-benzyl-7-methoxy-9H-carbazol-4-yl)oxy]acetonitrile (0.9 g, 2.6 mmol) in dry THF (50 mL) is added borane-methylsulfide complex (0.75 mL, 7.9 mmol). The mixture is heated at 40 °C overnight. Methanol is slowly added to mixture until addition of methanol did not evolve gas. The solvents are removed under reduced pressure. Methanol (50 mL) is added to the residue then removed under reduced pressure. Methanol (100 mL) and concentrated hydrochloric acid (3 mL) is added to the residue. The mixture is heated at 75 °C for 2.5 h. The mixture is neutralized with saturated potassium carbonate and partitioned between water and ethyl acetate. The layers are separated and the organic layer washed twice with brine. The organic layer is dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography silica gel (100 mL) using CH_2Cl_2 / CH_3OH (95/5) as eluent gave 0.52 g (58%) of the title compound, ^1H NMR ($\text{DMSO}-d_6$) δ 2.48, 3.8, 4.12, 5.59, 6.69, 6.8, 7.14, 7.2, 8.03. Anal. Calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2$: C, 76.28, H, 6.40, N, 8.09. Found: C, 76.00, H, 6.54, N, 7.92.

CHART A



60203771.051200

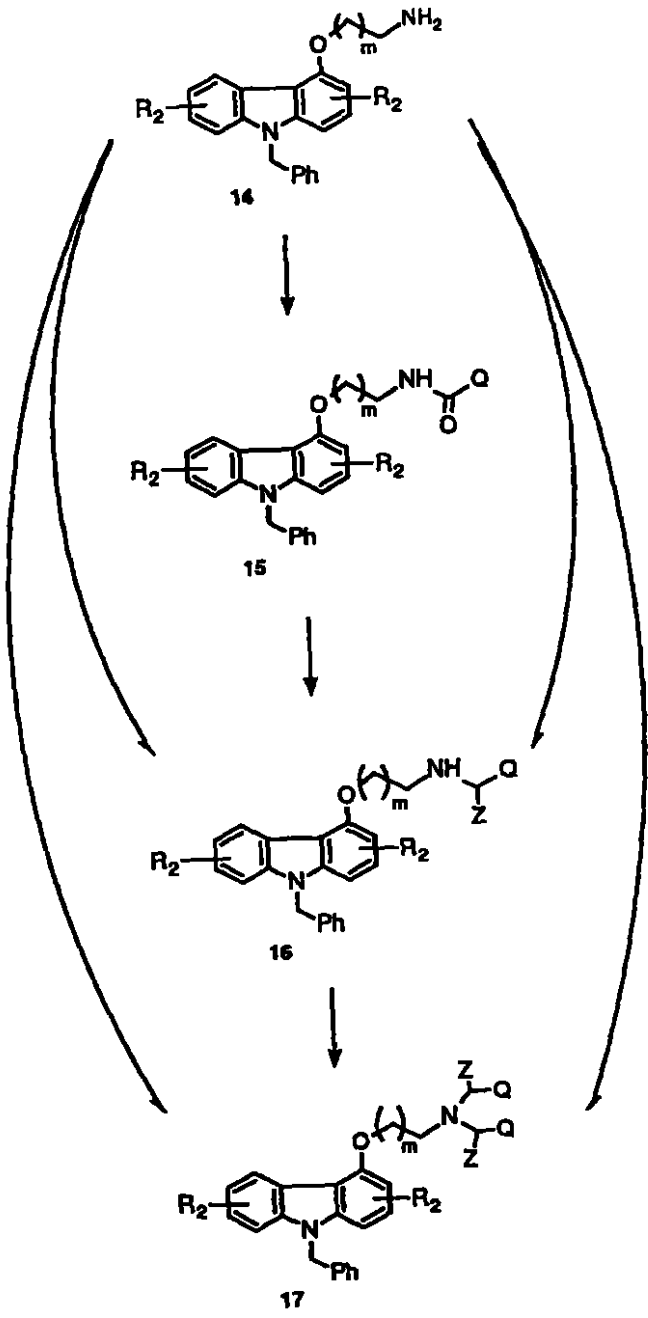
CHART B



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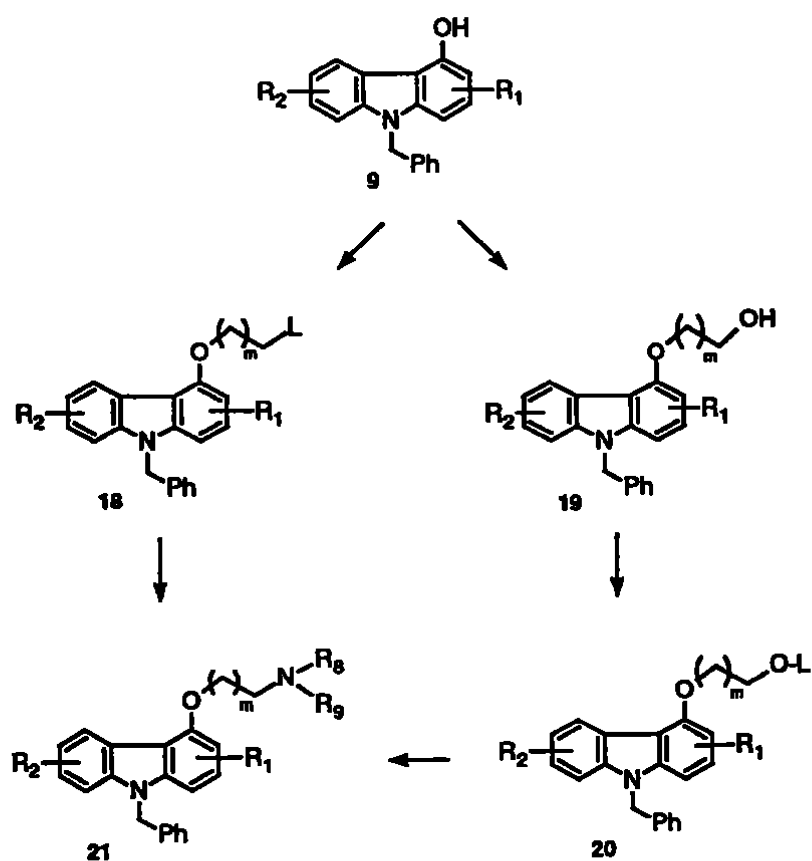
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CHART C



60203771.05120

CHART D

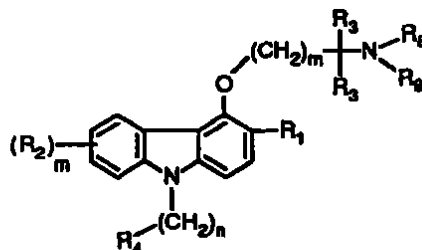


5

CLAIMS

What is claimed is

1 A compound of formula I



I

5

wherein

R₁ is

- (a) H
- (b) halo, or
- (c) C₁₋₆ alkyl,

10

R₂ is

- (a) H,
- (b) halo,
- (c) -OH
- (d) -CN,
- (e) -CF₃
- (f) -O(C₁₋₆)alkyl,
- (g) C₁₋₆ alkyl,
- (h) C₃₋₆ cycloalkyl,
- (i) -NR₃R₆,
- (j) -CONR₃R₆,
- (k) -SO₂NR₃R₆,
- (l) -COOR₇,
- (m) -OCF₃, or

15

20

(n) phenyl, optionally substituted with halo, OH, O(C₁₋₄) alkyl, or C₁₋₆ alkyl,

25

each R₃ is independently

- (a) H
- (b) C₁₋₆ alkyl, or
- (c) C₃₋₆ cycloalkyl

R₄ is

- (a) aryl, or
- (b) heteroaryl,

5 **R₅ and R₆ are independently**

- (a) H
- (b) C₁₋₆ alkyl, or
- (c) C₃₋₆ cycloalkyl,

R₇ is

- 10 (a) H,
- (b) C₁₋₆ alkyl, or
- (c) (C₁₋₃ alkyl)-phenyl wherein phenyl may be substituted with R₃,

