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SUPERINDUSTRIA Y COMERCIO
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. 01.017.369
Solicitud de Patente en nombre de
ORTHO-McNEIL PHARMACEUTICAL, INC.

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 A No. 94-76 Of. 305, obrando como apoderada de la sociedad ORTHO-McNEIL PHARMACEUTICAL, INC., solicitante de la patente de la referencia, anexo al presente memorial los siguientes documentos:

Copias certificadas de las solicitudes de Patentes Números 60/186,778 y 09/791,246 presentadas en los Estados Unidos de América los días 3 de marzo de 2000 y 22 de febrero de 2001, respectivamente, con las debidas traducciones de lo pertinente, incluyendo el capítulo reivindicatorio.

A este mismo respecto, debe tenerse en cuenta que en las primeras páginas de las copias en mención la Oficina de Patentes correspondiente certificó la fecha de presentación de esas solicitudes, cumpliéndose de esta forma todos y cada uno de los requisitos establecidos en el inciso segundo del artículo 10 de la Decisión 486 de la Comisión de la Comunidad Andina.

Señor Superintendente,


JIMENA ESCOBAR URIBE
C.C.39.779.452 de usaquén
T.P. 68228

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**ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS A QUIENES EL PRESENTE
LLEGUE:**

**DEPARTAMENTO DE COMERCIO DE LOS ESTADOS
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Oficina de Patentes y Marcas de los Estados Unidos**

mayo 3, 2001

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con 35 USC 111.

Número de Solicitud: 09/791,246

Fecha de Presentación: febrero 22, 2001

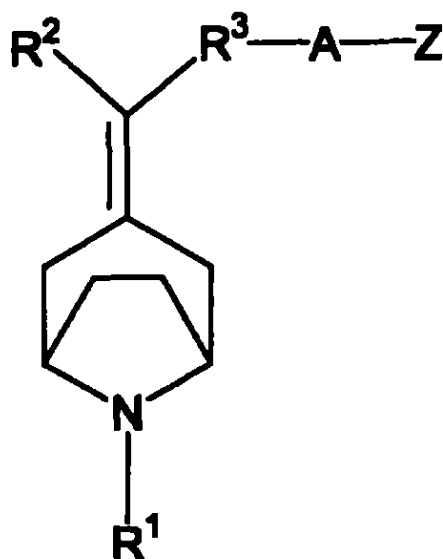
**Por la autoridad del
Comisionado de Patentes y Marca**

**(fdo) T. WALLACE
Oficial Certificador
Sello oficial de la Oficina de Patentes y Marcas de los
Estados Unidos de América**

LO QUE SE REIVINDICA ES:

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1. Un compuesto modulador receptor opiáceo seleccionado del grupo formado por un compuesto modulador recepto δ -opiáceos y un μ -opiáceos representado por la Formula (I):



(I)

en donde:

R¹ se selecciona del grupo conformado por hidrógeno, C₁₋₈ alquil, halo, (C₁₋₈) alquil, C₂₋₈ alquenil, C₁₋₈ alcoxi(C₂₋₈) alquenil, C₂₋₈ alquinil, C₁₋₈ alcoxi (C₂₋₈) alquinil, cicloalquil, cicloalquil(C₁₋₈) alquil, cicloalquilcarbonil(C₁₋₈) alquil, cicloalquil (C₂₋₈) alquenil, cicloalquil (C₂₋₈) alquinil, heterociclil, heterociclil (C₁₋₈) alquil, heterociclilcarbonil (C₁₋₈) alquil, heterociclil (C₂₋₈) alquenil, heterociclil (C₂₋₈) alquinil, aril, aril (C₁₋₈) alquil, arilcarbonil (C₁₋₈) alquil, aril (C₂₋₈) alquenil, aril (C₂₋₈) alquinil, arilaminocarbonil (C₁₋₈)

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alquil, heteroaril (C_{1-8}) alquil, heteroarilcarbonil (C_{1-8}) alquil, heteroaril (C_{2-8}) alquenil, heteroaril (C_{2-8}) alquinil, heteroarilaminocarbonil (C_{1-8}) alquil, $(R^1)_2-N-(C_{1-8})$ alquil, $R^{1a}-O-(C_{1-8})$ alquil, $R^{1a}-S-(C_{1-8})$ alquil, $R^{1a}-SO-(C_{1-8})$ alquil y $R^{1a}-SO_2-(C_{1-8})$ alquil; donde: el radical heterociclil es substituido opcionalmente con uno a tres sustituyentes seleccionados independientemente del grupo formado por C_{1-6} alquil, C_{2-6} alquenil, C_{1-6} alcoxi, amino, C_{1-6} alquilamino, di(C_{1-6} alquil)amino, C_{1-6} alquilcarbonil, C_{1-6} alquilcarboniloxi, C_{1-6} alquilcarbonilamino, C_{1-6} alquiltio, C_{1-6} alquilsulfonil, halógeno, hidroxil, oxo, ciano, trifluorometil y trifluorometoxil; y, donde los radicales aril y heteroaril están substituidos opcionalmente por uno a tres sustituyentes seleccionados independientemente del grupo conformado por C_{1-6} alquil, C_{2-6} alquenil, C_{1-6} alcoxi, amino, C_{1-6} alquilamino, di(C_{1-6} alquil) amino, C_{1-6} alquilcarbonil, C_{1-6} alquilcarboniloxi, C_{1-6} alquilcarbonilamino, C_{1-6} alquiltio, C_{1-6} alquilsulfonil, halógeno, hidroxil, ciano, trifluorometil y trifluorometoxil;

R^{1a} es seleccionado independientemente del grupo formado por hidrogeno, C_{1-8} alquil, C_{1-8} alcoxi $C_{(1-8)}$ alquil, hidroxil(C_{1-8}) alquil, halo $_{1-3}$ (C_{1-8}) alquil, Halo $_{1-3}$ (C_{1-8}) alcoxi(C_{1-8}) alquil, C_{2-8} alquenil, C_{2-8} alquinil, cicloalquil, cicloalquil(C_{1-8}) alquil, heterociclil, heterociclil(C_{1-8}) alquil, heterociclil(C_{1-8}) alquenil, heterociclil(C_{1-8}) alquinil, aril, aril(C_{1-8}) alquil, aril(C_{1-8}) alquenil, aril(C_{1-8}) alquinil, arilcarbonil(C_{1-8}) alquil, heteroaril, heteroaril(C_{1-8}) alquil, heteroaril(C_{1-8}) alquenil, heteroaril(C_{1-8}) alquinil y heteroarilcarbonil(C_{1-8}) alquil; donde el radical heterociclil es substituido opcionalmente por uno a tres sustituyentes seleccionados independientemente del grupo formado por C_{1-6} alquil, C_{2-6} alquenil, C_{1-6} alcoxi, amino, C_{1-6} alquilamino, di(C_{1-6} alquil)amino, C_{1-6} alquilcarbonil, C_{1-6} alquilcarboniloxi, C_{1-6} alquilcarbonilamino, C_{1-6} alquiltio, C_{1-6}

alquilsulfonil, halógeno, hidroxí, oxo, ciano, trifluorometil y trifluorometoxi; y, donde el radical aril y heteroaril son substituidos opcionalmente con uno a tres substituyentes seleccionados independientemente del grupo formado por C₁₋₆alquil, C₂₋₆alquenil, C₁₋₆alcoxi, amino, C₁₋₆alquilamino, di(C₁₋₆alquil)amino, C₁₋₆alquilcarbonil, C₁₋₆alquilcarboniloxi, C₁₋₆alquilcarbonilamino, C₁₋₆alquiltio, C₁₋₆alquilsulfonil, halógeno, hidroxí, ciano, trifluorometil y trifluorometoxi;

R² se selecciona del grupo formado por los radicales aril y heteroaril substituidos opcionalmente con uno a tres substituyentes seleccionados independientemente del grupo formado por C₁₋₆alquil, C₂₋₆alquenil, C₁₋₆alcoxi, amino, C₁₋₆alquilamino, di(C₁₋₆alquil)amino, C₁₋₆alquilcarbonil, C₁₋₆alquilcarboniloxi, C₁₋₆alquilocarbonil, C₁₋₆alquilaminocarbonil, C₁₋₆alquilcarbonilamino, C₁₋₆alquiltio, C₁₋₆alquilsulfonil, halógeno, hidroxí, ciano, trifluorometil y trifluorometoxi; Alternativamente, cuando los radicales aril y heteroaril son reemplazados por dos substituyentes unidos a los átomos adyacentes de carbono, los dos substituyentes pueden formar juntos una porción única y fusionada; en donde esta porción se selecciona del grupo formado por -(CH₂)₃₋₅- y -O(CH₂)₁₋₃O-,

R³ se selecciona del grupo formado por aril y heteroaril substituidos opcionalmente con uno o dos substituyentes adicionales a la porción -A-Z seleccionada independientemente del grupo formado por C₁₋₆alquil, C₂₋₆alquenil, C₁₋₆alcoxi, amino, C₁₋₆alquilamino, di(C₁₋₆alquil)amino, C₁₋₆alquilcarbonil, C₁₋₆alquilcarboniloxi, C₁₋₆alquilocarbonil, C₁₋₆alquilaminocarbonil, C₁₋₆alquilcarbonilamino, C₁₋₆alquiltio, C₁₋₆alquilsulfonil, halógeno, hidroxí, ciano, trifluorometil y trifluorometoxi;

alternativamente cuyo los radicales aril y heteroaril son sustituidos con dos sustituyentes opcionales unidos a los átomos adyacentes de carbono, los dos sustituyentes pueden formar juntos una porción única y fusionada; donde esta parte se selecciona del grupo formado por $-(CH_2)_{3,5}-$ y $-O(CH_2)_{1,3}O-$;

A se selecciona del grupo formado por $-C(=X)-$ y $-SO_2-$;

X se selecciona del grupo formado por O y S;

Z se selecciona del grupo formado por $-O(R^4)$ y $-N(R^5)(R^6)$;

R^4 se selecciona del grupo formado por hidrogeno, C_{1-8} alquil (sustituido opcionalmente por uno a tres sustituyentes halógenos), C_{1-8} alcoxi(C_{1-8})alquil, C_{2-8} alquenil, cicloalquil, cicloalquil(C_{1-8})alquil, heterociclil, heterociclil (C_{1-8})alquil, aril, aril(C_{1-8})alquil, heteroaril, heteroaril(C_{1-8})alquil, amino(C_{1-8})alquil, C_{1-8} alquilamino(C_{1-8})alquil, di(C_{1-8})alquilamino(C_{1-8})alquil y hidroxi(C_{1-8})alquil; en donde el radical heterociclil se sustituye opcionalmente con uno a tres sustituyentes seleccionados independientemente del grupo formado por C_{1-8} alquil, C_{1-8} alcoxi, C_{1-8} alquenil, cicloalquil, trifluorometil, halógeno, hidroxi, oxo y ciano; y, donde el radical aril es sustituido opcionalmente por uno a cuatro sustituyentes seleccionados independientemente del grupo formado por C_{1-8} alquil, C_{1-8} alcoxi, C_{2-8} alquenil, cicloalquil, $-OCH_2O-$, $-O(CH_2)_2O-$, trifluorometil, halógeno, hidroxi y ciano; y,

R^5 y R^6 son seleccionados independientemente del grupo formado por hidrogeno, C_{1-8} alquil (opcionalmente sustituido por uno a tres

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sustituyentes halógenos) C_{1-6} alcoxi(C_{1-6})alquil, C_{2-6} alquenil, cicloalquil, cicloalquil(C_{1-6})alquil, heterociclil, heterociclil(C_{1-6})alquil, aril, aril(C_{1-6})alquil, heteroaril, heteroaril(C_{1-6})alquil, amino(C_{1-6})alquil, C_{1-6} alquilamino(C_{1-6})alquil, di(C_{1-6})alquilamino(C_{1-6})alquil, aminoimino, aminocarbonil, aminocarbonil(C_{1-6})alquil, ariloxycarbonilamino (C_{1-6})alquil, heteroariloxycarbonilamino (C_{1-6})alquil, hidroxil(C_{1-6})alquil y trifluoro(C_{1-6})alcoxi; donde el radical heterociclil es opcionalmente sustituido por uno a tres sustituyentes independientemente seleccionados del grupo formado por C_{1-6} alquil, C_{1-6} alcoxi, C_{2-6} alquenil, cicloalquil, trifluorometil, halógeno, hidroxil, oxo y ciano; y, donde el radical aril es opcionalmente sustituido por uno a cuatro sustituyentes independientemente seleccionados independientemente del grupo formado por C_{1-6} alquil, C_{1-6} alcoxi, C_{2-6} alquenil, cicloalquil, $-OCH_2O-$, $-O(CH_2)_2O-$, trifluorometil, halógeno, hidroxil y ciano; alternatively, R^5 y R^6 pueden, junto con el nitrógeno al cual están unidos, forman una porción fusionada heterociclil opcionalmente sustituida con uno a cuatro sustituyentes seleccionados independientemente del grupo formado por C_{1-6} alquil, C_{1-6} alcoxi, C_{2-6} alquenil, cicloalquil, trifluorometil, halógeno, hidroxil y ciano; y compuestos farmacéuticamente aceptados, tales como enantiómeros diastómeros y sus sales correspondientes

2. El compuesto de la reivindicación 1 donde R^1 se selecciona del grupo formado por hidrógeno, C_{1-6} alquil, C_{2-6} alquenil, C_{2-6} alquinil, cicloalquil, cicloalquil(C_{1-6})alquil, heterociclil, heterociclil(C_{1-6})alquil, heterociclilcarbonil (C_{1-6})alquil, aril(C_{1-6})alquil, arilcarbonil(C_{1-6})alquil, aril(C_{2-6})alquinil, arilaminocarbonil(C_{1-6})alquil, heteroaril(C_{1-6})alquil, $(R^{1a})_2N-(C_{1-6})alquil$ y $R^{1a}-O-(C_{1-6})alquil$; donde, el radical heterociclil se sustituye opcionalmente por uno a tres sustituyentes seleccionados independientemente del grupo formado por C_{1-6} alquil, C_{1-6} alcoxi, halógeno,

hidroxi, oxo y ciano; y, donde el radical aril es sustituido opcionalmente con uno a tres sustituyentes seleccionados independientemente del grupo formado por C₁₋₄alquil, C₁₋₄alcoxi, halógeno, hidroxi y ciano.

3. El compuesto de la reivindicación 1 donde R¹ se selecciona del grupo formado por hidrogeno, metil, etil, n-propil, i-propil, n-butil, t-butil, n-hexil, butenil, alil, 3,3-dimetil, ciclopropil, ciclopropil(C₁₋₃)alquil, ciclohexil, ciclohexil(C₁₋₃)alquil, pirrolidinil, pirrolidinil(C₁₋₃) alquil, 1,3-dioxolanil(C₁₋₃)alquil, 2-imidazolinil, 2-imidazolinil(C₁₋₃)alquil, imidazolidinil, imidazolidinil(C₁₋₃)alquil, 2-pirazolinil, 2-pirazolinil(C₁₋₃)alquil, pirazolidinil, pirazolidinil(C₁₋₃)alquil, piperidinil, piperidinil(C₁₋₃)alquil, morfolinil, morfolinil(C₁₋₃)alquil, tiomorfolinil, tiomorfolinil(C₁₋₃)alquil, piperazinil, piperazinil(C₁₋₃)alquil, [4-(C₁₋₃)alquil-5-oxo-1,4-dihidrotetrazol-1-il] (C₁₋₃)alquil, piperonil, (1,3-benzodioxol-5-il)(C₂₋₃)alquil, (2,3-dihidro-1,4-benzodioxin-6-il)carbonil(C₁₋₃)alquil, (3,4 dihidro-2H-1,5-benzodioxepin-7-il)carbonil(C₁₋₃)alquil, benzil, fenil(C₂₋₃)alquil, fenil(C₂₋₃)alquinil, difenil(C₁₋₃)alquil, fenilcarbonil(C₁₋₃) alquil, fenilaminocarbonil(C₁₋₃)alquil, furil(C₁₋₃)alquil, tienil(C₁₋₃)alquil, pirrolil(C₁₋₃) alquil, oxazolil(C₁₋₃)alquil, tiazolil(C₁₋₃)alquil, imidazolil(C₁₋₃)alquil, pirazolil(C₁₋₃) alquil, isoxazolil(C₁₋₃)alquil, isotiazolil(C₁₋₃)alquil, 1,2,3-oxadiazolil(C₁₋₃)alquil, 1,2,3-triazolil(C₁₋₃)alquil, 1,3,4-tiadiazolil(C₁₋₃)alquil, piridinil(C₁₋₃)alquil, piridazinil (C₁₋₃)alquil, pirimidinil(C₁₋₃)alquil, pirazinil(C₁₋₃)alquil, 1,3,5-triazinil (C₁₋₃) alquil, indolil(C₁₋₃)alquil, benzo[b]furil(C₁₋₃)alquil, benzo[b]tienil (C₁₋₃)alquil, (R^{1a})₂-N-(C₁₋₃) alquil y R^{1a}O-(C₁₋₃)alquil; en donde pirrolidinil, 2-imidazolinil, imidazolidinil, 2-pirazolinil, pirazolidinil, piperidinil, morfolinil, tiomorfolinil y piperazinil son sustituidos opcionalmente por uno a tres sustituyentes seleccionados de oxo; y, donde el radical fenil es sustituido opcionalmente con uno a tres sustituyentes seleccionados independientemente del grupo formado

por metil, etil, n-propil, n-butil, metoxi, etoxi, propoxi, butoxi, cloro, flúor, hidroxí y ciano.

4. El compuesto de la reivindicación 1 donde R¹ se selecciona del grupo formado por hidrogeno, metil, n-propil, n-butil, alil, 3,3-dimetil, ciclopropilmetil, ciclohexil, 2-(4-etil-5-oxo-1,4-dihidrotetrazol-1-il)etil, piperonil, 2-(1,3-benzodioxol-5-il)etil, 2-(2,3-dihidro-1,4-benzodioxin-6-il)-2-oxoetil, 2-(3,4-dihidro-2H-1,5-benzodioxepin-7-il)-2-oxoetil, benzil, fenetil, fenilpropil, fenoxietil, fenilcarbonilmetil, fenilcarboniletal, fenilaminocarbonilmetil, tienilmetil, tieniletal, imidazolilmetil, piridinilmetil y indoliletal; En donde el radical fenil se sustituye opcionalmente con uno a tres sustituyentes seleccionados independientemente del grupo formado por metoxi, flúor, hidroxí y ciano.
5. El compuesto de la reivindicación 1 donde R^{1a} se selecciona del grupo formado por hidrogeno, C₁₋₆alquil y aril; en donde el radical aril se sustituye opcionalmente por uno a tres sustituyentes seleccionados independientemente del grupo formado por C₁₋₆ alquil, C₂₋₆alquenil, C₁₋₆alcoxi, amino, C₁₋₆alquilamino, di (C₁₋₆alquil)amino, C₁₋₆ alquilcarbonil, C₁₋₆ alquilcarboniloxi, C₁₋₆alquilcarbonilamino, C₁₋₆alquiltio, C₁₋₆ alquilsulfonil, halógeno, hidroxí, ciano, trifluorometil y trifluorometoxi.
6. El compuesto de la reivindicación 1 donde R^{1a} se selecciona independientemente del grupo formado por hidrogeno, metil, etil, n-propil, i-propil, n-butil, t-butil y fenil; de donde el radical fenil se sustituye opcionalmente con uno a tres sustituyentes seleccionados independientemente del grupo formado por C₁₋₆alquil, C₁₋₆alcoxi, di(C₁₋₆ alquil) amino, halógeno, trifluorometil y trifluorometoxi.