R₈ and R₉ are independently

- (a) H
- 15 (b) C₁₋₆ alkyl, optionally substituted with aryl, heteroaryl, or C₃₋₆ cycloalkyl,
- (c) C₂₋₆ alkene,
- (d) C₃₋₆ cycloalkyl,
- (e) C₂₋₆ alkyl substituted with R₁₀
- (f) -CHO, provided that only one of the R₈ and R₉ is CHO the other one is H
- 20 (g) aryl,
- (h) heterocyclic, wherein heterocyclic is bonded via carbon atom to the nitrogen to which it is attached or
- (i) R₈ and R₉ taken together with the nitrogen to which they are attached form a heterocyclic ring wherein the heterocyclic ring may have one to two additional heteroatoms
- 25 selected from the group consisting of oxygen, sulfur and N(Y) and wherein the carbon atoms of the heterocyclic ring is optionally substituted with one or two R₁₄,

R₁₀ is

- (a) -OH,
- (b) -O(C₁₋₄ alkyl), optionally alkyl is substituted with OH,
- 30 (c) -O(C₁₋₄ alkyl)-NR₁₁R₁₂
- (d) heterocyclic, or
- (e) -CO₂R₅

R₁₁ and R₁₂ are independently,

536
331

(c) H or

(d) C₁₋₄ alkyl,

aryl is phenyl or naphthyl optionally substituted with one or more R₁₃,

heteroaryl is a radical of a five- or six membered monocyclic aromatic ring having one or

5 two heteroatoms each selected from the group consisting of oxygen, sulfur, and N(X) or a

radical of a nine- or ten-membered ortho-fused bicyclic aromatic ring having one, two or

three heteroatoms each selected from the group consisting of oxygen, sulfur, and N(X),

wherein carbon atoms of heteroaryl may be substituted with R₁₃,

heterocyclic is a radical of a five-, six-, or seven-membered partially-saturated or unsaturated

10 heterocyclic ring having one, two or three heteroatoms selected from the group consisting of

oxygen, sulfur and N(Y) wherein the carbon atoms of the heterocyclic ring may be

substituted with R₁₄

X is absent, H or C₁₋₄ alkyl,

Y is

15

(a) H

(b) C₁₋₆ alkyl, optionally substituted with aryl or heteroaryl,

(c) C₃₋₆ cycloalkyl, or

(d) C₂₋₆ alkyl substituted with -OH, -O(C₁₋₄ alkyl), -O(C₁₋₄ alkyl)-NR₁₁R₁₂,
-CO₂R₅ or NHCHO or

20

(e) -OH

R₁₃ is

(a) halo,

(b) -OH,

(c) -CN,

25

(d) -CF₃,

(e) -O(C₁₋₆)alkyl,

(f) C₁₋₆ alkyl,

(g) C₃₋₆ cycloalkyl,

(h) -NR₅R₆,

30

(i) -CONR₃R₆

(j) -SO₂NR₃R₆,

(k) -COOR₇

(l) -OCF₃, or

(m) phenyl, optionally substituted with halo OH O(C₁₋₄) alkyl, or C₁₋₆ alkyl,

R₁₄ is

(a) C₁₋₆ alkyl

(b) C₃₋₆ cycloalkyl,

5 (c) C₂₋₆ alkyl substituted with -OH, -O(C₁₋₄ alkyl) -O(C₁₋₄ alkyl)-NR₁₁R₁₂ or -CO₂R₅

(d) -OH or

(e) oxo (=O),

m is 1 2 3 or 4

10 n is 1, 2, 3, or 4

C₃₋₆ cycloalkyl in each of the above definitions, may be each and independently substituted with -OH, C₁₋₄ alkyl, or oxo (=O) and with the following provisos

(a) when R₄ is aryl substituted with fluoro, R₂ cannot be fluoro or chloro at the C-6 position of formula I,

15 (b) when R₄ is 4-thiazolyl, it cannot be substituted with 4-chlorophenyl, or a pharmaceutically acceptable salt, racemate, solvate, tautomer optical isomer or prodrug derivative thereof

(c) when R₄ is heteroaryl, heteroaryl is not 4-pyridyl.

20 2 A compound of claim 1 wherein R₁ is H, halo, or C₁₋₆ alkyl

3 A compound of claim 1 wherein R₁ is H, CH₃, fluoro or chloro

4 A compound of claim 1 wherein R₁ is H

25

5 A compound of claim 1 wherein R₂ is H, halo, -OH, -CN, -CF₃, -O(C₁₋₆)alkyl, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, -NR₅R₆, -CONR₅R₆, -SO₂NR₅R₆, -COOR₇ or phenyl, optionally substituted with halo OH, O(C₁₋₄) alkyl, or C₁₋₆ alkyl, wherein R₅ R₆ and R₇ are the same as defined in claim 1

30

6 A compound of claim 1 wherein R₂ is H, halo, or C₁₋₆ alkyl.

7 A compound of claim 1 wherein R₂ is H

- 8 A compound of claim 1 wherein R₂ chloro or fluoro
- 9 A compound of claim 1 wherein R₂ is methyl
- 5 10 A compound of claim 1 wherein m is 1
- 11 A compound of claim 1 wherein R₄ aryl or heteroaryl
- 10 12 A compound of claim 1 wherein R₄ is phenyl
- 13 A compound of claim 1 wherein R₄ is phenyl substituted with fluoro or chloro
- 14 A compound of claim 1 wherein R₄ is pyridyl, thiophene, benzothiophene,
15 benzofuran, benzimidazole, imidazole or thiazole
- 15 A compound of claim 1 wherein R₄ is 2-methyl-1,3-thiazol-4-yl or 5-chloro-1-benzothiophen-3-yl
- 20 16 A compound of claim 1 wherein each R₃ is independently H, C₁₋₆ alkyl, or C₃₋₆ cycloalkyl
- 17 A compound of claim 1 wherein each R₃ is independently H
- 25 18 A compound of claim 1 wherein R₈ and R₉ are independently
- (a) H
- (b) C₁₋₆ alkyl, optionally substituted with aryl, heteroaryl, or C₃₋₆ cycloalkyl,
- (c) C₂₋₆ alkene,
- (d) C₃₋₆ cycloalkyl,
- 30 (e) C₂₋₆ alkyl substituted with R₁₀,
- (f) -CHO,
- (g) aryl,

(h) heterocyclic, wherein heterocyclic is bonded via carbon atom to the nitrogen to which it is attached or

(i) R_8 and R_9 taken together with the nitrogen to which they are attached form a heterocyclic ring wherein the heterocyclic ring may have one to two additional heteroatoms selected from the group consisting of oxygen, sulfur and N(Y) and wherein the carbon atoms of the heterocyclic ring is optionally substituted with one or two R_{14} wherein R_{10} and Y are the same as defined in claim 1

19 A compound of claim 1 wherein R_8 is H, R_9 is H

10

20 A compound of claim 1 wherein R_8 is H, R_9 is C_{1-6} alkyl, C_{2-4} alkene, or -CHO

21 A compound of claim 1 wherein R_8 is H, R_9 is methyl

15

22 A compound of claim 1 wherein R_8 is H, R_9 is C_{1-6} alkyl substituted with C_{3-6} cycloalkyl, wherein cycloalkyl is optionally substituted with -OH, C_{1-4} alkyl or oxo

23 A compound of claim 22 wherein cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl

20

24 A compound of claim 1 wherein R_8 is H, R_9 is C_{2-6} alkyl substituted with -OH, $O(C_{1-4}$ alkyl), $-O(C_{1-4}$ alkyl-OH), or $-CO_2C_{1-4}$ alkyl,

25 A compound of claim 1 wherein R_8 is H, R_9 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, optionally substituted with -OH, C_{1-4} alkyl or oxo

26 A compound of claim 1 wherein R_8 is H, R_9 is C_{1-6} alkyl substituted with

(a) phenyl, optionally substituted with fluoro or chloro,

(b) pyridyl, thiophene, benzothiophene, benzofuran, benzimidazole, imidazole or thiazole, or

30

(c) heterocyclic, which is bonded via carbon atom to the nitrogen to which it is attached.

27 A compound of claim 21 wherein R_8 is H, R_9 is C_{1-4} alkyl substituted with fluorophenyl, chlorophenyl, pyridyl, benzimidazole, or 1-benzyl-piperidinyl.