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7. El compuesto de la reivindicación 1 donde R^{1a} se selecciona independientemente del grupo formado por metil, etil y fenil.
 8. El compuesto de la reivindicación 1 donde R² se selecciona del grupo formado por fenil, naftalenil, furil, tienil, pirrolil, oxazolil, tiazolil, imidazolil, pirazolil, isoxazolil, isotiazolil, 1,2,3-oxadiazolil, 1,2,3-triazolil, 1,3,4-tiadiazolil, piridinil, piridazinil, pirimidinil, pirazinil, 1,3,5-triazinil, indolil, benzo[b]furil y benzo[b]itienil sustituidos opcionalmente por uno a tres sustituyentes seleccionados independientemente del grupo formado por C_{1,3}alquil, C_{2,3}alquenil, C_{1,3}alcoxi, amino, C_{1,3} alquilamino, di(C_{1,3}alquil)amino, C_{1,3}alquilcarbonil, C_{1,3}alquilcarboniloxi, C_{1,3}alquilcarbonilamino, cloro, flúor, hidroxil, trifluorometil y trifluorometoxi.
 9. El compuesto de la reivindicación 1 donde R² se selecciona del grupo formado por fenil, furil, tienil, piridinil y benzo[b]furil sustituidos opcionalmente por uno de los sustituyentes seleccionados del grupo formado por metil, etil, metoxi, etoxi, metilamino, etilamino, dimetilamino, dietilamino, metilcarbonil, metilcarboniloxi, metilcarbonilamino, flúor, hidroxil, trifluorometil y trifluorometoxi.
 10. El compuesto de la reivindicación 1 donde R² se selecciona de fenil sustituido opcionalmente por uno de los sustituyentes seleccionados del grupo formado por metoxi e hidroxil.
 11. El compuesto de la reivindicación 1 donde R³ se selecciona del grupo formado por fenil, naftalenil, furil, tienil, pirrolil, oxazolil, tiazolil,

imidazolil, pirazolil, isoxazolil, isotiazolil, 1,2,3-oxadiazolil, 1,2,3-triazolil, 1,3,4-tiadiazolil, piridinil, piridazinil, pirimidinil, pirazinil, 1,3,5-triazinil, indolil, benzo[b]furil y benzo[b]tienil sustituidos opcionalmente con uno o dos sustituyentes además de la porción -A-Z seleccionada independientemente del grupo formado por metil, etil, n-propil, i-propil, alil, metoxi, etoxi, amino, C₁₋₃alquilamino, di(C₁₋₃)alquilamino, C₁₋₃alquilcarbonil, C₁₋₃alquilcarboniloxi, C₁₋₃alquilcarbonil, C₁₋₃alquilaminocarbonil, C₁₋₃alquilcarbonilamino, C₁₋₃alquiltio, C₁₋₃alquilsulfonil, cloro, flúor, hidroxil, ciano, trifluorometil y trifluorometoxi; Alternativamente, cuyo fenil es sustituido con dos sustituyentes opcionales unidos a átomos de carbono adyacentes, los dos sustituyentes pueden formar juntos una parte única y fusionada; donde dicha parte se selecciona del grupo formado por -(CH₂)₃₋₅- y -O(CH₂)₁₋₃-O-

12.El compuesto de la reivindicación 1 donde R³ es fenil sustituido con la porción -A-Z en la posición 3 o 4

13.El compuesto de la reivindicación 1 donde A es -C(-X)-.

14.El compuesto de la reivindicación 1 donde Z es -N(R⁵)(R⁶).

15.El compuesto de la reivindicación 1 donde R⁴ se selecciona del grupo formado por C₁₋₄alquil (opcionalmente sustituido con uno a tres sustituyentes halógenos), C₂₋₄alquenil, aril y aril(C₁₋₄)alquil; en donde el radical aril se selecciona opcionalmente por uno a dos sustituyentes seleccionados independientemente del grupo formado por C₁₋₄alquil, -OCH₂O-, -O(CH₂)₂O- y halógeno.

16. El compuesto de la reivindicación 1 donde R⁴ se selecciona del grupo formado por C₁₋₃alquil (sustituido opcionalmente con uno a tres sustituyentes flúor), C₂₋₄ alquenil, fenil y benzil; en donde el radical fenil es sustituido opcionalmente por uno a dos sustituyentes seleccionados del grupo formado por C₁₋₃alquil, -OCH₂O-, -O(CH₂)₂O- y flúor.
17. El compuesto de la reivindicación 1 donde R⁴ se selecciona del grupo formado por metil, etil, 3-metil, fenil y benzil; en donde el radical fenil se sustituye opcionalmente con un sustituyente seleccionado del grupo formado por metil y flúor.
18. El compuesto de la reivindicación 1 donde R⁵ y R⁶ son seleccionados independientemente del grupo formado por hidrogeno, C₁₋₄alquil, fluoro (C₁₋₃) alquil, trifluoro(C₁₋₃)alquil, C₁₋₃alcoxi(C₁₋₃)alquil, C₂₋₅alquenil, ciclopropil, ciclopropil(C₁₋₃)alquil, ciclopentil, ciclopentil(C₁₋₃)alquil, ciclohexil, ciclohexil(C₁₋₃) alquil, pirrolidinil, pirrolidinil(C₁₋₃)alquil, 1,3-dioxolanil, 1,3-dioxolanil(C₁₋₃)alquil, 2-imidazolinil, 2-imidazolinil(C₁₋₃)alquil, imidazolidinil, imidazolidinil(C₁₋₃)alquil, 2-pirazolinil, 2-pirazolinil(C₁₋₃)alquil, pirazolidinil(C₁₋₃)alquil, piperidinil, piperidinil(C₁₋₃)alquil, morfolinil, morfolinil(C₁₋₃)alquil, tiomorfolinil, tiomorfolinil(C₁₋₃)alquil, piperazinil, piperazinil(C₁₋₃)alquil, piperonil, fenil, benzil, fenil(C₂₋₃)alquil, furil, furil(C₁₋₃)alquil, tienil, tienil(C₁₋₃)alquil, pirrolil(C₁₋₃)alquil, oxazolil, oxazolil(C₁₋₃)alquil, tiazolil, tiazolil(C₁₋₃)alquil, imidazolil, imidazolil (C₁₋₃) alquil, pirazolil, pirazolil(C₁₋₃)alquil, isoxazolil, isoxazolil(C₁₋₃)alquil, isotiazolil, isotiazolil(C₁₋₃)alquil, 1,2,3-oxadiazolil, 1,2,3-oxadiazolil(C₁₋₃)alquil, 1,2,3-triazolil, 1,2,3-triazolil(C₁₋₃)alquil, 1,3,4-tiadiazolil, 1,3,4-tiadiazolil(C₁₋₃)alquil, piridinil, piridinil(C₁₋₃)alquil, piridazinil, piridazinil(C₁₋₃)alquil, pirimidinil, pirimidinil(C₁₋₃)alquil, pirazinil, pirazinil(C₁₋₃)alquil, 1,3,5-triazinil, 1,3,5-triazinil(C₁₋₃)alquil, indolil(C₁₋₃)alquil, benzo[b]furil,

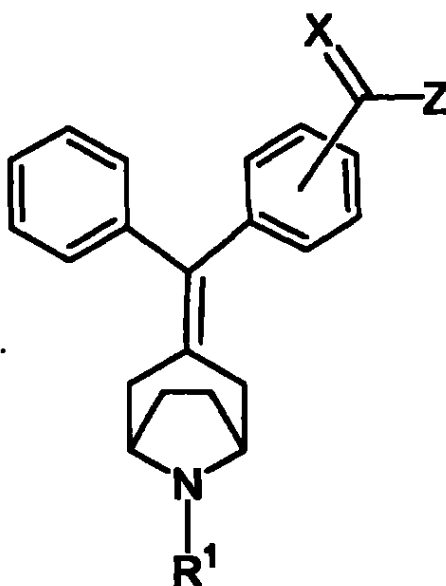
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benzo[b]furil(C₁₋₃)alquil, benzo[b]tienil, benzo[b]tienil(C₁₋₃)alquil, benzimidazolil, benzimidazolil(C₁₋₃) alquil, amino(C₁₋₃)alquil, C₁₋₃alquilamino(C₁₋₃)alquil, di(C₁₋₃)alquilamino(C₁₋₃) alquil, aminoimino, hidroxil(C₁₋₃)alquil y trifluoro(C₁₋₄)alcoxi; en donde pirrolidinil, 1,3-dioxolanil, 2-imidazolinil, imidazolidinil, 2-pirazolinil, pirazolidinil, piperidinil, morfolinil, tiomorfolinil, piperazinil son sustituidos opcionalmente con uno a tres sustituyentes seleccionados independientemente del grupo formado por C₁₋₄alquil y oxo; y, en donde el radical fenil es sustituido opcionalmente con uno a cuatro sustituyentes seleccionados independientemente del grupo formado por C₁₋₄alquil, C₁₋₄alcoxi, -OCH₂O-, -O(CH₂)₂O-, halógeno, hidroxil y ciano; alternativamente, R⁵ y R⁶ pueden formar, junto con el nitrógeno al cual están unidos, una porción heterocíclica fusionada seleccionada del grupo formado por pirrolidinil, imidazolidinil, pirazolidinil, piperidinil, morfolinil, tiomorfolinil y piperazinil opcionalmente sustituido con uno a cuatro sustituyentes seleccionados independientemente de C₁₋₄alquil.

19. El compuesto de la reivindicación 1 donde R⁵ y R⁶ son seleccionados independientemente del grupo formado por hidrógeno, metil, etil, n-propil, i-propil, t-butil, fluoro(C₁₋₃)alquil, metoxil(C₁₋₃)alquil, metalil, ciclopropil, ciclohexil, fenil, tiazolil, imidazolil (C₁₋₃) alquil, benzimidazolil(C₁₋₃)alquil, dimetilamino(C₁₋₃)alquil y hidroxil(C₁₋₃)alquil; en donde fenil es sustituido opcionalmente de sustituyentes seleccionado de flúor; alternativamente, R⁵ y R⁶ pueden formar, junto con el nitrógeno al cual están unidos, una porción heterocíclica fusionada seleccionada del grupo formado por pirrolidinil, piperidinil y morfolinil sustituidos opcionalmente con uno a cuatro sustituyentes seleccionados independientemente del grupo formado por metil, etil, n-propil y n-butil.

20.El compuesto de la reivindicación 1 donde R^5 y R^6 son seleccionados independientemente del grupo formado por hidrogeno, metil, etil, n-propil, i-propil, t-butil, 2-fluoroetil, metoxietil, metilil, ciclopropil, ciclohexil, fenil, tiazolil, 2-(2-imidazolil)etil, benzimidazolilmetil, dimetilaminopropil y hidroxietil; en donde el radical fenil es sustituido opcionalmente con flúor; alternatively, R^5 y R^6 pueden formar junto con el nitrógeno al cual están unidos una porción heterocíclica fusionada seleccionada del grupo formado por pirrolidinil, piperidinil y morfolinil; en donde piperidinil es sustituido con dos o cuatro sustituyentes seleccionados de metil.

21.El compuesto de la reivindicación 1 representado por la formula:



En donde la porción -C(=X)- es sustituida por fenil en la posición 3 o 4 y R¹, -C(=X)- y Z son seleccionados dependientemente del grupo formado por

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Ex #	R ¹	-C(=X)-	Z
1	metil	-4- C(=O)-	N, N-dietilamino;
2	H	-4- C(=O)-	N, N-dietilamino;
5	alil	-4- C(=O)-	N, N-dietilamino;
7	2-(4-fluorofenil)etil	-4- C(=O)-	N, N-dietilamino;
8	2-(2-tienil)etil	-4- C(=O)-	N, N-dietilamino;
9	2-(3-indolil)etil	-4- C(=O)-	N, N-dietilamino;
10	2-ciclohexiletal	-4- C(=O)-	N, N-dietilamino;
11	2-fenoxietil	-4- C(=O)-	N, N-dietilamino;
12	2-(4-etil-5-oxo-1,4-dihidrotetrazol-1-il)etil	-4- C(=O)-	N, N-dietilamino;
13	2-fenil-2-oxoetil	-4- C(=O)-	N, N-dietilamino;
14	2-(4-metoxifenil)-2-oxoetil	-4- C(=O)-	N, N-dietilamino;
15	2-(3-cianofenil)-2-oxoetil	-4-	N, N-dietilamino;

		C(=O)-	
16	2-(2,3-dihidro-1,4- benzodioxin-6-il)- 2-oxoetil	4-C(=O)-	N, N-dietilamino;
17	2-(3,4-dihidro-2H-1,5- benzodioxepin-7-il)-2- oxoetil	-4- C(=O)-	N, N-dietilamino;
18	propil	-4- C(=O)-	N, N-dietilamino;
19	2-feniletil	-4- C(=O)-	N, N-dietilamino;
20	piperonil	-4- C(=O)-	N, N-dietilamino;
21	3-fenilpropil	-4- C(=O)-	N, N-dietilamino;
22	metil	-3- C(=O)-	N-metil-N-(3-fluorofenil)amino;
25	2-feniletil	4-C(=S)-	N, N-dietilamino;
26	2-feniletil	4-C(=O)-	N-etilamino;
29	2-feniletil	4-C(=O)-	amino;
30	2-feniletil	-4- C(=O)-	4-morfolinil;
31	2-feniletil	4-C(=O)-	N, N-diisopropilamino;
32	2-feniletil	4-C(=O)-	N, N-bis(metoxietil)amino;
33	2-feniletil	-4- C(=O)-	1-pirrolidinil;
34	2-feniletil	4-C(=O)-	2,6-dimetil-1-piperidinil;
35	2-feniletil	4-C(=O)-	N-etil-N-

			(metilalil)amino;
36	2-feniletıl	-4- C(=O)-	N, N-dipropilamino;
37	2-feniletıl	-4- C(=O)-	N-t-butilamino;
38	2-feniletıl	-4- C(=O)-	N-(2-fluoroetil)amino;
39	2-feniletıl	-4- C(=O)-	N-(2-tiazolıl)amino;
40	2-feniletıl	-4- C(=O)-	N-(2-metoksietıl)amino;
41	2-feniletıl	-4- C(=O)-	N-(1 H-benzimidazol-2-ilmetıl)amino;
42	2-feniletıl	-4- C(=O)-	N-ciklohexilamino;
43	2-feniletıl	-4- C(=O)-	N-fenilamino;
44	2-feniletıl	-4- C(=O)-	N-[2-(2-imidazolıl)etil]amino;
45	2-feniletıl	-4- C(=O)-	N-ciklopropilamino;
46	2-feniletıl	-4- C(=O)-	N, N-(dimetilaminopropil)amino;
47	2-feniletıl	-4- C(=O)-	N-etıl-N-(hidroksietıl)amino;
48	2-(1,3-benzodioxol-5-il)etil	-4- C(=O)-	N-etilamino;
49	2-(1,3-benzodioxol-5-il)etil	-4-	N, N-dietilamino;

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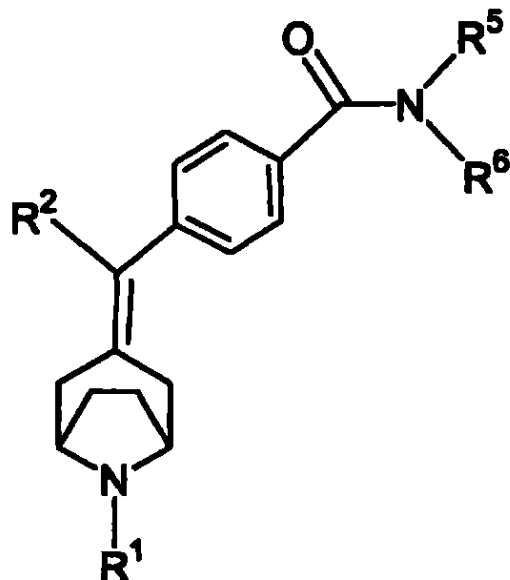
		C(=O)-	
50	metil	-4- C(=O)-	N-etilamino;
51	H	-4- C(=O)-	N-etilamino;
52	alil	-4- C(=O)-	N-etilamino;
53	2-(4-metoxifenil)etil	-4- C(=O)-	N, N-dietilamino;
54	2-(4-metoxifenil)etil morfolinil;	-4-C(=O)- 4-	
55	2-(4-metoxifenil)etil	-4- C(=O)-	N-etilamino;
56	2-(4-metoxifenil)etil	-4- C(=O)-	N, N-bis(2-metoxietil)amino;
57	2-(4-metoxifenil)etil	-4- C(=O)-	1-pirrolidinil;
58	2-(4-metoxifenil)etil	-4- C(=O)-	2,6-dimetil-1-piperidinil;
59	2-(4-metoxifenil)etil	-4- C(=O)-	N-etil-N-(metilalil)amino;
60	2-(4-metoxifenil)etil	-4- C(=O)-	N, N-(di-n-propil)amino;
61	2-(4-metoxifenil)etil	-4- C(=O)-	2,2,6,6-tetrametil-1-piperidinil;
62	2-(4-metoxifenil)etil	-4- C(=O)-	N, N-(di-2-propil)amino;
69	2-(4-hidroxifenil)etil	-4- C(=O)-	N-etilamino; y,

70	2-(4-hidroxifenil)etil	-4- C(=O)-	N, N-dietilamino;
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y compuestos farmacéuticamente aceptados, tales como enantiómeros diastómeros y sus sales correspondientes

22. El compuesto de la reivindicación 1 donde representado por la formula:



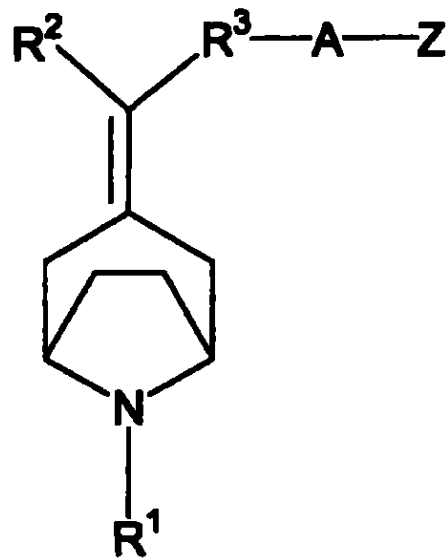
en donde R¹, R², R⁵ y R⁶ son seleccionados dependientemente del grupo formado por:

Ex	R ¹	R ²	(R ⁵)(R ⁶)
63	metil	4-MeOF	(H)(Et);
64	H	4-HOF	(H)(Et)
65	metil	4-MeOF	Et ₂ ;

66	H	4-HOF	Et ₂
67	2-(4-MeOF)etil	4-MeOF	Et ₂ y,
68	2-(4-HOF)etil	4-HOF	Et ₂

y compuestos farmacéuticamente aceptados, tales como enantiómeros diastómeros y sus sales correspondientes

- 23.El compuesto de la reivindicación 1 el cual tiene un efecto analgésico
- 24.El compuesto de la reivindicación 1 el cual es un efectivo agente inmunosupresores, antiinflamatorios, agentes para el tratamiento de condiciones neurológicas y psiquiátricas, medicamentos para casos de abuso de droga y alcohol, agentes para el tratamiento de gastritis y diarrea, agente cardiovascular o agente para el tratamiento de enfermedades respiratorias
25. Un compuesto farmacéutico que comprende el compuesto de la reivindicación 1 y un agente de carga aceptado farmacéuticamente
- 26.Un método para el tratamiento de una condición farmacológica en un sujeto en necesidad de este, comprendiendo la administración al sujeto de una cantidad terapéuticamente efectiva de un compuesto modulador receptor opiáceo seleccionado del grupo formado por un compuesto modulador receptor δ -opiáceos y un μ - opiáceos representado por la Formula (I):



(I)

en donde:

R^1 se selecciona del grupo conformado por hidrógeno, C_{1-8} alquil, halo, (C_{1-8}) alquil, C_{2-8} alquenil, C_{1-8} alcoxi(C_{2-8}) alquenil, C_{2-8} alquinil, C_{1-8} alcoxi(C_{2-8}) alquinil, cicloalquil, cicloalquil(C_{1-8}) alquil, cicloalquilcarbonil(C_{1-8}) alquil, cicloalquil (C_{2-8}) alquenil, cicloalquil (C_{2-8}) alquinil, heterociclil, heterociclil (C_{1-8}) alquil, heterociclilcarbonil (C_{1-8}) alquil, heterociclil (C_{2-8}) alquenil, heterociclil (C_{2-8}) alquinil, aril, aril (C_{1-8}) alquil, arilcarbonil (C_{1-8}) alquil, aril (C_{2-8}) alquenil, aril (C_{2-8}) alquinil, arilaminocarbonil (C_{1-8}) alquil, heteroaril (C_{1-8}) alquil, heteroarilcarbonil (C_{1-8}) alquil, heteroaril (C_{2-8}) alquenil, heteroaril (C_{2-8}) alquinil, heteroarilaminocarbonil (C_{1-8}) alquil, $(R^1)_2$ -N-(C_{1-8}) alquil, R^{1a} -O-(C_{1-8}) alquil, R^{1a} -S-(C_{1-8}) alquil, R^{1a} -SO-(C_{1-8}) alquil y R^{1a} -SO₂-(C_{1-8}) alquil; donde: el radical heterociclil es

substituido opcionalmente con uno a tres sustituyentes seleccionados independientemente del grupo formado por C_{1-6} alquil, C_{2-6} alquenil, C_{1-6} alcoxi, amino, C_{1-6} alquilamino, $di(C_{1-6}$ alquil)amino, C_{1-6} alquilcarbonil, C_{1-6} alquilcarboniloxi, C_{1-6} alquilcarbonilamino, C_{1-6} alquiltio, C_{1-6} alquilsulfonil, halógeno, hidroxil, oxo, ciano, trifluorometil y trifluorometoxi; y, donde los radicales aril y heteroaril están substituidos opcionalmente por uno a tres sustituyentes seleccionados independientemente del grupo conformado por C_{1-6} alquil, C_{2-6} alquenil, C_{1-6} alcoxi, amino, C_{1-6} alquilamino, $di(C_{1-6}$ alquil) amino, C_{1-6} alquilcarbonil, C_{1-6} alquilcarboniloxi, C_{1-6} alquilcarbonilamino, C_{1-6} alquiltio, C_{1-6} alquilsulfonil, halógeno, hidroxil, ciano, trifluorometil y trifluorometoxi;

R^{1a} es seleccionado independientemente del grupo formado por hidrogeno, C_{1-8} alquil, C_{1-8} alcoxi $C_{(1-8)}$ alquil, hidroxil(C_{1-8})alquil, halo $_{1-3}$ (C_{1-8})alquil, Halo $_{1-3}$ (C_{1-8})alcoxi(C_{1-8})alquil, C_{2-8} alquenil, C_{2-8} alquinil, cicloalquil, cicloalquil(C_{1-8})alquil, heterociclil, heterociclil(C_{1-8})alquil, heterociclil(C_{1-8})alquenil, heterociclil(C_{1-8})alquinil, aril, aril(C_{1-8})alquil, aril(C_{1-8})alquenil, aril(C_{1-8})alquinil, arilcarbonil(C_{1-8})alquil, heteroaril, heteroaril(C_{1-8})alquil, heteroaril(C_{1-8})alquenil, heteroaril(C_{1-8})alquinil y heteroarilcarbonil(C_{1-8})alquil; donde el radical heterociclil es substituido opcionalmente por uno a tres sustituyentes seleccionados independientemente del grupo formado por C_{1-6} alquil, C_{2-6} alquenil, C_{1-6} alcoxi, amino, C_{1-6} alquilamino, $di(C_{1-6}$ alquil)amino, C_{1-6} alquilcarbonil, C_{1-6} alquilcarboniloxi, C_{1-6} alquilcarbonilamino, C_{1-6} alquiltio, C_{1-6} alquilsulfonil, halógeno, hidroxil, oxo, ciano, trifluorometil y trifluorometoxi; y, donde el radical aril y heteroaril son substituidos opcionalmente con uno a tres sustituyentes seleccionados independientemente del grupo formado por C_{1-6} alquil, C_{2-6} alquenil, C_{1-6}

,alcoxi, amino, C₁₋₆alquilamino, di(C₁₋₆alquil)amino, C₁₋₆ alquilcarbonil, C₁₋₆alquilcarboniloxi, C₁₋₆alquilcarbonilamino, C₁₋₆alquiltio, C₁₋₆ alquilsulfonil, halógeno, hidroxí, ciano, trifluorometil y trifluorometoxi;

R² se selecciona del grupo formado por los radicales aril y heteroaril sustituidos opcionalmente con uno a tres sustituyentes seleccionados independientemente del grupo formado por C₁₋₆alquil, C₂₋₆alquenil, C₁₋₆alcoxi, amino, C₁₋₆ alquilamino, di(C₁₋₆alquil)amino, C₁₋₆alquilcarbonil, C₁₋₆alquilcarboniloxi, C₁₋₆ alquilocarbonil, C₁₋₆alquilaminocarbonil, C₁₋₆alquilcarbonilamino, C₁₋₆alquiltio, C₁₋₆alquilsulfonil, halógeno, hidroxí, ciano, trifluorometil y trifluorometoxi; Alternativamente, cuando los radicales aril y heteroaril son reemplazados por dos sustituyentes unidos a los átomos adyacentes de carbono, los dos sustituyentes pueden formar juntos una porción única y fusionada; en donde esta porción se selecciona del grupo formado por -(CH₂)₃₋₅ y -O(CH₂)₁₋₃ O-,

R³ se selecciona del grupo formado por aril y heteroaril sustituidos opcionalmente con uno o dos sustituyentes adicionales a la porción -A-Z seleccionada independientemente del grupo formado por C₁₋₆alquil, C₂₋₆ alquenil, C₁₋₆alcoxi, amino, C₁₋₆alquilamino, di(C₁₋₆alquil)amino, C₁₋₆ alquilcarbonil, C₁₋₆ alquilcarboniloxi, C₁₋₆alquilocarbonil, C₁₋₆ alquilaminocarbonil, C₁₋₆ alquilcarbonilamino, C₁₋₆alquiltio, C₁₋₆ alquilsulfonil, halógeno, hidroxí, ciano, trifluorometil y trifluorometoxi; alternativamente cuyo los radicales aril y heteroaril son sustituidos con dos sustituyentes opcionales unidos a los átomos adyacentes de carbono, los dos sustituyentes pueden formar juntos una porción única

y fusionada; donde esta parte se selecciona del grupo formado por $-(CH_2)_{3-5}-$ y $-O(CH_2)_{1-3}O-$;

A se selecciona del grupo formado por $-C(=X)-$ y $-SO_2-$;

X se selecciona del grupo formado por O y S;

Z se selecciona del grupo formado por $-O(R^4)$ y $-N(R^5)(R^6)$;

R^4 se selecciona del grupo formado por hidrogeno, C_{1-8} alquil (sustituido opcionalmente por uno a tres sustituyentes halógenos), C_{1-8} alcoxi(C_{1-8})alquil, C_{2-8} alquenil, cicloalquil, cicloalquil(C_{1-8})alquil, heterociclil, heterociclil (C_{1-8})alquil, aril, aril(C_{1-8})alquil, heteroaril, heteroaril(C_{1-8})alquil, amino(C_{1-8})alquil, C_{1-8} alquilamino(C_{1-8})alquil, di(C_{1-8})alquilamino(C_{1-8})alquil y hidroxil(C_{1-8})alquil; en donde el radical heterociclil se sustituye opcionalmente con uno a tres sustituyentes seleccionados independientemente del grupo formado por C_{1-8} alquil, C_{1-8} alcoxi, C_{1-8} alquenil, cicloalquil, trifluorometil, halógeno, hidroxil, oxo y ciano; y, donde el radical aril es sustituido opcionalmente por uno a cuatro sustituyentes seleccionados independientemente del grupo formado por C_{1-8} alquil, C_{1-8} alcoxi, C_{2-8} alquenil, cicloalquil, $-OCH_2O-$, $-O(CH_2)_2O-$, trifluorometil, halógeno, hidroxil y ciano; y,

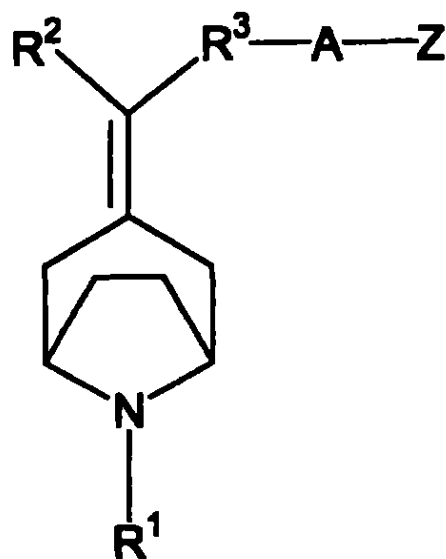
R^5 y R^6 son seleccionados independientemente del grupo formado por hidrogeno, C_{1-8} alquil (opcionalmente sustituido por uno a tres sustituyentes halógenos) C_{1-8} alcoxi(C_{1-8})alquil, C_{2-8} alquenil, cicloalquil, cicloalquil(C_{1-8})alquil, heterociclil, heterociclil(C_{1-8})alquil, aril, aril(C_{1-8})alquil, heteroaril, heteroaril(C_{1-8}) alquil, amino(C_{1-8})alquil, C_{1-8}

,alquilamino(C₁₋₆)alquil, di(C₁₋₆)alquilamino(C₁₋₆) alquil, aminoimino, aminocarbonil, aminocarbonil(C₁₋₆)alquil, ariloxycarbonilamino (C₁₋₆) alquil, heteroariloxycarbonilamino (C₁₋₆) alquil, hidrox(C₁₋₆)alquil y trifluoro(C₁₋₆)alcoxi; donde el radical heterociclil es opcionalmente sustituido por uno a tres sustituyentes independientemente seleccionados del grupo formado por C₁₋₆alquil, C₁₋₆alcoxi, C₂₋₆alquenil, cicloalquil, trifluorometil, halógeno, hidrox, oxo y ciano; y, donde el radical aril es opcionalmente sustituido por uno a cuatro sustituyentes independientemente seleccionados independientemente del grupo formado por C₁₋₆alquil, C₁₋₆alcoxi, C₂₋₆alquenil, cicloalquil, -OCH₂O-, -O(CH₂)₂O-, trifluorometil, halógeno, hidrox y ciano; alternativamente, R⁵ y R⁶ pueden, junto con el nitrógeno al cual están unidos, forman una porción fusionada heterociclil opcionalmente sustituida con uno a cuatro sustituyentes seleccionados independientemente del grupo formado por C₁₋₆alquil, C₁₋₆alcoxi, C₂₋₆alquenil, cicloalquil, trifluorometil, halógeno, hidrox y ciano; y compuestos farmacéuticamente aceptados, tales como enantiómeros diastómeros y sus sales correspondientes

- 27.El método de la reivindicación 26 en donde la cantidad terapéuticamente efectiva esta desde aproximadamente 0.01 Mg/ día hasta aproximadamente 15.000 Mg / día
- 28.El método de la reivindicación 26 en donde el compuesto modulador receptor δ -opiáceo o μ - opiáceo es un analgésico efectivo
- 29.El método de la reivindicación 26 donde el compuesto modulador receptor δ -opiáceos o μ - opiáceos es un efectivo agente inmunosupresor, antiinflamatorio, agente para el tratamiento de condiciones neurológicas y siquiátricas, medicamento para casos de abuso de droga y alcohol, agente para el tratamiento de gastritis y diarrea, agente cardiovascular o agente para el tratamiento de enfermedades respiratorias

30.El método de la reivindicación 26 donde la condición farmacológica es dolor

31.Una composición farmacéutica que comprende una combinación de un compuesto modulador receptor μ - opiáceo y un compuesto modulador receptor seleccionado del grupo formado por un δ -opiáceo y un compuesto modulador receptor μ - opiáceo representado por la Formula (I):



(I)

en donde:

R¹ se selecciona del grupo conformado por hidrógeno, C₁₋₈ alquil, halo, (C₁₋₈) alquil, C₂₋₈alquenil, C₁₋₈alcoxi(C₂₋₈)alquenil, C₂₋₈alquinil, C₁₋₈alcoxi (C₂₋₈)alquinil, cicloalquil, cicloalquil(C₁₋₈) alquil, cicloalquilcarbonil(C₁₋₈)alquil, cicloalquil (C₂₋₈) alquenil, cicloalquil (C₂₋₈) alquinil, heterociclil,

heterociclil (C_{1-8}) alquil, heterociclilcarbonil (C_{1-8}) alquil, heterociclil (C_{2-8}) alquenil, heterociclil (C_{2-8}) alquinil, aril, aril (C_{1-8}) alquil, arilcarbonil (C_{1-8}) alquil, aril (C_{2-8}) alquenil, aril (C_{2-8}) alquinil, arilaminocarbonil (C_{1-8}) alquil, heteroaril (C_{1-8}) alquil, heteroarilcarbonil (C_{1-8}) alquil, heteroaril (C_{2-8}) alquenil, heteroaril (C_{2-8}) alquinil, heteroarilaminocarbonil (C_{1-8}) alquil, $(R^1)_2-N-(C_{1-8})$ alquil, $R^{1a}-O-(C_{1-8})$ alquil, $R^{1a}-S-(C_{1-8})$ alquil, $R^{1a}-SO-(C_{1-8})$ alquil y $R^{1a}-SO_2-(C_{1-8})$ alquil; donde: el radical heterociclil es substituido opcionalmente con uno a tres sustituyentes seleccionados independientemente del grupo formado por C_{1-8} alquil, C_{2-8} alquenil, C_{1-8} alcoxi, amino, C_{1-8} alquilamino, di(C_{1-8} alquil)amino, C_{1-8} alquilcarbonil, C_{1-8} alquilcarboniloxi, C_{1-8} alquilcarbonilamino, C_{1-8} alquiltio, C_{1-8} alquilsulfonil, halógeno, hidroxil, oxo, ciano, trifluorometil y trifluorometoxil; y, donde los radicales aril y heteroaril están substituidos opcionalmente por uno a tres sustituyentes seleccionados independientemente del grupo conformado por C_{1-8} alquil, C_{2-8} alquenil, C_{1-8} alcoxi, amino, C_{1-8} alquilamino, di(C_{1-8} alquil) amino, C_{1-8} alquilcarbonil, C_{1-8} alquilcarboniloxi, C_{1-8} alquilcarbonilamino, C_{1-8} alquiltio, C_{1-8} alquilsulfonil, halógeno, hidroxil, ciano, trifluorometil y trifluorometoxil;

R^{1a} es seleccionado independientemente del grupo formado por hidrogeno, C_{1-8} alquil, C_{1-8} alcoxi $C_{(1-8)}$ alquil, hidroxil(C_{1-8}) alquil, halo $_{1-3}$ (C_{1-8}) alquil, Halo $_{1-3}$ (C_{1-8}) alcoxi(C_{1-8}) alquil, C_{2-8} alquenil, C_{2-8} alquinil, cicloalquil, cicloalquil(C_{1-8}) alquil, heterociclil, heterociclil(C_{1-8}) alquil, heterociclil(C_{1-8}) alquenil, heterociclil(C_{1-8}) alquinil, aril, aril(C_{1-8}) alquil, aril(C_{1-8}) alquenil, aril(C_{1-8}) alquinil, arilcarbonil(C_{1-8}) alquil, heteroaril, heteroaril(C_{1-8}) alquil, heteroaril(C_{1-8}) alquenil, heteroaril(C_{1-8}) alquinil y heteroarilcarbonil(C_{1-8}) alquil; donde el radical heterociclil es substituido opcionalmente por uno a tres sustituyentes seleccionados

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independientemente del grupo formado por C_{1-6} alquil, C_{2-6} alquenil, C_{1-6} alcoxi, amino, C_{1-6} alquilamino, di(C_{1-6} alquil)amino, C_{1-6} alquilcarbonil, C_{1-6} alquilcarboniloxi, C_{1-6} alquilcarbonilamino, C_{1-6} alquiltio, C_{1-6} alquilsulfonil, halógeno, hidroxí, oxo, ciano, trifluorometil y trifluorometoxi; y, donde el radical aril y heteroaril son substituidos opcionalmente con uno a tres substituyentes seleccionados independientemente del grupo formado por C_{1-6} alquil, C_{2-6} alquenil, C_{1-6} alcoxi, amino, C_{1-6} alquilamino, di(C_{1-6} alquil)amino, C_{1-6} alquilcarbonil, C_{1-6} alquilcarboniloxi, C_{1-6} alquilcarbonilamino, C_{1-6} alquiltio, C_{1-6} alquilsulfonil, halógeno, hidroxí, ciano, trifluorometil y trifluorometoxi;