28 A compound of claim 1 wherein R_8 is H, R_9 is C_{2-6} alkyl substituted with
 5 azetidyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl,
 1-benzyl-piperidinyl, 1-methyl-piperidinyl, dioxolane, imidazolidine, oxazolidinyl,
 oxathiolane, 4-hydroxy-1-piperidinyl, 4-ethanol-1-piperazinyl-, 4-ethylformamide-1-
 piperazinyl-, or 4-methyl-1-piperazinyl.

10 29 A compound of claim 1 wherein R_8 and R_9 taken together with the nitrogen to which
 they are attached form a heterocyclic ring wherein the heterocyclic ring may have one to two
 additional heteroatoms selected from the group consisting of oxygen, sulfur and N(Y),
 wherein Y is the same as defined in claim 1

15 30 A compound of claim 1 wherein R_8 and R_9 taken together with the nitrogen to which
 they are attached form 4-morpholinyl, 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl,
 4-hydroxy-1-piperidinyl, 4-ethanol-1-piperazinyl-, 4-ethylformamide-1-piperazinyl-, or 4-
 methyl-1-piperazinyl.

20 31 A compound of claim 1 wherein R_8 and R_9 are independently H, methyl, ethyl,
 propyl, 1-propanol, 2-propanol, 1-pentanol, 2-methyl-1-propanol, 2-butanol, 1-ethanol,
 ethoxy-1-ethanol, $-CH_2CH_2CO_2$ ethyl, 2-methoxyethyl, 4-chlorophenethyl, or
 4-fluorophenethyl.

25 32 A compound of claim 1 wherein R_8 and R_9 taken together with the nitrogen to which
 they are attached form 4-methyl-1-piperazinyl.

33 A compound of claim 1 which is

- 30 a) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine,
 b) N-{2-[(9-benzyl-8-chloro-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine,
 c) N-(2-{[8-chloro-9-(4-fluorobenzyl)-9H-carbazol-4-yl]oxy}ethyl)-N,N-diethylamine,
 d) N-{2-[(9-benzyl-8-methyl-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine,
 e) N,N-diethyl-N-(2-{[9-(4-fluorobenzyl)-8-methyl-9H-carbazol-4-yl]oxy}ethyl)amine,

- f) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-(2-pyridinylmethyl)amine,
g) N-{2-[(9-benzyl-8-fluoro-9H-carbazol-4-yl)oxy]ethyl}-N,N-diethylamine,
h) 9-benzyl-4-[2-(4-morpholinyl)ethoxy]-9H-carbazole,
i) 2-(4-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-1-piperazinyl)-1-ethanol,
5 j) 3-({2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}amino)-1-propanol,
k) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-2-propen-1-amine
l) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-3-(4-morpholinyl)-1-propanamine,
m) 5-({2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}amino)-1-pentanol,
n) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-1-propanamine,
10 o) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-propyl-1-propanamine,
p) 1-benzyl-N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-4-piperidinamine,
q) 2-({2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}amino)-2-methyl-1-propanol,
r) 2-[(9-benzyl-9H-carbazol-4-yl)oxy]-N-(4-chlorophenethyl)-1-ethanamine,
s) 2-[(9-benzyl-9H-carbazol-4-yl)oxy]-N-(cyclohexylmethyl)-1-ethanamine,
15 t) 2-[(9-benzyl-9H-carbazol-4-yl)oxy]-N-[2-(4-morpholinyl)ethyl]-1-ethanamine,
u) 1-({2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}amino)-2-butanol,
v) 2-[(9-benzyl-9H-carbazol-4-yl)oxy]-N-(4-fluorophenethyl)-1-ethanamine,
w) 2-[2-({2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}amino)ethoxy]-1-ethanol,
x) (1S,2S)-2-({2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}amino)cyclohexanol,
20 y) ethyl 3-({2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}amino)propanoate,
z) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}cyclobutanamine,
aa) 2-(4-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-1-piperazinyl)ethylformamide,
bb) N-(1H-benzimidazol-2-ylmethyl)-2-[(9-benzyl-9H-carbazol-4-yl)oxy]-1-ethanamine,
cc) 1-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-4-piperidinol,
25 dd) 9-benzyl-4-[2-(4-methyl-1-piperazinyl)ethoxy]-9H-carbazole,
ee) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-cyclopropylamine,
ff) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N,N-dimethylamine,
gg) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}formamide,
hh) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-methylamine, or its maleic acid salt,
30 ii) 2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethylamine,
jj) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-(2-methoxyethyl)amine,
kk) N-ethyl-N-([(1-phenyl-1,2-dihydro[1,4]oxazino[2,3,4-jk]carbazol-7-yl)oxy]ethyl)amine, or its maleic acid salt,