R^2 se selecciona del grupo formado por los radicales aril y heteroaril substituidos opcionalmente con uno a tres substituyentes seleccionados independientemente del grupo formado por C_{1-6} alquil, C_{2-6} alquenil, C_{1-6} alcoxi, amino, C_{1-6} alquilamino, di(C_{1-6} alquil)amino, C_{1-6} alquilcarbonil, C_{1-6} alquilcarboniloxi, C_{1-6} alquilocarbonil, C_{1-6} alquilaminocarbonil, C_{1-6} alquilcarbonilamino, C_{1-6} alquiltio, C_{1-6} alquilsulfonil, halógeno, hidroxí, ciano, trifluorometil y trifluorometoxi; Alternativamente, cuando los radicales aril y heteroaril son reemplazados por dos substituyentes unidos a los átomos adyacentes de carbono, los dos substituyentes pueden formar juntos una porción única y fusionada; en donde esta porción se selecciona del grupo formado por $-(CH_2)_{3-5}$ y $-O(CH_2)_{1-3}O-$,

R^3 se selecciona del grupo formado por aril y heteroaril substituidos opcionalmente con uno o dos substituyentes adicionales a la porción -A-Z seleccionada independientemente del grupo formado por C_{1-6} alquil, C_{2-6} alquenil, C_{1-6} alcoxi, amino, C_{1-6} alquilamino, di(C_{1-6} alquil)amino, C_{1-6}

alquilcarbonil, C_{1-6} alquilcarboniloxi, C_{1-6} alquiloxicarbonil, C_{1-6} alquilaminocarbonil, C_{1-6} alquilcarbonilamino, C_{1-6} alquiltio, C_{1-6} alquilsulfonil, halógeno, hidroxil, ciano, trifluorometil y trifluorometoxi; alternativamente cuyo los radicales aril y heteroaril son sustituidos con dos sustituyentes opcionales unidos a los átomos adyacentes de carbono, los dos sustituyentes pueden formar juntos una porción única y fusionada; donde esta parte se selecciona del grupo formado por $-(CH_2)_{3-5}-$ y $-O(CH_2)_{1-3}O-$;

A se selecciona del grupo formado por $-C(=X)-$ y $-SO_2-$;

X se selecciona del grupo formado por O y S;

Z se selecciona del grupo formado por $-O(R^4)$ y $-N(R^5)(R^6)$;

R^4 se selecciona del grupo formado por hidrogeno, C_{1-6} alquil (sustituido opcionalmente por uno a tres sustituyentes halógenos), C_{1-6} alcoxi(C_{1-6})alquil, C_{2-6} alquenil, cicloalquil, cicloalquil(C_{1-6})alquil, heterociclil, heterociclil (C_{1-6})alquil, aril, aril(C_{1-6})alquil, heteroaril, heteroaril(C_{1-6})alquil, amino(C_{1-6})alquil, C_{1-6} alquilamino(C_{1-6})alquil, di(C_{1-6})alquilamino(C_{1-6})alquil y hidroxil(C_{1-6})alquil; en donde el radical heterociclil se sustituye opcionalmente con uno a tres sustituyentes seleccionados independientemente del grupo formado por C_{1-6} alquil, C_{1-6} alcoxi, C_{1-6} alquenil, cicloalquil, trifluorometil, halógeno, hidroxil, oxo y ciano; y, donde el radical aril es sustituido opcionalmente por uno a cuatro sustituyentes seleccionados independientemente del grupo formado por C_{1-6} alquil, C_{1-6} alcoxi, C_{2-6} alquenil, cicloalquil, $-OCH_2O-$, $-O(CH_2)_2O-$, trifluorometil, halógeno, hidroxil y ciano; y,

R⁵ y R⁶ son seleccionados independientemente del grupo formado por hidrogeno, C₁₋₆alquil (opcionalmente sustituido por uno a tres sustituyentes halógenos) C₁₋₆alcoxi(C₁₋₆)alquil, C₂₋₆alquenil, cicloalquil, cicloalquil(C₁₋₆)alquil, heterociclil, heterociclil(C₁₋₆)alquil, aril, aril(C₁₋₆)alquil, heteroaril, heteroaril(C₁₋₆) alquil, amino(C₁₋₆)alquil, C₁₋₆alquilamino(C₁₋₆)alquil, di(C₁₋₆)alquilamino(C₁₋₆) alquil, aminoimino, aminocarbonil, aminocarbonil(C₁₋₆)alquil, ariloxycarbonilamino (C₁₋₆) alquil, heteroariloxycarbonilamino (C₁₋₆) alquil, hidroxil(C₁₋₆)alquil y trifluoro(C₁₋₆)alcoxi; donde el radical heterociclil es opcionalmente sustituido por uno a tres sustituyentes independientemente seleccionados del grupo formado por C₁₋₆alquil, C₁₋₆alcoxi, C₂₋₆alquenil, cicloalquil, trifluorometil, halógeno, hidroxil, oxo y ciano; y, donde el radical aril es opcionalmente sustituido por uno a cuatro sustituyentes independientemente seleccionados independientemente del grupo formado por C₁₋₆alquil, C₁₋₆alcoxi, C₂₋₆alquenil, cicloalquil, -OCH₂O-, -O(CH₂)₂O-, trifluorometil, halógeno, hidroxil y ciano; alternatively, R⁵ y R⁶ pueden, junto con el nitrógeno al cual están unidos, forman una porción fusionada heterociclil opcionalmente sustituida con uno a cuatro sustituyentes seleccionados independientemente del grupo formado por C₁₋₆alquil, C₁₋₆alcoxi, C₂₋₆alquenil, cicloalquil, trifluorometil, halógeno, hidroxil y ciano; y compuestos farmacéuticamente aceptados, tales como enantiómeros diastómeros y sus sales correspondientes

32. La composición farmacéutica de la reivindicación 31 en donde el compuesto modulador receptor μ - opiáceo se selecciona de alfentanil, alilprodina, alfaprodina, anileridina, bezitramida, buprenorfina, clonitazene, ciclazocine, dextromoramida, dihidrocodeina, dihidromorfina, etoheptazina, etilmorfina, etonitazeno, fentanil, heroína, hidromorfona, hidroxipetidina, isometadona, ketobemidona, levallorfan, levorfanol,

- lofentanil, meperidina, meptazinol, metazocina, metadona, morfina, nalbupina, norlevorfanol, normetadona, nalorfina, normorfina, opio, oxycodona, oximorfona, fenazocina, piritramida, propiram, propoxifene, sufentanil, tramadol y diastómeros, sales, complejos y las mezclas de cualquiera de los anteriores.
33. Un método para el tratamiento de una condición farmacológica en un sujeto que necesite de este comprendiendo la administración al sujeto de una cantidad terapéuticamente efectiva de la composición farmacéutica de la reivindicación 31
34. El método de la reivindicación 33 en donde la cantidad terapéuticamente efectiva esta desde aproximadamente 0.01 Mg/ día hasta aproximadamente 15.000 Mg /día
35. El método de la reivindicación 33 donde la composición farmacéutica es un analgésico efectivo
36. El método de la reivindicación 33 donde la composición farmacéutica es un efectivo agente inmunosupresor, antiinflamatorio, agente para el tratamiento de condiciones neurológicas y psiquiátricas, medicamento para casos de abuso de droga y alcohol, agente para el tratamiento de gastritis y diarrea, agente cardiovascular o agente para el tratamiento de enfermedades respiratorias
37. El método de la reivindicación 26 donde la condición farmacológica es dolor

PA 406100



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THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

May 03, 2001

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 09/791,246

FILING DATE: February 22, 2001



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

T. Wallace
T. WALLACE
Certifying Officer

Please type a plus sign (+) inside this box ☐

UTILITY
PATENT APPLICATION
TRANSMITTAL

Attorney Docket No.

ORT-1375

First Inventor

Carson et al

Title

3-(DIARYLMETHYLENE)-8-AZABICYCLO[3.2.1]OCTANE
DERIVATIVES

Express Mail Label No.

EL457881376US

(only for new nonprovisional applications under 37 CFR 1.53(a))

APPLICATION ELEMENTS

ADDRESS TO:

Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

See MPEP Chapter 800 concerning utility patent application contents.

1. ☒ Fee Transmittal Form (e.g., PTO/SB/17)
(submit an original and a duplicate for fee processing)
2. ☐ Applicant claims small entity status.
3. ☒ Specification [Total Pages 75]
(Preferred arrangement set forth below)
 - Descriptive Title of the Invention
 - Cross Reference to Related Applications
 - Statement Regarding Fed sponsored R&D
 - Reference to sequence listing, a table, or a computer program listing appendix
 - Background of the Invention
 - Brief Summary of the Invention
 - Brief Description of the Drawings (if filed)
 - Detailed Description
 - Claim(s)
 - Abstract of the Disclosure
4. ☐ Drawing(s) (35 USC 113) [Total Sheets]
5. Oath or Declaration [Total Pages 4]
 - a. ☒ Newly un-executed (original or copy)
 - b. ☐ Copy from a prior application (37 CFR 1.53(d))
(for continuation/divisional with Box 18 completed)
 - 1. ☐ DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.53(d)(2) and 1.53(b).

7. ☐ CD-ROM or CD-R in duplicate, large table or Computer Program (Appendix)
8. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
 - a. ☐ Computer Readable Form (CRF)
 - b. ☐ Specification Sequence Listing on:
 - 1. ☐ CD-ROM or CD-R (2 copies); or
 - 2. ☐ paper
 - c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

9. ☐ Assignment Papers (cover sheet & document(s))
10. ☐ 37 CFR 3.73(b) Statement ☐ Power of Attorney
(when there is an assignee)
11. ☐ English Translation Document (if applicable)
12. ☐ Information Disclosure Statement
(IDS) PTO-1449 ☐ Copies of IDS Citations
13. ☐ Preliminary Amendment
14. ☒ Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
15. ☐ Certified Copy of Priority Document(s)
(if foreign priority is claimed)
16. ☐ Request and Certifications under 35 U.S.C. 122
(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or its equivalent.
17. ☐ Other

6. ☐ Application Data Sheet. See 37 CFR 1.76

18. ☐ If a CONTINUING APPLICATION, check appropriate box and supply the requisite information below and in a preliminary amendment, or in an Application Data Sheet under 37 CFR 1.76:

☐ Continuation ☐ Divisional ☐ Continuation-in-Part (CIP) of prior application No.: , filed

Prior application information: Examiner Group Art Unit:

For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 5b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

19. CORRESPONDENCE ADDRESS

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or ☐ Correspondence Address below

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Address: Johnson & Johnson
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New Brunswick, NJ 08833-7003 USA

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Please direct all telephone calls or telefaxes to John W. Harbour at:

Telephone: (732) 524-2189 Fax: (732) 524-2808

21. SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

NAME

John W. Harbour

Reg. No. 31365

SIGNATURE



DATE

February 22, 2001

02/22/01

09791246-022201

02-26-01

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FEE TRANSMITTAL	<i>Complete if Known</i>	
	Application Number	
	Filing Date	February 22, 2001
	First Named Inventor	Carson et al
	Group Art Unit	
	Examiner Name	
	Attorney Docket Number	ORT-1375

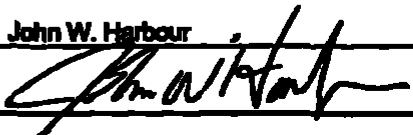
FEE CALCULATION

CLAIMS AS FILED

(1)	(2)	(3)	(4)	(5)
FOR:	NUMBER FILED	NUMBER EXTRA	RATE	BASIC FEE \$710.00
TOTAL CLAIMS	37 - 20 =	17	x 18.00	\$ 306.00
INDEPENDENT CLAIMS	3 - 3 =	0	x 80.00	\$ 0.00
MULTIPLE DEPENDENT CLAIMS	☐	N/A	\$270.00	
			TOTAL FEES	\$1,016.00

METHOD OF PAYMENT

- ☒ Please charge Deposit Account No. 10-0750/ORT1375/JWH in the amount of \$1,016.00. Three copies of this sheet are enclosed.
- ☒ The Commissioner is hereby authorized to charge any additional fees which may be required in connection with the filing of this communication, or credit any overpayment, to Account No. 10-0750/ORT1375/JWH. Three copies of this sheet are enclosed.

SUBMITTED BY:		<i>Complete (if applicable)</i>	
Typed or Printed Name	John W. Harbour	Reg. No. 31,385	
Signature		Date: 2/22/01	Deposit Account No. 10-0750

09791246.022201

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DOCKET NO. ORT-1375

IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

Applicant: Carson et al.

For : 3- (DIARYLMETHYLENE) -8-AZABICYCLO[3.2.1]OCTANE
DERIVATIVES

Express Mail Certificate

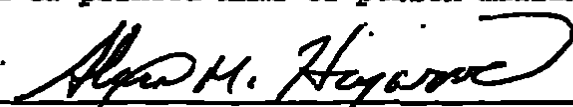
"Express Mail" mailing number: EL457891376US

Date of Deposit: February 22, 2001

I hereby certify that this complete Non-provisional application, including specification pages and claims 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 Assistant Commissioner for Patents, Washington, D.C. 20231.

A Combined Declaration and Power of Attorney will be submitted to the United States Patent and Trademark Office upon receipt of the U.S. Serial Number for this patent application.

Alwin M. Haywood
(Typed or printed name of person mailing paper or fee)


(Signature of person mailing paper or fee)

0 791246.022201

3-(DIARYLMETHYLENE)-8-AZABICYCLO[3.2.1]OCTANE DERIVATIVES

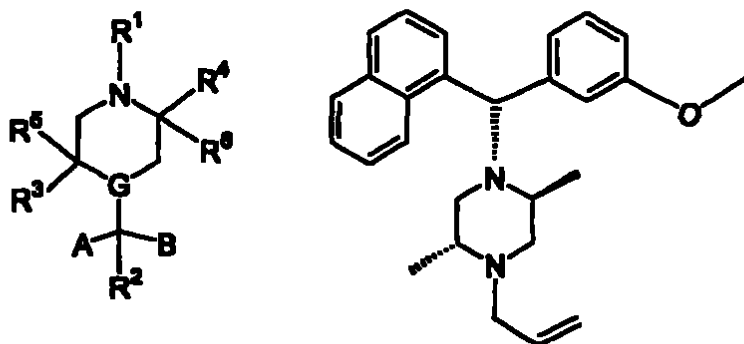
FIELD OF THE INVENTION

The present invention is directed to compounds useful as delta-opioid and mu-opioid receptor modulators. More particularly, the present invention is directed to 3-(diarylmethylene)-8-azabicyclo[3.2.1]octane derivatives useful as delta-opioid or mu-opioid receptor modulators.

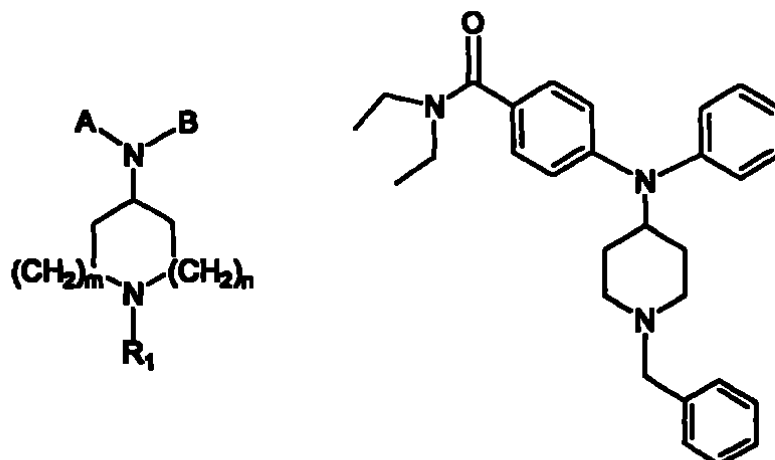
BACKGROUND OF THE INVENTION

WO 97/23466 describes compounds as having an analgesic effect of a general and one preferred formula:

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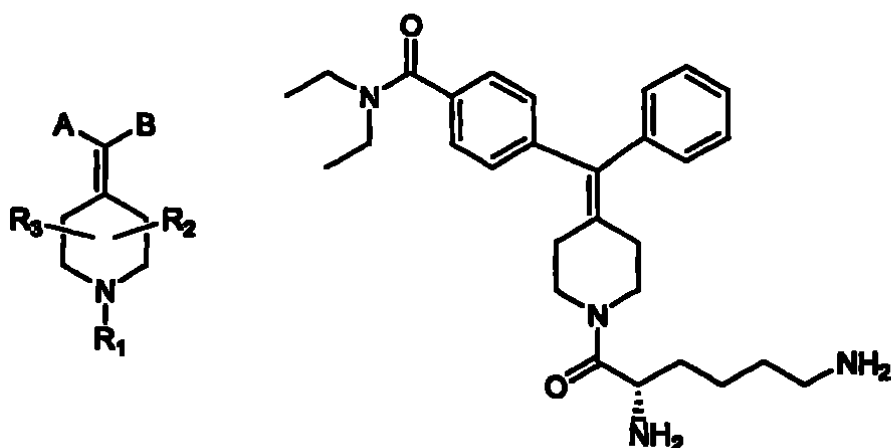


WO 98/28270 describes compounds as having an analgesic effect of a general and one preferred formula:



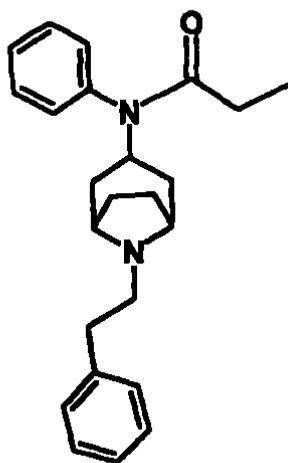
WO 98/28275 describes compounds as having an analgesic effect of a general and one preferred formula:

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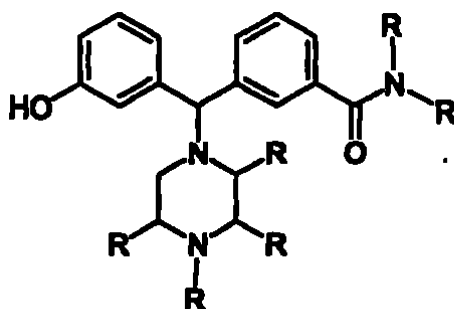
Amide derivatives of 3-aminotropane have been prepared and described as having potential pharmacological activity (Gutkowska, B., et al., *Acta Pol. Pharm.*, 1984, 41(6), 613-617), of the formula:

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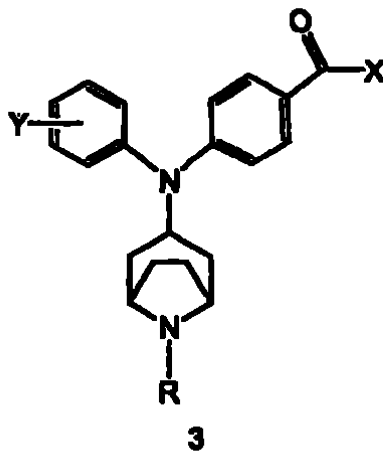
WO 93/15062 describes compounds as delta-opioid (δ -opioid) and μ -opioid (μ -opioid) receptor agonists of (approximately) the general formula:

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The synthesis and binding affinities for 4-Diarylaminotropans compounds as δ -opioid agonists have been described (Boyd, R.E., Carson, J.R., Codd, E.E., Gauthier, A.D., Nelson, L.A and Zhang, S-P., *Biorg. Med. Chem. Lett.*, 2000, 10: 1109-1111) of the general formula:

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wherein R is hydrogen, methyl, propyl, hexyl, 2-ethylbutyl, allyl, 3,3-dimethyl, cyclohexylmethyl, phenethyl, phenylpropyl, 2,2-diphenylethyl, 3,4-dimethoxyphenethyl, 4-fluorophenethyl, 2-furylmethyl, 3,4-methylenedioxybenzyl, cyano and X is *N,N*-dimethylamino, *N,N*-diethylamino, *N,N*-dipropylamino, *N*-methyl-*N*-ethylamino, *N*-methyl-*N*-propylamino, *N*-methyl-*N*-phenylamino, *N*-ethyl-*N*-(4-methyl)benzylamino, *N*-butyl-*N*-ethylamino, *N*-butyl-*N*-propylamino, [*N*-ethyl-*N*-(2-methyl)allyl]amino, hydroxy, *O*-*t*-butyl and 1-pyrrolidinyl; and, Y is hydrogen, methoxy and methylthio.

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Other selective 4-[(8-alkyl-8-azabicyclo[3.2.1]octyl-3-yl)-3-arylanilino]-*N,N*-diethylbenzamide δ -opioid ligands have also been described (Thomas, J.B., Atkinson, R.N., Rothman, R.B., Burgess, J.P., Mascarella, S.W., Dersch, C.M., Xu, H. and Carroll, F.I., *Biorg. Med. Chem. Lett.*, 2000, 10: 1281-1284).

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The present invention is directed to compounds useful as delta-opioid and mu-opioid receptor modulators. More particularly, the present invention is directed to delta-opioid and mu-opioid receptor modulators.

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It is an object of the present invention to provide 3-(diarylmethylene)-8-azabicyclo[3.2.1]octane derivatives useful as δ -opioid or μ -opioid receptor modulators. It is also an object of the present invention to provide δ -opioid and μ -opioid receptor selective agonists as analgesics having reduced side-effects. It is another object of the present invention to provide δ -opioid and μ -opioid receptor selective antagonists as immunosuppressants, antiinflammatory agents, agents for the treatment of neurological and psychiatric conditions, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents and agents for the treatment of respiratory diseases, having reduced side-effects. It is also another object of the present invention to provide a useful pharmaceutical composition comprising a compound of the present invention useful as a δ -opioid or μ -opioid receptor modulator. It is a further object of the present invention to provide a useful

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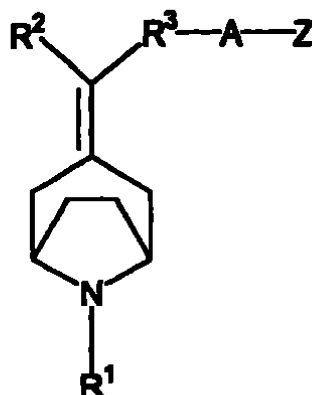
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pharmaceutical composition comprising a δ -opioid or μ -opioid receptor modulator compound of Formula (I) in combination with a μ -opioid receptor modulator or a δ -opioid or μ -opioid receptor modulator compound of Formula (I) wherein the combination has a synergistic therapeutic effect.

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SUMMARY OF THE INVENTION

The present invention provides an opioid receptor modulator compound selected from the group consisting of a δ -opioid and a μ -opioid receptor modulator compound of Formula (I):



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(I)

wherein:

R¹ is selected from the group consisting of hydrogen, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy(C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy(C₂₋₆alkynyl, cycloalkyl, cycloalkyl(C₁₋₆alkyl, cycloalkylcarbonyl(C₁₋₆alkyl, cycloalkyl(C₂₋₆alkenyl, cycloalkyl(C₂₋₆alkynyl, heterocyclyl, heterocyclyl(C₁₋₆alkyl, heterocyclylcarbonyl(C₁₋₆alkyl, heterocyclyl(C₂₋₆alkenyl, heterocyclyl(C₂₋₆alkynyl, aryl, aryl(C₁₋₆alkyl, arylcarbonyl(C₁₋₆alkyl, aryl(C₂₋₆alkenyl, aryl(C₂₋₆alkynyl, arylaminocarbonyl(C₁₋₆alkyl, heteroaryl(C₁₋₆alkyl, heteroarylcarbonyl(C₁₋₆alkyl, heteroaryl(C₂₋₆alkenyl, heteroaryl(C₂₋₆alkynyl, heteroarylaminocarbonyl(C₁₋₆alkyl, (R^{1a})₂-N-(C₁₋₆alkyl, R^{1a}-O-(C₁₋₆alkyl, R^{1a}-S-(C₁₋₆alkyl, R^{1a}-SO-(C₁₋₆alkyl and R^{1a}-SO₂-(C₁₋₆alkyl; wherein

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heterocyclyl is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, oxo, cyano, trifluoromethyl and trifluoromethoxy; and, wherein aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, cyano, trifluoromethyl and trifluoromethoxy;

R^{1a} is independently selected from the group consisting of hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy(C₁₋₆alkyl, hydroxy(C₁₋₆alkyl, halo₁₋₃(C₁₋₆alkyl, halo₁₋₃(C₁₋₆alkoxy(C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, cycloalkyl, cycloalkyl(C₁₋₆alkyl, heterocyclyl, heterocyclyl(C₁₋₆alkyl, heterocyclyl(C₁₋₆alkenyl, heterocyclyl(C₁₋₆alkynyl, aryl, aryl(C₁₋₆alkyl, aryl(C₁₋₆alkenyl, aryl(C₁₋₆alkynyl, arylcarbonyl(C₁₋₆alkyl, heteroaryl, heteroaryl(C₁₋₆alkyl, heteroaryl(C₁₋₆alkenyl, heteroaryl(C₁₋₆alkynyl and heteroarylcarbonyl(C₁₋₆alkyl; wherein heterocyclyl is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, oxo, cyano, trifluoromethyl and trifluoromethoxy; and, wherein aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, cyano, trifluoromethyl and trifluoromethoxy;

R² is selected from the group consisting of aryl and heteroaryl optionally substituted with one to three substituents independently selected from the

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- group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, amino, C_{1-6} alkylamino, $di(C_{1-6}$ alkyl)amino, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylaminocarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, halogen, hydroxy, cyano, trifluoromethyl and trifluoromethoxy; alternatively, when aryl and heteroaryl are substituted with two substituents attached to adjacent carbon atoms, the two substituents can together form a single fused moiety; wherein the moiety is selected from the group consisting of $-(CH_2)_{2-8}-$ and $-O(CH_2)_{1-3}O-$;
- 5
- 10 R^3 is selected from the group consisting of aryl and heteroaryl optionally substituted with one or two substituents in addition to the -A-Z moiety independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, amino, C_{1-6} alkylamino, $di(C_{1-6}$ alkyl)amino, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylaminocarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, halogen, hydroxy, cyano, trifluoromethyl and trifluoromethoxy; alternatively, when aryl and heteroaryl are substituted with two optional substituents attached to adjacent carbon atoms, the two substituents can together form a single fused moiety; wherein the moiety is selected from the group consisting of
- 15
- 20 $-(CH_2)_{2-8}-$ and $-O(CH_2)_{1-3}O-$;

A is selected from the group consisting of $-C(=X)-$ and $-SO_2-$;

X is selected from the group consisting of O and S;

25

Z is selected from the group consisting of $-O(R^4)$ and $-N(R^6)(R^6)$;

- R^4 is selected from the group consisting of hydrogen, C_{1-6} alkyl (optionally substituted with one to three halogen substituents), C_{1-6} alkoxy(C_{1-6} alkyl, C_{2-6} alkenyl, cycloalkyl, cycloalkyl(C_{1-6} alkyl, heterocyclyl, heterocyclyl(C_{1-6} alkyl, aryl, aryl(C_{1-6} alkyl, heteroaryl, heteroaryl(C_{1-6} alkyl, amino(C_{1-6} alkyl, C_{1-6} alkylamino(C_{1-6} alkyl, $di(C_{1-6})$ alkylamino($C_{1-6})$ alkyl and hydroxy($C_{1-6})$ alkyl; wherein heterocyclyl is optionally substituted with one to
- 30

three substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, cycloalkyl, trifluoromethyl, halogen, hydroxy, oxo and cyano; and, wherein aryl is optionally substituted with one to four substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, cycloalkyl, -OCH₂O-, -O(CH₂)₂O-, trifluoromethyl, halogen, hydroxy and cyano; and,

R^a and R^b are independently selected from the group consisting of hydrogen, C₁₋₆alkyl (optionally substituted with one to three halogen substituents), C₁₋₆alkoxy(C₁₋₆)alkyl, C₂₋₆alkenyl, cycloalkyl, cycloalkyl(C₁₋₆)alkyl, heterocyclyl, heterocyclyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, amino(C₁₋₆)alkyl, C₁₋₆alkylamino(C₁₋₆)alkyl, di(C₁₋₆)alkylamino(C₁₋₆)alkyl, aminomino, aminocarbonyl, aminocarbonyl(C₁₋₆)alkyl, aryloxy carbonylamino(C₁₋₆)alkyl, heteroaryloxy carbonylamino(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl and trifluoro(C₁₋₆)alkoxy; wherein heterocyclyl is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, cycloalkyl, trifluoromethyl, halogen, hydroxy, oxo and cyano; and, wherein aryl is optionally substituted with one to four substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, cycloalkyl, -OCH₂O-, -O(CH₂)₂O-, trifluoromethyl, halogen, hydroxy and cyano; alternatively, R^a and R^b may, together with the nitrogen to which they are attached, form a fused heterocyclyl moiety optionally substituted with one to four substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, cycloalkyl, trifluoromethyl, halogen, hydroxy and cyano;

and pharmaceutically acceptable enantiomers, diastereomers and salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Embodiments of a compound of Formula (I) include those compounds

wherein, preferably, R¹ is selected from the group consisting of hydrogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₂₋₃alkynyl, cycloalkyl, cycloalkyl(C₁₋₃)alkyl, heterocyclyl, heterocyclyl(C₁₋₃)alkyl, heterocyclcarbonyl(C₁₋₃)alkyl, aryl(C₁₋₃)alkyl, arylcarbonyl(C₁₋₃)alkyl, aryl(C₂₋₃)alkynyl, arylaminocarbonyl(C₁₋₃)alkyl, heteroaryl(C₁₋₃)alkyl, (R^{1a})₂N-(C₁₋₃)alkyl and R^{1a}-O-(C₁₋₃)alkyl; wherein heterocyclyl is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₃alkyl, C₁₋₃alkoxy, halogen, hydroxy, oxo and cyano; and, wherein aryl is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₃alkyl, C₁₋₃alkoxy, halogen, hydroxy and cyano.

More preferably, R¹ is selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *n*-hexyl, butenyl, allyl, 3,3-dimethyl, cyclopropyl, cyclopropyl(C₁₋₃)alkyl, cyclohexyl, cyclohexyl(C₁₋₃)alkyl, pyrrolidinyl, pyrrolidinyl(C₁₋₃)alkyl, 1,3-dioxolanyl(C₁₋₃)alkyl, 2-imidazolynyl, 2-imidazolynyl(C₁₋₃)alkyl, imidazolidinyl, imidazolidinyl(C₁₋₃)alkyl, 2-pyrazolynyl, 2-pyrazolynyl(C₁₋₃)alkyl, pyrazolidinyl, pyrazolidinyl(C₁₋₃)alkyl, piperidinyl, piperidinyl(C₁₋₃)alkyl, morpholynyl, morpholynyl(C₁₋₃)alkyl, thiomorpholynyl, thiomorpholynyl(C₁₋₃)alkyl, piperazinyl, piperazinyl(C₁₋₃)alkyl, [4-(C₁₋₃)alkyl-5-oxo-1,4-dihydro-1,2,4-triazol-1-yl](C₁₋₃)alkyl, piperonyl, (1,3-benzodioxol-5-yl)(C₂₋₃)alkyl, (2,3-dihydro-1,4-benzodioxin-6-yl)carbonyl(C₁₋₃)alkyl, (3,4-dihydro-2*H*-1,5-benzodioxepin-7-yl)carbonyl(C₁₋₃)alkyl, benzyl, phenyl(C₂₋₃)alkyl, phenyl(C₂₋₃)alkynyl, diphenyl(C₁₋₃)alkyl, phenylcarbonyl(C₁₋₃)alkyl, phenylaminocarbonyl(C₁₋₃)alkyl, furyl(C₁₋₃)alkyl, thienyl(C₁₋₃)alkyl, pyrimidinyl(C₁₋₃)alkyl, oxazolyl(C₁₋₃)alkyl, thiazolyl(C₁₋₃)alkyl, imidazolyl(C₁₋₃)alkyl, pyrazolyl(C₁₋₃)alkyl, isoxazolyl(C₁₋₃)alkyl, isothiazolyl(C₁₋₃)alkyl, 1,2,3-oxadiazolyl(C₁₋₃)alkyl, 1,2,3-triazolyl(C₁₋₃)alkyl, 1,3,4-thiadiazolyl(C₁₋₃)alkyl, pyridinyl(C₁₋₃)alkyl, pyridazinyl(C₁₋₃)alkyl, pyrimidinyl(C₁₋₃)alkyl, pyrazinyl(C₁₋₃)alkyl, 1,3,5-triazinyl(C₁₋₃)alkyl, indolyl(C₁₋₃)alkyl, benzo[b]furyl(C₁₋₃)alkyl, benzo[b]thienyl(C₁₋₃)alkyl, (R^{1a})₂N-(C₁₋₃)alkyl and R^{1a}-O-(C₁₋₃)alkyl; wherein pyrrolidinyl, 2-imidazolynyl, imidazolidinyl, 2-pyrazolynyl, pyrazolidinyl, piperidinyl, morpholynyl, thiomorpholynyl and piperazinyl are optionally substituted with one to three substituents selected

from oxo; and, wherein phenyl is optionally substituted with one to three substituents independently selected from the group consisting of methyl, ethyl, *n*-propyl, *n*-butyl, methoxy, ethoxy, propoxy, butoxy, chlorine, fluorine, hydroxy and cyano.

5

Most preferably, R¹ is selected from the group consisting of hydrogen, methyl, *n*-propyl, *n*-butyl, allyl, 3,3-dimethyl, cyclopropylmethyl, cyclohexylethyl, 2-(4-ethyl-5-oxo-1,4-dihydro-1,2,4-triazol-1-yl)ethyl, piperonyl, 2-(1,3-benzodioxol-5-yl)ethyl, 2-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-oxoethyl, 2-(3,4-dihydro-2*H*-1,5-benzodioxepin-7-yl)-2-oxoethyl, benzyl, phenethyl, phenylpropyl, phenoxyethyl, phenylcarbonylmethyl, phenylcarbonylethyl, phenylaminocarbonylmethyl, thienylmethyl, thienylethyl, imidazolylmethyl, pyridinylmethyl and indolylethyl; wherein phenyl is optionally substituted with one to three substituents independently selected from the group consisting of methoxy, fluorine, hydroxy and cyano.

15

Embodiments of a compound of Formula (i) include those compounds wherein, preferably, R^{1a} is independently selected from the group consisting of hydrogen, C₁₋₆alkyl and aryl; wherein aryl is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, cyano, trifluoromethyl and trifluoromethoxy. More preferably, R^{1a} is independently selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl and phenyl; wherein phenyl is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, di(C₁₋₆alkyl)amino, halogen, trifluoromethyl and trifluoromethoxy. Most preferably, R^{1a} is independently selected from the group consisting of methyl, ethyl and phenyl.

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Embodiments of a compound of Formula (I) include those compounds wherein, preferably, R² is selected from the group consisting of phenyl, naphthalenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl,

- isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, indolyl, benzo[b]furyl and benzo[b]thienyl optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₃alkyl, C₂₋₃alkenyl,
- 5 C₁₋₃alkoxy, amino, C₁₋₃alkylamino, di(C₁₋₃alkyl)amino, C₁₋₃alkylcarbonyl, C₁₋₃alkylcarbonyloxy, C₁₋₃alkylcarbonylamino, chlorine, fluorine, hydroxy, trifluoromethyl and trifluoromethoxy.

- More preferably, R² is selected from the group consisting of phenyl,
- 10 furyl, thienyl, pyridinyl and benzo[b]furyl optionally substituted with one substituent selected from the group consisting of methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, methylcarbonyl, methylcarbonyloxy, methylcarbonylamino, fluorine, hydroxy, trifluoromethyl and trifluoromethoxy.

- 15 Most preferably, R² is selected from phenyl optionally substituted with one substituent selected from the group consisting of methoxy and hydroxy.

- Embodiments of a compound of Formula (I) include those compounds
- 20 wherein, preferably, R³ is selected from the group consisting of phenyl, naphthalenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, indolyl, benzo[b]furyl and benzo[b]thienyl optionally substituted with one or two substituents in
- 25 addition to the -A-Z moiety independently selected from the group consisting of methyl, ethyl, *n*-propyl, *i*-propyl, allyl, methoxy, ethoxy, amino, C₁₋₃alkylamino, di(C₁₋₃)alkylamino, C₁₋₃alkylcarbonyl, C₁₋₃alkylcarbonyloxy, C₁₋₃alkylcarbonyl, C₁₋₃alkylaminocarbonyl, C₁₋₃alkylcarbonylamino, C₁₋₃alkylthio, C₁₋₃alkylsulfonyl, chloro, fluoro, hydroxy, cyano, trifluoromethyl and trifluoromethoxy;
- 30 alternatively, when phenyl is substituted with two optional substituents attached to adjacent carbon atoms, the two substituents can together form a single fused moiety; wherein the moiety is selected from the group consisting of -(CH₂)₂₋₆- and -O(CH₂)₁₋₃O-.

More preferably, R^3 is phenyl substituted with the moiety -A-Z at the 3 or 4 position.

- 5 Embodiments of a compound of Formula (I) include those compounds wherein, preferably, A is $-C(=X)-$.

Embodiments of a compound of Formula (I) include those compounds wherein, preferably, Z is $-N(R^6)(R^6)$.

10

An embodiment of a compound of Formula (I) includes those compounds wherein, preferably, R^4 is selected from the group consisting of C_{1-6} alkyl (optionally substituted with one to three halogen substituents), C_{2-6} alkenyl, aryl and aryl(C_{1-3})alkyl; wherein aryl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3} alkyl, $-OCH_2O-$, $-O(CH_2)_2O-$ and halogen.

15

More preferably, R^4 is selected from the group consisting of C_{1-3} alkyl (optionally substituted with one or three fluorine substituents), C_{2-4} alkenyl, phenyl and benzyl; wherein phenyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3} alkyl, $-OCH_2O-$, $-O(CH_2)_2O-$ and fluorine.