- ll) 9-benzyl-4-[2-(1-pyrrolidinyl)ethoxy]-9H-carbazole
 mm) 9-benzyl-4-[2-(1-piperidinyl)ethoxy]-9H-carbazole,
 nn) 9-benzyl-4-[2-(1-piperazinyl)ethoxy]-9H-carbazole
 oo) 2-[(9-benzyl-8-fluoro-9H-carbazol-4-yl)oxy]ethylamine,
 5 pp) N,N-diethyl-N-(2-[[8-fluoro-9-(4-fluorobenzyl)-9H-carbazol-4-yl]oxy]ethyl)amine,
 qq) N-(2-[(9-benzyl-6-chloro-9H-carbazol-4-yl)oxy]ethyl)-N,N-diethylamine,
 rr) N-(2-[(9-benzyl-6-fluoro-9H-carbazol-4-yl)oxy]ethyl)-N,N-diethylamine,
 ss) N-(2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethyl)-N,N-diethylamine,
 tt) 2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethylamine,
 10 uu) N-(2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethyl)-N-methylamine,
 vv) N,N-diethyl-N-(2-[[9-(4-fluorobenzyl)-6-methyl-9H-carbazol-4-yl]oxy]ethyl)amine,
 ww) 2-((2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl)amino)-1-ethanol or its maleic acid salt,
 xx) 2-((9-[(5-chloro-1-benzothiophen-3-yl)methyl]-9H-carbazol-4-yl)oxy)ethylamine or
 15 its methane sulfonate salt,
 yy) 2-((9-[(2-methyl-1,3-thiazol-4-yl)methyl]-9H-carbazol-4-yl)oxy)ethylamine or its methane sulfonate salt,
 zz) 2-[(9-benzyl-3-chloro-9H-carbazol-4-yl)oxy]ethylamine, methanesulfonate salt,
 aaa) 2-[[9-(3-bromobenzyl)-9H-carbazol-4-yl]oxy]ethylamine, maleic acid salt,
 20 bbb) 2-[[9-(3-fluorobenzyl)-9H-carbazol-4-yl]oxy]ethylamine, maleic acid salt,
 ccc) 2-[[9-(2-bromobenzyl)-9H-carbazol-4-yl]oxy]ethylamine, maleic acid salt
 ddd) 2-[[9-(4-methylbenzyl)-9H-carbazol-4-yl]oxy]ethylamine, maleic acid salt,
 eee) 2-[[9-(2-fluorobenzyl)-9H-carbazol-4-yl]oxy]ethylamine, maleic acid salt,
 fff) 2-[[9-(3-methoxybenzyl)-9H-carbazol-4-yl]oxy]ethylamine, maleic acid salt,
 25 ggg) 2-[[9-(3,5-dimethoxybenzyl)-9H-carbazol-4-yl]oxy]ethylamine, maleic acid salt,
 hhh) 2-[[9-(4-bromobenzyl)-9H-carbazol-4-yl]oxy]ethylamine, maleic acid salt,
 iii) 2-[[9-(3-methylbenzyl)-9H-carbazol-4-yl]oxy]ethylamine, maleic acid salt,
 jjj) 2-[[9-(2-methylbenzyl)-9H-carbazol-4-yl]oxy]ethylamine, maleic acid salt,
 kkk) 2-[(9-benzyl-6-methoxy-9H-carbazol-4-yl)oxy]ethylamine or
 30 III) 2-[(9-benzyl-7-methoxy-9H-carbazol-4-yl)oxy]ethylamine

 34 A compound of claim 1 which is
 a) 2-[(9-benzyl-8-fluoro-9H-carbazol-4-yl)oxy]ethylamine, or

b) 2 [(9-benzyl 8-fluoro-9H-carbazol 4-yl)oxy]ethylamine.