20

Most preferably, R^4 is selected from the group consisting of methyl, ethyl, 3-methyl, phenyl and benzyl; wherein phenyl is optionally substituted with one substituent selected from the group consisting of methyl and fluorine.

25

An embodiment of a compound of Formula (I) includes those compounds wherein, preferably, R^5 and R^6 are independently selected from the group consisting of hydrogen, C_{1-4} alkyl, fluoro(C_{1-3})alkyl, trifluoro(C_{1-3})alkyl, C_{1-3} alkoxy(C_{1-3})alkyl, C_{2-6} alkenyl, cyclopropyl, cyclopropyl(C_{1-3})alkyl, cyclopentyl, cyclopentyl(C_{1-3})alkyl, cyclohexyl, cyclohexyl(C_{1-3})alkyl, pyrrolidinyl, pyrrolidinyl(C_{1-3})alkyl, 1,3-dioxolanyl, 1,3-dioxolanyl(C_{1-3})alkyl, 2-imidazolynyl,

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- 2-imidazoliny(C₁₋₃)alkyl, imidazolidinyl, imidazolidinyl(C₁₋₃)alkyl, 2-pyrazoliny, 2-pyrazoliny(C₁₋₃)alkyl, pyrazolidinyl(C₁₋₃)alkyl, piperidinyl, piperidinyl(C₁₋₃)alkyl, morpholinyl, morpholinyl(C₁₋₃)alkyl, thiomorpholinyl, thiomorpholinyl(C₁₋₃)alkyl, piperazinyl, piperazinyl(C₁₋₃)alkyl, piperonyl, phenyl, benzyl, phenyl(C₁₋₃)alkyl, 5 furyl, furyl(C₁₋₃)alkyl, thienyl, thienyl(C₁₋₃)alkyl, pyrrolyl(C₁₋₃)alkyl, oxazolyl, oxazolyl(C₁₋₃)alkyl, thiazolyl, thiazolyl(C₁₋₃)alkyl, imidazolyl, imidazolyl(C₁₋₃)alkyl, pyrazolyl, pyrazolyl(C₁₋₃)alkyl, isoxazolyl, isoxazolyl(C₁₋₃)alkyl, isothiazolyl, isothiazolyl(C₁₋₃)alkyl, 1,2,3-oxadiazolyl, 1,2,3-oxadiazolyl(C₁₋₃)alkyl, 1,2,3-triazolyl, 1,2,3-triazolyl(C₁₋₃)alkyl, 1,3,4-thiadiazolyl, 10 1,3,4-thiadiazolyl(C₁₋₃)alkyl, pyridinyl, pyridinyl(C₁₋₃)alkyl, pyridazinyl, pyridazinyl(C₁₋₃)alkyl, pyrimidinyl, pyrimidinyl(C₁₋₃)alkyl, pyrazinyl, pyrazinyl(C₁₋₃)alkyl, 1,3,5-triazinyl, 1,3,5-triazinyl(C₁₋₃)alkyl, indolyl(C₁₋₃)alkyl, benzo[b]furyl, benzo[b]furyl(C₁₋₃)alkyl, benzo[b]thienyl, benzo[b]thienyl(C₁₋₃)alkyl, benzimidazolyl, benzimidazolyl(C₁₋₃)alkyl, 15 amino(C₁₋₃)alkyl, C₁₋₃alkylamino(C₁₋₃)alkyl, di(C₁₋₃)alkylamino(C₁₋₃)alkyl, aminolmino, hydroxy(C₁₋₃)alkyl and trifluoro(C₁₋₃)alkoxy; wherein pyrrolidinyl, 1,3-dioxolanyl, 2-imidazoliny, imidazolidinyl, 2-pyrazoliny, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl are optionally substituted with one to three substituents independently selected from the group consisting 20 of C₁₋₄alkyl and oxo; and, wherein phenyl is optionally substituted with one to four substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄alkoxy, -OCH₂O-, -O(CH₂)₂O-, halogen, hydroxy and cyano; alternatively, R^a and R^b may, together with the nitrogen to which they are attached, form a fused heterocycliy moiety selected from the group consisting of pyrrolidinyl, 25 imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl and piperazinyl optionally substituted with one to four substituents independently selected from C₁₋₄alkyl.

More preferably, R^a and R^b are independently selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *t*-butyl, fluoro(C₁₋₃)alkyl, methoxy(C₁₋₃)alkyl, methyl, cyclopropyl, cyclohexyl, phenyl, thiazolyl, imidazolyl(C₁₋₃)alkyl, benzimidazolyl(C₁₋₃)alkyl, dimethylamino(C₁₋₃)alkyl and hydroxy(C₁₋₃)alkyl; wherein phenyl is optionally substituted with one to three

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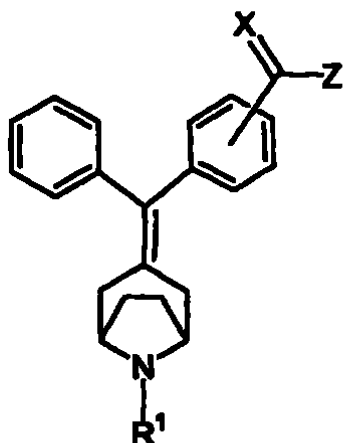
substituents selected from fluorine; alternatively, R⁶ and R⁶ may, together with the nitrogen to which they are attached, form a fused heterocyclyl moiety selected from the group consisting of pyrrolidiny, piperidiny and morpholiny optionally substituted with one to four substituents independently selected from the group consisting of methyl, ethyl, *n*-propyl and *n*-butyl.

Most preferably, R⁶ and R⁶ are independently selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *t*-butyl, 2-fluoroethyl, methoxyethyl, methallyl, cyclopropyl, cyclohexyl, phenyl, thiazolyl, 2-(2-imidazolyl)ethyl, benzimidazolymethyl, dimethylaminopropyl and hydroxyethyl; wherein phenyl is optionally substituted with fluorine; alternatively, R⁶ and R⁶ may, together with the nitrogen to which they are attached, form a fused heterocyclyl moiety selected from the group consisting of pyrrolidiny, piperidiny and morpholiny; wherein piperidiny is substituted with two or four substituents selected from methyl.

5

10 Table 1 lists compounds exemplified in the present invention of the formula:

Table 1



15 wherein the moiety -C(=X)- is substituted on phenyl at the 3 or 4 position and R¹, -C(=X)- and Z are dependently selected from the group consisting of:

Ex #	R ¹	-C(=X)-	Z
1	methyl	-4-C(=O)-	N,N-diethylamino;

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2	H	-4-C(=O)-	N,N-diethylamino;
5	allyl	-4-C(=O)-	N,N-diethylamino;
7	2-(4-fluorophenyl)ethyl	-4-C(=O)-	N,N-diethylamino;
8	2-(2-thienyl)ethyl	-4-C(=O)-	N,N-diethylamino;
9	2-(3-indolyl)ethyl	-4-C(=O)-	N,N-diethylamino;
10	2-cyclohexylethyl	-4-C(=O)-	N,N-diethylamino;
11	2-phenoxyethyl	-4-C(=O)-	N,N-diethylamino;
12	2-(4-ethyl-5-oxo-1,4-dihydro-1H-tetrazol-1-yl)ethyl	-4-C(=O)-	N,N-diethylamino;
13	2-phenyl-2-oxoethyl	-4-C(=O)-	N,N-diethylamino;
14	2-(4-methoxyphenyl)-2-oxoethyl	-4-C(=O)-	N,N-diethylamino;
15	2-(3-cyanophenyl)-2-oxoethyl	-4-C(=O)-	N,N-diethylamino;
16	2-(2,3-dihydro-1,4-benzodioxin-8-yl)-2-oxoethyl	-4-C(=O)-	N,N-diethylamino;
17	2-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)-2-oxoethyl	-4-C(=O)-	N,N-diethylamino;
18	propyl	-4-C(=O)-	N,N-diethylamino;
19	2-phenylethyl	-4-C(=O)-	N,N-diethylamino;
20	piperonyl	-4-C(=O)-	N,N-diethylamino;
21	3-phenylpropyl	-4-C(=O)-	N,N-diethylamino;
22	methyl	-3-C(=O)-	N-methyl-N-(3-fluorophenyl)amino;
25	2-phenylethyl	-4-C(=S)-	N,N-diethylamino;
28	2-phenylethyl	-4-C(=O)-	N-ethylamino;
29	2-phenylethyl	-4-C(=O)-	amino;
30	2-phenylethyl	-4-C(=O)-	4-morpholinyl;
31	2-phenylethyl	-4-C(=O)-	N,N-diisopropylamino;
32	2-phenylethyl	-4-C(=O)-	N,N-bis(methoxyethyl)amino;
33	2-phenylethyl	-4-C(=O)-	1-pyrrolidinyl;
34	2-phenylethyl	-4-C(=O)-	2,6-dimethyl-1-piperidinyl;
35	2-phenylethyl	-4-C(=O)-	N-ethyl-N-(methylallyl)amino;

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36	2-phenylethyl	-4-C(=O)-	N,N-dipropylamino;
37	2-phenylethyl	-4-C(=O)-	N-t-butylamino;
38	2-phenylethyl	-4-C(=O)-	N-(2-fluoroethyl)amino;
39	2-phenylethyl	-4-C(=O)-	N-(2-thiazolyl)amino;
40	2-phenylethyl	-4-C(=O)-	N-(2-methoxyethyl)amino;
41	2-phenylethyl	-4-C(=O)-	N-(1H-benzimidazol-2-ylmethyl)amino;
42	2-phenylethyl	-4-C(=O)-	N-cyclohexylamino;
43	2-phenylethyl	-4-C(=O)-	N-phenylamino;
44	2-phenylethyl	-4-C(=O)-	N-[2-(2-imidazolyl)ethyl]amino;
45	2-phenylethyl	-4-C(=O)-	N-cyclopropylamino;
46	2-phenylethyl	-4-C(=O)-	N,N-(dimethylaminopropyl)amino;
47	2-phenylethyl	-4-C(=O)-	N-ethyl-N-(hydroxyethyl)amino;
48	2-(1,3-benzodioxol-5-yl)ethyl	-4-C(=O)-	N-ethylamino;
49	2-(1,3-benzodioxol-5-yl)ethyl	-4-C(=O)-	N,N-diethylamino;
50	methyl	-4-C(=O)-	N-ethylamino;
51	H	-4-C(=O)-	N-ethylamino;
52	allyl	-4-C(=O)-	N-ethylamino;
53	2-(4-methoxyphenyl)ethyl	-4-C(=O)-	N,N-diethylamino;
54	2-(4-methoxyphenyl)ethyl	-4-C(=O)-	4-morpholinyl;
55	2-(4-methoxyphenyl)ethyl	-4-C(=O)-	N-ethylamino;
56	2-(4-methoxyphenyl)ethyl	-4-C(=O)-	N,N-bis(2-methoxyethyl)amino;
57	2-(4-methoxyphenyl)ethyl	-4-C(=O)-	1-pyrrolidinyl;
58	2-(4-methoxyphenyl)ethyl	-4-C(=O)-	2,6-dimethyl-1-piperidinyl;
59	2-(4-methoxyphenyl)ethyl	-4-C(=O)-	N-ethyl-N-(methylallyl)amino;
60	2-(4-methoxyphenyl)ethyl	-4-C(=O)-	N,N-(di-n-propyl)amino;
61	2-(4-methoxyphenyl)ethyl	-4-C(=O)-	2,2,6,6-tetramethyl-1-piperidinyl;
62	2-(4-methoxyphenyl)ethyl	-4-C(=O)-	N,N-(di-2-propyl)amino;

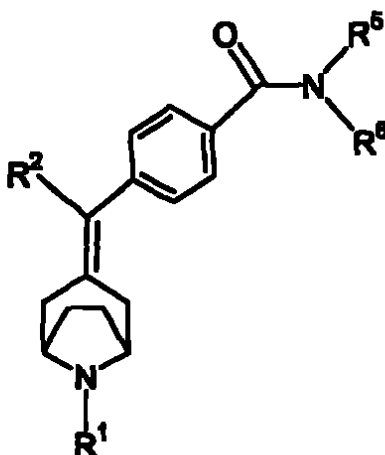
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69	2-(4-hydroxyphenyl)ethyl	-C(=O)-	N-ethylamino; and,
70	2-(4-hydroxyphenyl)ethyl	-C(=O)-	N,N-diethylamino;

and pharmaceutically acceptable enantiomers, diastereomers and salts thereof.

5 Table 2 lists compounds exemplified in the present invention of the formula:

Table 2



wherein R¹, R², R⁵ and R⁶ are dependently selected from the group consisting of:

Ex #	R ¹	R ²	(R ⁵)(R ⁶)
63	methyl	4-MeOPh	(H)(Et);
64	H	4-HOPh	(H)(Et);
65	methyl	4-MeOPh	Et ₂ ;
66	H	4-HOPh	Et ₂ ;
67	2-(4-MeOPh)ethyl	4-MeOPh	Et ₂ ; and,
68	2-(4-HOPh)ethyl	4-HOPh	Et ₂ ;

10

and pharmaceutically acceptable enantiomers, diastereomers and salts thereof.

Instant compounds of the invention may also be present in the form of a
15 pharmaceutically acceptable salt. The pharmaceutically acceptable salt

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generally takes a form in which the basic nitrogen is protonated with an inorganic or organic acid. Representative organic or inorganic acids include hydrochloric, hydrobromic, hydroiodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzolic, mandelic, methanesulfonic, hydroxyethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharic or trifluoroacetic.

It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

The compounds of this invention are chiral and, thus, may exist as enantiomers. In addition, the compounds may exist as diastereomers. It is to be understood that all such enantiomers and diastereomers, as well as all mixtures thereof, are encompassed within the scope of the present invention.

Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention.

In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention.

The present invention also contemplates a pharmaceutical composition comprising a combination of a δ -opioid or μ -opioid receptor modulator compound of Formula (I) and a μ -opioid receptor modulator compound known to those skilled in the art or a δ -opioid or μ -opioid receptor modulator

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compound of Formula (I) wherein the combination has a synergistic therapeutic effect.

Suitable μ -opioid receptor modulator compounds known to those skilled in the art for use in such a combination include, without limitation, the compounds alfentanil, allylprodine, alphaprodine, anileridine, buprenorphine, clonitazene, cyclazocine, dextromoramide, dihydrocodeine, dihydromorphine, ethoheptazine, ethylmorphine, etonitazene, fentanyl, heroin, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, lofentanil, meperidine, meptazinol, metazocine, methadone, morphine, nalbuphine, norlevorphanol, normethadone, naltorphine, normorphine, opium, oxycodone, oxymorphone, phenazocine, piritramide, propiram, propoxyphene, sufentanil, tramadol and diastereomers, salts, complexes and mixtures thereof of any of the foregoing.

The terms used in describing the invention are commonly used and known to those skilled in the art. However, the terms that could have other meanings are hereinafter defined. These definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

An "independently" selected substituent refers to a group of substituents, wherein the substituents may be different. Therefore, designated numbers of carbon atoms (e.g., C₁-C₈) shall refer independently to the number of carbon atoms in an alkyl or cycloalkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

The term "alkyl" refers to straight and branched-chain alkyl radical groups with 1 to 8 carbon atoms or any number within this range. The terms "alkenyl" and "alkynyl" refer to radical groups having straight and branched chains with 2 to 8 carbon atoms or any number within this range. For alkenyl chains, one double bond is formed between adjacent members of a two or three carbon chain and one or two double bonds are formed between adjacent

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members of a four to eight carbon chain. For alkynyl chains, one triple bond is formed between adjacent members of a two or three carbon chain and one or two triple bonds are formed between adjacent members of a four to eight carbon chain. Correspondingly, the terms "alkylene," "alkenylene" and "alkynylene" refer to alkyl, alkenyl and alkynyl linking groups wherein alkyl, alkenyl and alkynyl are as defined supra. Preferably, alkenylene and alkynylene linking group chains have at least one saturated carbon atom on each side of the unsaturated bond. More preferably, when an aryl or heteroaryl substituent is attached to the terminal carbon of an alkenylene or alkynylene linking group, at least one saturated carbon atom is between the unsaturated bond and the substituent. The term "alkoxy" refers to O-alkyl groups wherein alkyl is as defined supra.

Whenever the term "alkyl" appears in the name of a substituent (e.g., hydroxy(C₁₋₄)alkyl) it shall be interpreted as including those limitations given above for "alkyl." Designated numbers of carbon atoms (e.g., C₁₋₄) shall refer independently to the number of carbon atoms in an alkyl or cycloalkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

The term "cycloalkyl" refers to branched or unbranched cyclic aliphatic hydrocarbon chains of three to seven carbon atom members. Examples of such cyclic alkyl rings include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term "heterocyclyl" refers to a nonaromatic cyclic ring of five to seven members in which one to four members are nitrogen or a nonaromatic cyclic ring of five to seven members in which zero, one or two members are nitrogen and one member is oxygen or sulfur, and in which,

- a) optionally, the ring contains zero, one or two unsaturated bonds;
- b) optionally, up to three carbon members adjacent to nitrogen members may be oxo substituted.

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Optionally, the heterocyclyl ring is fused:

- a) to a benzene ring;
- b) to a 5 or 6 membered heteroaryl containing one of O, S or N and, optionally, one additional nitrogen;
- 5 c) to a 5 to 7 membered alicyclic ring;
- d) to a 5 to 7 membered heterocyclyl ring of the same definition as above but absent the option of a further fused ring.

For instant compounds of the invention, the carbon atom ring members
10 that form the heterocyclyl ring are fully saturated. Other compounds of the invention may have a partially saturated heterocyclyl ring. Preferred partially unsaturated heterocyclyl rings may have one or two double bonds. Such compounds are not considered to be fully aromatic and are not referred to as heteroaryl compounds. Therefore, a five member heterocyclyl ring may
15 optionally have a double bond formed in the ring between adjacent ring members; a six or seven member heterocyclyl ring may have two double bonds formed in the ring between adjacent ring members.

The term aryl refers to a single aromatic ring of six carbon members or a
20 bicyclic aromatic ring of ten carbon members. Examples of such aryl rings include phenyl and naphthyl.

The term heteroaryl refers to an aromatic ring of five or six members wherein the ring has at least one heteroatom member. Suitable heteroatoms include nitrogen, oxygen or sulfur. In the case of five-membered rings, the
25 heteroaryl ring contains one member of nitrogen, oxygen or sulfur and, in addition, may contain up to two additional nitrogens. In the case of six-membered rings, the heteroaryl ring may contain from one to three nitrogen atoms. For the case wherein the six member ring has three nitrogens, at most two nitrogen atoms are adjacent.