35 A compound of claim 1 which is

- a) N-{2-[(9-benzyl-9H-carbazol-4-yl)oxy]ethyl}-N-methylamine or its maleic acid salt,
 5 b) 9-benzyl-4-[2-(4-methyl-1-piperazinyl)ethoxy]-9H-carbazole or
 c) N-{2-[(9-benzyl-6-methyl-9H-carbazol-4-yl)oxy]ethyl}-N-methylamine.

- 36 A method for treating or preventing psychosis, paraphrenia, psychotic depression,
 mania, schizophrenia, schizophreniform disorders, schizoaffective disorder, delusional
 10 disorder panic disorder a phobia, obsessive compulsive disorder, post-traumatic-stress
 syndrome, immune system depression, a stress induced problem with the urinary a stress
 related disease such as anxiety, migraine headache, drug addiction, convulsive disorders,
 personality disorders, post-traumatic stress syndrome, alcoholism, panic attacks, obsessive-
 compulsive disorders, sleep disorders, gastrointestinal or cardiovascular system (e g , stress
 15 incontinence), neurodegenerative disorders, autism, chemotherapy-induced vomiting,
 hypertension, cluster headaches, sexual dysfunction in a mammal (e.g a human), addictive
 disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and
 mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general
 medical conditions attention-deficit hyperactivity disorder, behavioral disturbance (including
 20 agitation in conditions associated with diminished cognition (e g , dementia, mental
 retardation or delirium)), bipolar disorder, bulimia nervosa, chronic fatigue syndrome,
 conduct disorder, cyclothymic disorder, dysthymic disorder, fibromyalgia and other
 somatoform disorders, an inhalation disorder an intoxication disorder, movement disorder
 (e g Huntington's disease or Tardive Dyskinesia), oppositional defiant disorder, peripheral
 25 neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic
 disorder (brief and long duration disorders, psychotic disorder due to medical condition,
 psychotic disorder NOS), mood disorder (major depressive or bipolar disorder with
 psychotic features) seasonal affective disorder a specific developmental disorder agitation
 disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome or a Tic
 30 disorder (e.g , Tourette's syndrome), comprising administering to a mammal in need of such
 treatment, a therapeutically effective amount of a compound of formula (I) or a
 pharmaceutically acceptable salt thereof

37 A method for treating a disease or condition in a mammal wherein the 5-HT receptor is implicated and modulation of 5-HT function is desired comprising administering a therapeutically effective amount of a compound of any one of claim 1 to the mammal.

5 38 The method of claim 36 wherein the receptor is a 5-HT₆ receptor

39 The method of claim 36 wherein the disease or condition is anxiety, depression, schizophrenia, a stress related disease, panic disorder, a phobia, obsessive compulsive disorder post-traumatic-stress syndrome, immune system depression, psychosis,
10 paraphrenia, mania, convulsive disorders, personality disorders, migraine headache, drug addiction, alcoholism, obesity, eating disorders, or sleep disorders

40 The method of claim 36 wherein the disease or condition is psychotic, affective, vegetative, and psychomotor symptoms of schizophrenia and the extrapyramidal motor side
15 effects of other antipsychotic drugs

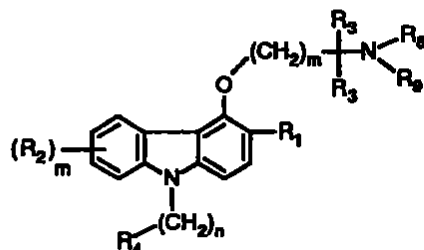
41 The method of claim 36 wherein the disease is anxiety, obesity depression, or a stress related disease

20 42 A method for modulating 5-HT receptor function, comprising contacting the receptor with an effective inhibitory amount of a compound of claim 1

43 The method of claim 42 wherein the receptor is a 5-HT₆ receptor

ABSTRACT

The present invention provides aminoalkoxy carbazole derivatives, and more specifically, provides compounds of formula (I)



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wherein R_1 , R_2 , R_3 , R_4 , R_5 and R_6 are described herein. These compounds are 5-HT ligands, and are useful for treating diseases wherein modulation of 5-HT activity is desired.

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