30 The terms "halo₁₋₃(C₁₋₆)alkyl," "cycloalkyl(C₁₋₆)alkyl" or "hydroxy(C₁₋₆)alkyl" refer to an alkylene group substituted at the terminal carbon with a halo,

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5 cycloalkyl or hydroxy group, respectively. Similarly, the term
 "C₁₋₈alkoxy(C₁₋₈alkenyl)" or "C₁₋₈alkoxy(C₁₋₈alkynyl)" refers to an alkenylene or
 alkynylene group substituted at the terminal carbon with an alkoxy group. The
 term "carbonyl" refers to the linking group -C=O-. Furthermore, the term
 10 "methylenedioxy" refers to the substituent moiety -OCH₂O-, the term
 "ethylenedioxy" refers to the substituent moiety -O(CH₂)₂O- and the term
 "trimethylenedioxy" refers to the substituent moiety -O(CH₂)₃O-. The term
 "hydroxy" refers to the group -OH and the term "oxo" refers to the group =O.
 The term "halo" or "halogen" refers to the group iodine, bromine, chlorine and
 15 fluorine.

Where the compounds according to this invention are chiral, they may
 accordingly exist as enantiomers. In addition, the compounds may exist as
 diastereomers. It is to be understood that all such isomers and mixtures
 thereof are encompassed within the scope of the present invention.

15 The terms used in describing the invention are commonly used and
 known to those skilled in the art. As used herein, the following abbreviations
 have the indicated meanings:

DCE	1,2-dichloroethane
Et ₂ O	Diethyl ether
20 EtOH	Ethanol
h	Hour
K ₂ CO ₃	Potassium carbonate
MeOH	Methanol
NaBH ₄	Sodium borohydride
25 NaBH(OAc) ₃	Sodium triacetoxyborohydride
min	Minute
2-PrOH	2-Propanol
rt	Room temperature
TiCl ₄	Titanium(IV) tetrachloride

30 General Synthetic Methods

Representative compounds of the present invention can be synthesized

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in accordance with the general synthetic methods described below and are illustrated in the schemes that follows. Since the schemes are an illustration, the invention should not be construed as being limited by the chemical reactions and conditions expressed. The preparation of the various starting materials used in the schemes is well within the skill of persons versed in the art.

Scheme 1 describes a general scheme for the preparation of certain target 3-(diarylmethylene)-8-azabicyclo[3.2.1]octane derivatives of the invention using synthetic methods to prepare intermediate compounds also intended to be within the scope of the present invention.

A Suzuki reaction is used to couple a boronic acid Compound 1a with an iodinated Compound 1b in the presence of carbon monoxide to produce an intermediate Compound 1c. Alternatively, Compound 1b may also be substituted with bromine or OTF (trifluoromethylsulfonyloxy) in place of iodine. For Compound 1a and Compound 1b, the R² and R³ substituents and -A-Z moiety may be varied by using appropriate starting materials or may be added in later steps.

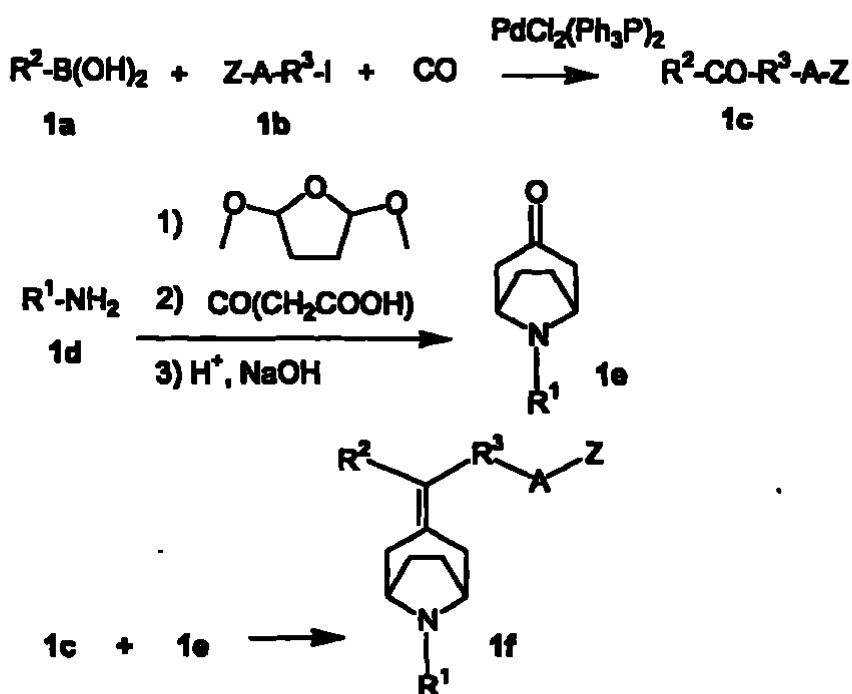
For example, the -A- portion of the -A-Z moiety may be varied using -C(=O)- or -SO₂- (more preferably, -C(=O)-) and the -Z- portion of the -A-Z moiety may be varied using -OH, -O(R⁴) or -N(R⁵)(R⁶) (more preferably, -O(R⁴) or -N(R⁵)(R⁶)) to produce other intermediate compounds of the present invention. Similarly, target compounds wherein Z is -O(R⁴) and R⁴ is hydrogen may be conveniently produced by conventional hydrolysis of the Z is -N(R⁵)(R⁶) group; furthermore, other compounds wherein Z is -O(R⁴) and R⁴ is hydrogen may be esterified by conventional methods to produce other target compounds wherein R⁴ is C₁₋₆alkyl.

A Robinson-Schöpf condensation is used to prepare tropinone intermediate Compounds 1e bearing an R¹ substituent on nitrogen by mixing an R¹ substituted amine Compound 1e with a succinaldehyde precursor such

as 2,5-dimethoxytetrahydrofuran and acetonedicarboxylic acid. For a Compound 1e, the R¹ substituent may be varied by using appropriate starting materials or may be added in later steps.

- 5 Compound 1c and Compound 1e may be coupled using a titanium mediated "McMurray" reaction to produce a target Compound 1f.

Scheme 1



- 10 Scheme 2 describes another general scheme for the preparation of certain 3-(diarylmethylene)-8-azabicyclo[3.2.1]octane derivatives.

As shown below in Scheme 2, the intermediate Compound 1c may be coupled with an 8-methyl-8-azabicyclo[3.2.1]octanone compound using

15 titanium mediated coupling to produce an intermediate Compound 2a.

The intermediate Compound 2a may be treated with 2,2,2-trichloroethyl chloroformate followed by reflux with zinc powder in MeOH to obtain the N-demethylated Compound 2b. Compound 2c is produced by alkylation of

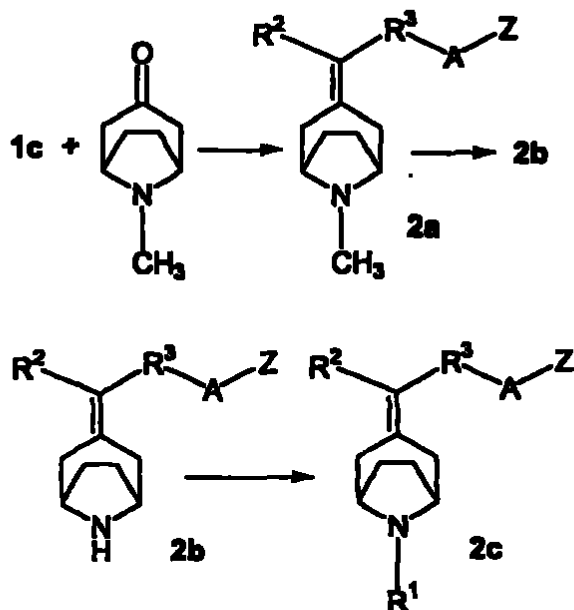
20 Compound 2b with an alkyl halide or reductive alkylation with sodium

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triacetoxyborohydride and a carbonyl compound.

- As desired, the identity of the -A-Z moiety may be varied by conversion of one -A-Z moiety to another. For example, an -A-Z moiety where the -A portion is -C(=O)- and the -Z- portion is -O(R¹), the -Z- portion may be hydrolyzed to the acid, wherein -O(R¹) becomes -OH. Subsequently, the resulting carboxyl group may be converted to the desired amide; and, conversely, an amide group may be hydrolyzed to an acid.

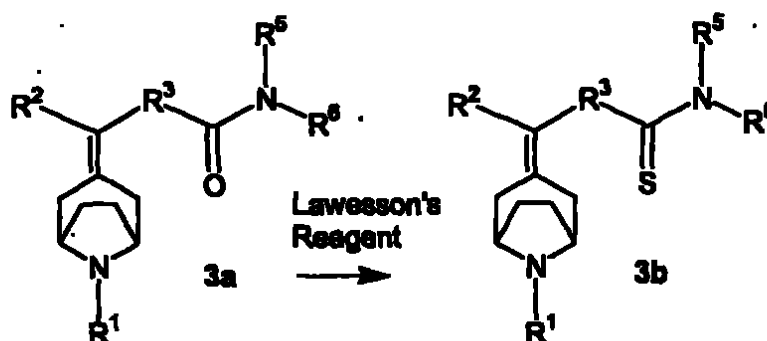
Scheme 2



As shown in Scheme 3, a Compound 3a wherein X is O may also be further treated with a suitable thionating agent such as P₂S₅ or Lawesson's Reagent to prepare a Compound 3b wherein X is S.

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Scheme 3



The compounds of the present invention may be used to treat mild to moderately severe pain in warm-blooded animals such as humans by administration of an analgesically effective dose. The dosage range would be from about 0.01 mg to about 15,000 mg, in particular from about 0.1 mg to about 3500 mg or, more particularly from about 0.1 mg to about 1000 mg of active ingredient in a regimen of about 1 to 4 times per day for an average (70 kg) human; although, it is apparent to one skilled in the art that the therapeutically effective amount for active compounds of the invention will vary as will the types of pain being treated.

Examples of pain intended to be within the scope of the present invention include, but are not limited to, centrally mediated pain, peripherally mediated pain, structural or soft tissue injury related pain, progressive disease related pain, neuropathic pain and acute pain such as caused by acute injury, trauma or surgery and chronic pain such as caused by neuropathic conditions, diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, post-stroke pain syndromes or cluster or migraine headaches.

In regard to the use of the present compounds as immunosuppressants, antiinflammatory agents, agents for the treatment of neurological and psychiatric conditions, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents and agents for the treatment of respiratory diseases, a therapeutically effective dose can be determined by persons skilled in the art by the use of established animal

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models. Such a dose would likely fall in the range of from about 0.01 mg to about 15,000 mg of active ingredient administered 1 to 4 times per day for an average (70 kg) human.

5 Pharmaceutical compositions of the invention comprise the formula (I) compounds as defined above, particularly in admixture with a pharmaceutically acceptable carrier. Illustrative of the invention, therefore, is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and any of the compounds described above. Another illustration of the invention is a
10 pharmaceutical composition made by mixing any of the compounds described above and a pharmaceutically acceptable carrier. A further illustration of the invention is a process for making a pharmaceutical composition comprising
15 mixing any of the compounds described above and a pharmaceutically acceptable carrier.

15 To prepare the pharmaceutical compositions of this invention, one or more compounds of the invention or salt thereof, as the active ingredient, is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide
20 variety of forms depending of the form of preparation desired for administration, e.g., oral or parenteral such as intramuscular. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols,
25 flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral
30 dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding

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solubility or for preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful
5 and the like, an amount of the active ingredient necessary to deliver an effective dose as described above.

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment,
10 observation or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by
15 a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

Specific Synthetic Methods

20 Specific compounds which are representative of this invention may be prepared as per the following examples offered by way of illustration and not by way of limitation. For the sake of clarity, bracketed numbers following compound names indicate the stoichiometric salt associated with the compound, which is further exemplified by the calculated analytical data. Also,
25 examples specifically used to prepare intermediates for the further synthesis of compounds of the invention are designated by "Procedure." As well, instant compounds may also be used as starting materials in subsequent examples to produce additional compounds of the present invention. No attempt has been made to optimize the yields obtained in any of the reactions. One skilled in the
30 art would know how to increase such yields through routine variations in reaction times, temperatures, solvents and/or reagents.

Procedure A

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N,N-Diethyl-4-benzoylbenzamide

A solution of 25 g (110 mmol) 4-benzoylbenzoic acid [611-95-0] and 20 mL SOCl_2 was allowed to reflux for 2 h then allowed to cool. The excess SOCl_2 was evaporated off and the resulting clear oil was dissolved in 10 mL CH_2Cl_2 then slowly added to 12 mL (116 mmol) diethylamine in a mixture of 10 mL 3N NaOH and 50 mL CH_2Cl_2 . The mixture was allowed to stir for 30 min then partitioned between H_2O and CH_2Cl_2 . The organic layer was washed with brine, dried over K_2CO_3 , filtered and concentrated. The product precipitated from EtOAc/hexane to give 29.8 g (105 mmol) white crystals. MS m/z (MH^+) 282.

Example 1**N,N-Diethyl-4-[(8-methyl-8-azabicyclo[3.2.1]****oct-3-ylidene)phenylmethyl]benzamide Hydrochloride [1:1]**

A 100 mL dry THF slurry of 18.6 g (284 mmol) zinc powder and 15.6 mL (142 mmol) TiCl_4 was stirred and allowed to reflux for 2 h under Ar. The reaction was allowed to cool then a 20 mL THF solution of 10 g (35.5 mmol) N,N-diethyl-4-benzoylbenzamide and 5 g (35.5 mmol) tropinone was added slowly. Once the addition was complete, the reaction was allowed to reflux for 3 h, cooled, then quenched with 10% K_2CO_3 in H_2O . The resulting slurry was partitioned between water and Et_2O . The organic fraction was washed with brine, dried over MgSO_4 , filtered, and concentrated. The remaining yellow oil was absorbed onto silica gel then purified by flash chromatography eluted with 10% 0.5 M NH_3 in MeOH 90% CH_2Cl_2 to produce the product N,N-diethyl-4-[(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide (4.27g, 11 mmol). The HCl salt was precipitated from Et_2O after the addition of ethereal HCl; mp 145-147°C. MS m/z (MH^+) 389. ^1H NMR 300 MHz ($\text{DMSO}-d_6$) δ 7.2-7.45 (m, 9H), 3.8-3.9 (m, 2H), 3.15-3.25 (m, 2H), 2.75-2.95 (m, 4H), 2.65 (s, 3H), 2.25-2.4 (m, 2H), 2.15-2.25 (m, 2H), 1.75-1.9 (m, 2H), 0.95-1.2 (m, 6H). Anal calc $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}\cdot\text{HCl}$ (3% H_2O): C, 71.21; H, 7.93; N, 6.39. Found: C, 71.16; H, 7.95; N, 6.27.

Example 2**N,N-Diethyl-4-[(8-azabicyclo[3.2.1]****oct-3-ylidene)phenylmethyl]benzamide Hydrochloride [1:1]**

A 100 mL benzene suspension of 3.1 g (5.6 mmol) N,N-diethyl-4-[(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide, 3.45 g (25 mmol) K_2CO_3 , and 1.5 mL (10 mmol) 2,2,2-trichloroethyl chloroformate was allowed to reflux for 2 h. The reaction was cooled, filtered, and the solvent evaporated. The residual oil was dissolved in MeOH then stirred at reflux with 2.6 g (40 mmol) zinc powder for 1 h. After cooling, the reaction was filtered through celite and partitioned between 3N NaOH and CH_2Cl_2 . The organic layer was washed with brine, dried over K_2CO_3 , filtered, and concentrated (2.1 g, 5.6 mmol). The resulting clear oil was dissolved in Et_2O , filtered, and the product precipitated after the addition of ethereal HCl; mp 128-132°C. MS m/z (MH^+) 375. ^1H NMR 300 MHz ($DMSO-d_6$) δ 7.15-7.4 (m, 9H), 3.9-4.0 (m, 2H), 3.15-3.3 (m, 2H), 2.55-2.65 (m, 2H), 2.25-2.35 (m, 4H), 1.9-2.0 (m, 2H), 1.75-1.85 (m, 2H), 1.0-1.2 (m, 6H). Anal calc $C_{22}H_{29}N_2O \cdot HCl$ (3% H_2O): C, 70.89; H, 7.71; N, 6.61. Found: C, 70.52; H, 7.41; N, 6.24.

Example 3**(+)-N,N-Diethyl-4-[(1R,5S)-8-azabicyclo[3.2.1]****oct-3-ylidene)phenylmethyl]benzamide Fumarate [1:1]**

N,N-Diethyl-4-[(8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide was chromatographed on a CHIRALPAK® AS™ eluting with 90:9.9:0.1 acetonitrile:2-propanol:diethylamine. The first enantiomer to elute was converted to its fumarate salt in 2-PrOH. $[\alpha]_D^{25} = +29^\circ$. MS m/z (MH^+) 375.

Example 4**(-)-N,N-Diethyl-4-[(1R,5S)-8-azabicyclo[3.2.1]****oct-3-ylidene)phenylmethyl]benzamide Fumarate [1:1]**

The second enantiomer to elute in the chromatography from the foregoing example was collected. $[\alpha]_D^{25} = -22^\circ$. MS m/z (MH^+) 375.

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Example 5**N,N-Diethyl-4-[(8-allyl-8-azabicyclo[3.2.1]****oct-3-ylidene)phenylmethyl]benzamide Hydrochloride [1:1]**

A 20 mL acetonitrile suspension of 0.4 g (1.0 mmol) N,N-diethyl-4-[(8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide, 0.4 g (3.0 mmol) K_2CO_3 , and 0.09 mL allyl bromide was allowed to stir for 3 h. The reaction was filtered and concentrated. The remaining oil was absorbed onto silica gel then purified by flash chromatography eluted with 5% 0.5 M NH_3 in MeOH 95% CH_2Cl_2 . The pure product (0.2 g, 0.4 mmol) was taken up in Et_2O , filtered, and precipitated after the addition of ethereal HCl. MS m/z (MH^+) 415. ^1H NMR 300 MHz ($DMSO-d_6$) δ 7.15-7.45 (m, 9H), 5.95-6.10 (m, 1H), 5.4-5.55 (m, 2H), 3.85-3.95 (m, 2H), 3.55-3.65 (t, 2H), 3.35-3.45 (m, 2H), 3.1-3.25 (m, 2H), 2.75-2.85 (t, 2H), 2.2-2.3 (m, 2H), 2.1-2.25 (m, 2H), 1.75-1.9 (m, 2H), 1.0-1.2 (m, 6H).

Example 6**(-)-N,N-Diethyl-4-[(1R,5S)-8-allyl-8-azabicyclo[3.2.1]****oct-3-ylidene)phenylmethyl]benzamide Hydrochloride**

Following the protocol for Example 5 and substituting (+)-N,N-diethyl-4-[(1R,5S)-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide for N,N-diethyl-4-[(8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide the title compound was obtained: MS m/z (MH^+) 415. $[\alpha]_D^{25} = -3.8^\circ$. ^1H NMR 300 MHz ($DMSO-d_6$) δ 7.15-7.45 (m, 9H), 5.95-6.10 (m, 1H), 5.4-5.55 (m, 2H), 3.85-3.95 (m, 2H), 3.55-3.65 (t, 2H), 3.35-3.45 (m, 2H), 3.1-3.25 (m, 2H), 2.75-2.85 (t, 2H), 2.2-2.3 (m, 2H), 2.1-2.25 (m, 2H), 1.75-1.9 (m, 2H), 1.0-1.2 (m, 6H).

Examples 7-17**N,N-Diethyl-4-[(8-R'-8-azabicyclo[3.2.1]****oct-3-ylidene)phenylmethyl]benzamides**

Following the procedure of Example 5 and substituting the appropriate alkyl bromide for allyl bromide the following compounds were prepared:

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Ex#	Alkyl bromide	R'	MS <i>m/z</i> : (MH ⁺)
7	2-(4-fluorophenyl)ethyl bromide	2-(4-fluorophenyl)ethyl	497
8	2-(2-thienyl)ethyl bromide	2-(2-thienyl)ethyl	485
9	3-(2-bromoethyl)indole	2-(3-indolyl)ethyl	518
10	1-bromo-2-cyclohexylethane	2-cyclohexylethyl	485
11	2-phenoxyethyl bromide	2-phenoxyethyl	495
12	1-(bromoethyl)-4-ethyl-1,4-dihydrotetrazol-5-one	2-(4-ethyl-5-oxo-1,4-dihydrotetrazol-1-yl)ethyl	515
13	2-bromo-1-phenylethanone	phenylcarbonylmethyl	493
14	2-bromo-1-(4-methoxyphenyl)ethanone	(4-methoxyphenyl)carbonylmethyl	523
15	2-bromo-1-(3-cyanophenyl)ethanone	(3-cyanophenyl)carbonylmethyl	518
16	2-bromo-1-[3,4-(ethylenedioxy)phenyl]ethanone	3,4-(ethylenedioxyphenyl)carbonylmethyl	551
17	2-bromo-1-[3,4-(trimethylenedioxy)phenyl]ethanone	3,4-(trimethylenedioxyphenyl)carbonylmethyl	565

Example 18**N,N-Diethyl-4-[(8-propyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide Hydrochloride [1:1]**

- 5 A slurry of 0.4 g (1.0 mmol) N,N-diethyl-4-[(8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide, 0.11 mL (1.5 mmol) propionaldehyde, 0.1 mL (1.7 mmol) HOAc, and 0.5 g (2.3 mmol) NaBH(OAc)₃ in 20 mL DCE was allowed to stir for 16 h. The reaction was made strongly basic with 3N NaOH and diluted with CH₂Cl₂. The organic layer was separated, washed with brine,
- 10 dried over K₂CO₃, filtered, and concentrated. The remaining oil was absorbed onto silica gel and purified by flash chromatography eluted with 5% 0.5 M NH₃ in MeOH 95% CH₂Cl₂. The pure product (0.25 g, 0.6 mmol) was taken up in Et₂O, filtered, and precipitated after the addition of ethereal HCl; mp 184-184°C. MS *m/z* (MH⁺) 417. ¹H NMR 300 MHz (CD₃OD) δ 7.2-7.45 (m, 9H),
- 15 3.95-4.05 (m, 2H), 3.45-3.6 (m, 2H), 3.2-3.3 (m, 2H), 2.95-3.05 (m, 2H), 2.55-

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2.7 (m, 4H), 2.2-2.3 (m, 2H), 1.95-2.05 (m, 2H), 1.7-1.85 (m, 2H), 1.0-1.35 (br m, 9H). Anal calc $C_{22}H_{33}N_2O \cdot HCl \cdot 0.5H_2O$: C, 72.78; H, 8.29; N, 6.06. Found: C, 73.01; H, 7.94; N, 5.85.

5

Examples 19-21

N,N-Diethyl-4-[(8-R¹-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamides

Following the procedure of Example 18 and substituting the appropriate carbonyl compound for propionaldehyde the following compounds were

10 prepared:

Ex#	Carbonyl Compound	R ¹	MS <i>m/z</i> (MH ⁺)
19	phenylacetaldehyde	2-phenylethyl	479
20	piperonal	piperonyl	509
21	hydrocinnamaldehyde	3-phenylpropyl	493

Procedure B

N-(3-Fluorophenyl)-N-methyl-3-benzoylbenzamide

Following Procedure A with the substitution of 20 g (88 mmol) 3-benzoylbenzoic acid [579-18-0] and 8.5 mL (88 mmol) 3-fluoroaniline for 4-benzoylbenzoic acid and diethyl amine, the product N-(3-fluorophenyl)-3-benzoylbenzamide was generated (28 g, 88 mmol) as a clear oil. The oil was dissolved in 50 mL dry THF to which a 10 mL THF slurry of 2.1 g (90 mmol) NaH was slowly added. The mixture was allowed to stir for 5 min then 5.6 mL (90 mmol) of MeI was added and continued stirring for 16 h. The reaction was carefully quenched with water and partitioned between water and CH₂Cl₂. The organic layer was washed with brine, dried over K₂CO₃, filtered, and concentrated to yield 29.3 g (88 mmol) product. MS *m/z* (MH⁺) 334.

Example 22

N-(3-Fluorophenyl)-N-methyl-3-[(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide Fumarate [1:1]

Following the procedure of Example 1 with the substitution of N-(3-fluorophenyl)-N-methyl-3-benzoylbenzamide obtained in Procedure B for N,N-

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diethyl-4-benzoylbenzamide, the product N-(3-fluorophenyl)-N-methyl-3-[(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide was produced. The fumarate salt was precipitated from 2-PrOH/hexane, mp 122-125°C. MS m/z (MH^+) 441. ^1H NMR 300 MHz ($DMSO-d_6$) δ 6.85-7.35 (m, 13H), 3.4 (s, 3H), 3.3-3.5 (m, 1H), 3.15-3.2 (m, 1H), 3.4-3.55 (m, 2H), 2.35 (s, 3H), 2.15-2.25 (m, 1H), 2.05-2.15 (m, 1H), 1.9-2.05 (m, 2H), 1.55-1.65 (m, 1H), 1.35-1.55 (br ms, 1H). Anal calc $C_{28}H_{29}FN_2O \cdot C_4H_4O_4$: C, 71.21; H, 5.98; N, 5.03. Found: C, 71.50; H, 6.20; N, 4.92.

10

Example 23

(-)-N,N-Diethyl-4-[(1R,5S)-8-phenethyl-8-azabicyclo[3:2:1]oct-3-ylidene]phenylmethyl]benzamide Hydrochloride [1:1]

A suspension of 52 g (0.8 mole) of zinc powder and 800 mL of THF was cooled in an ice bath 44 mL (0.4 mole) of $TiCl_4$ was added dropwise with stirring. The ice bath was removed and the reaction refluxed for 2 h. A solution of 26.45 g (0.094 mole) of N,N-diethyl-4-benzoylbenzamide and 23.9 g (0.094 mole) of 8-phenethyl-8-azabicyclo[3.2.1]octan-3-one, in 100 mL of THF was added dropwise and the reaction was refluxed 4h. After cooling, the reaction mixture was poured into a beaker containing excess K_2CO_3 and ice. The mixture was extracted with ether, washed with brine, dried (K_2CO_3) and concentrated. There was obtained 47 g (~0.1 mol) of crude ($\pm$)-N,N-diethyl-4-[(8-phenethyl-8-azabicyclo[3:2:1]oct-3-ylidene)phenylmethyl]benzamide as an oil. A sample of the oil and 38.33g (0.1 mole) of (+)-ditoluoyl-D-tartaric acid were combined in 600 mL of acetonitrile. The solid was collected and recrystallized twice from acetonitrile. The solid was collected and partitioned between dilute sodium hydroxide and CH_2Cl_2 . The organic solution was dried (K_2CO_3) and concentrated. The residue was converted to a hydrochloride salt (Et_2O/HCl). It was recrystallized from 2-PrOH to give 5.6g of white solid. Et_2O , filtered, and precipitated after the addition of ethereal HCl; mp 210-211°C. MS m/z (MH^+) 479. ^1H NMR 300 MHz ($CDCl_3$) δ 12.6 (s, 1H), 7.2-7.45 (m, 14H), 3.85 (s, 2H), 3.5-3.1 (m, 10H), 2.6 (d, 1H), 2.5 (d, 2H), 2.05 (m, 2H), 1.2 (br. s, 3H), 1.1 (br. s, 3H). $[\alpha]_D^{25} = -3.7^\circ$.

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Example 24

(+)-N,N-Diethyl-4-[[[(1S,5R)-8-phenethyl-8-azabicyclo[3:2:1]oct-3-ylidene]phenylmethyl]benzamide Hydrochloride [1:1]

The mother liquors from the foregoing example were concentrated and
 5 partitioned between dilute sodium hydroxide and CH_2Cl_2 . The organic solution was concentrated (40.5 g, 0.084 mole) and 32.7 g (0.084 mole) of (-)-dichloro-L-tartaric acid were combined in 500 mL of acetonitrile. The solid was collected and recrystallized twice from acetonitrile. The solid was collected and partitioned between dilute sodium hydroxide and CH_2Cl_2 . The organic solution
 10 was dried (K_2CO_3) and concentrated. The residue was converted to a hydrochloride salt ($\text{Et}_2\text{O}/\text{HCl}$) and recrystallized from 2-PrOH to give a white solid; mp 211-212°C. MS m/z (MH^+) 479. ^1H NMR 300 MHz (CDCl_3) δ 12.6 (s, 1H), 7.2-7.45 (m, 14H), 3.85 (s, 2H), 3.5-3.1 (m, 10H), 2.6 (d, 1H), 2.5 (d, 2H), 2.05 (m, 2H), 1.2 (br. s, 3H), 1.1 (br. s, 3H). $[\alpha]_D^{25} = +3.7^\circ$.

Example 25

(-)-N,N-Diethyl-4-[[8-phenethyl-8-aza(1R, 5S)bicyclo[3:2:1]oct-3-ylidene]phenylmethyl]thiobenzamide

A mixture of 1.48 g (3.1 mmol) of (-)-N,N-diethyl-4-[[8-phenethyl-8-aza(1R, 5S)bicyclo[3:2:1]oct-3-ylidene]phenylmethyl]benzamide and 1.87 g of Lawesson's reagent was heated at 80°C in 50 mL of benzene for 2 h. The resulting mixture was flash chromatographed using 5% MeOH in CH_2Cl_2 . MS
 20 m/z (MH^+) 495. ^1H NMR 300 MHz (CDCl_3) δ 8.2 (m, 2H), 7.3-7.0 (m, 10H), 6.8 (m, 2H), 4.0 (m, 4H), 3.7-3.2 (m, 10H), 2.7-2.4 (m, 3H), 2.1-1.6 (m, 4H), 1.4 (t, 3H), 1.1 (t, 3H).

Procedure C

Ethyl 4-[(8-phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoate

30 After a mixture of 52 g (0.8 mole) of zinc powder and 800 mL of THF was cooled in an ice bath 44 mL (0.4 mole) of TiCl_4 was added dropwise with stirring. The ice bath was removed and the reaction refluxed for 2 h. A solution of 21.5 g (0.094 mole) of ethyl 4-benzoylbenzoate, 23.9 g (0.094 mole)

of 8-phenethyl-8-azabicyclo[3.2.1]octan-3-one, in 100 mL of THF was added dropwise and the reaction was refluxed overnight. After cooling the reaction mixture was poured into a beaker containing K_2CO_3 and ice. Enough K_2CO_3 was added until basic. The solid was filtered off and the organics from the filtrate were separated. The aqueous layer was extracted with Et_2O and the organics were combined, washed with brine and dried over K_2CO_3 . The solvent was evaporated *in vacuo*. The residue was first passed through a flash column, silica gel, (9:1; CH_2Cl_2 :MeOH) then a second column using silica gel with 3:1 hexane:acetone to give 21.8 g of the title compound. MS m/z (MH^+) 452. ^1H NMR ($DMSO-d_6$) δ 8.0 (d, 2H); 7.35-7.1 (Ar, 12H); 4.3 (t, 2H); 2.8 (m, 2H); 2.7 (m, 2H); 2.4 (bd, 2H); 2.3-2.2 (m, 3H); 1.9 (m, 2H); 1.6 (m, 3H); 1.3 (q, 3H).

Procedure D

4-[(8-Phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoic Acid

A mixture of 22 g (0.048 mole) of ethyl 4-[(8-phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoate, 86 mL of 3N NaOH and 200 mL of EtOH was refluxed for 1 h. After cooling the mixture was made acidic with conc. HCl. The solvent was decanted away from the gum which formed. The gum was titrated with Et_2O and Et_2O/HCl and was placed into a drying oven overnight at 45°C to yield 19.2 g of 4-[(8-phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoic acid; mp. 285-290°C. MS m/z (MH^+) 425. ^1H NMR δ 7.9 (d, 2H); 7.4-7.2 (ar, 12H); 3.7 (bs, 2H); 3.0 (bs, 4H); 2.8 (bd, 2H); 2.2 (t, 2H); 2.0 (m, 2H); 1.65 (m, 2H).

Procedure E

4-[(8-Phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoyl Chloride

A mixture of 6 g (0.014 mole) of 4-[(8-phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoic acid, 20 mL of $CHCl_3$ and 3 mL (0.042 mole) of thionyl chloride were refluxed for 1.5 h. The solvent was evaporated *in vacuo* to give 6.2 g of 4-[(8-phenethyl-8-azabicyclo[3.2.1]oct-3-

ylidene)phenylmethyl]benzoyl chloride. MS m/z (MH^+) of CH_3OH quench 437.

Example 26

N-Ethyl-4-[(8-phenethyl-8-azabicyclo[3.2.1]

oct-3-ylidene)phenylmethyl]benzamide

A mixture of 11.4 g (0.14 mole) of ethylamine hydrochloride and 150 mL of 3N NaOH and 100 mL of CH_2Cl_2 were cooled in an ice bath. A solution of 4.7 g (0.015 mole) of 4-[(8-phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoyl chloride prepared using Procedure E in 60 mL of CH_2Cl_2 was added. After the addition was complete, the ice bath was removed and the reaction stirred at room temperature for 2 h. The organics were separated off and washed with water, brine and dried (K_2CO_3). The solvent was evaporated *in vacuo* and converted to the HCl salt with Et_2O/HCl to give 1.86 g of N-ethyl-4-[(8-phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide; mp 298-298°C (Decomp). MS m/z (MH^+) 451. ^1H NMR ($DMSO-d_6$) δ 8.5 (ar, 1H); 7.8 (d, 2H); 7.4-7.1 (ar, 12H); 4.05 (bs, 2H); 3.4-3.2 (m, 3H); 3.1 (s, 3H); 2.9 (d, 2H); 2.4 -2.1 (m, 4H); 1.8 (m, 2H); 1.1 (t, 3H).

20

Example 27

(-)-4-[(8-Phenethyl-8-aza(1R,5S)bicyclo[3.2.1]

oct-3-ylidene]phenylmethyl]benzamide

4-[(8-Phenethyl-8-aza(1R,5S)bicyclo[3.2.1]oct-3-ylidene]phenylmethyl]benzamide was chromatographed on a CHIRALPAK® Ad™ column eluting with $EtOH + 0.1\%$ dea. The first enantiomer to elute was collected and converted to the hydrochloride with Et_2O/HCl . $[\alpha]_D^{25} = -9.7^\circ$. MS m/z (MH^+) 451. ^1H NMR ($DMSO-d_6$) δ 8.5 (ar, 1H); 7.8 (d, 2H); 7.4-7.1 (ar, 12H); 4.05 (bs, 2H); 3.4-3.2 (m, 3H); 3.1 (s, 3H); 2.9 (d, 2H); 2.4 -2.1 (m, 4H); 1.8 (m, 2H); 1.1 (t, 3H).

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Example 28

(+)-4-[(8-Phenethyl-8-aza(1S,5R)bicyclo[3.2.1]

oct-3-ylidene]phenylmethyl]benzamide

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The second enantiomer to elute was collected and converted to the hydrochloride with Et₃O/HCl. $[\alpha]_D^{25} = +9.3^\circ$. MS m/z (MH⁺) 451. ¹H NMR (DMSO-d₆) δ 8.5 (ar, 1H); 7.8 (d, 2H); 7.4-7.1 (ar, 12H); 4.05 (bs, 2H); 3.4-3.2 (m, 3H); 3.1 (s, 3H); 2.9 (d, 2H); 2.4-2.1 (m, 4H); 1.8 (m, 2H); 1.1 (t, 3H).

5

Example 29

4-[(8-Phenethyl-8-azabicyclo[3.2.1]

oct-3-ylidene)phenylmethyl]benzamide Hydrochloride [1:1].

A 1.5 g (0.0034 mole) sample of 4-[(8-phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoyl chloride was cooled in an ice bath. 30 mL of NH₄OH was added dropwise. The ice bath was removed and the mixture was stirred at room temperature for 2 h. The solid was filtered off and dried. The product was passed through a Biotage Flash 40 L (silica gel, 9:1; CH₂Cl₂:MeOH). Conversion to the HCl salt and recrystallization from EtOH/Et₂O gave 0.45 g of 4-[(8-phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide; mp. 210-212°C. MS m/z (MH⁺) 423. ¹H NMR (DMSO-d₆) δ 7.95 (s, 1H); 7.9 (d, 2H); 7.4-7.2 (ar, 12H); 4.05 (bs, 1H); 3.6 (q, 2H); 2.9 (d, 2H); 2.4-2.1 (m, 5H); 1.8 (m, 3H); 1.1 (t, 3H).

20

Examples 30-47

N,N-R²,R³-4-[(8-Phenethyl-8-azabicyclo[3.2.1]

oct-3-ylidene)phenylmethyl]benzamides

By the method of Example 26 and substituting the appropriate amine for ethylamine hydrochloride, the title compound was prepared.

25

Ex	Amine	CIMS (MH ⁺)
30	morpholine	493
31	dilsopropylamine	506
32	bis(methoxyethyl)amine	538
33	pymolidine	477
34	cis-2,6-dimethylpiperidine	519
35	N-ethyl-N-(methylallyl)amine	505
36	dipropylamine	507

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37	t-butylamine	479
38	2-fluoroethylamine	489
39	2-aminothiazole	507
40	2-methoxyethylamine	481
41	(1H-benzimidazol-2-ylmethyl)amine	553
42	cyclohexylamine	505
43	aniline	499
44	histamine	517
45	cyclopropylamine	483
46	N,N-(dimethylaminopropyl)amine	508
47	N-ethyl-N-(hydroxyethyl)amine	495

Procedure F

8-(2-Benzo[1,3]dioxol-5-ylethyl)-8-azabicyclo[3.2.1]octan-3-one

A 41 g sample of 2,5-dimethoxytetrahydrofuran (0.32 ml) was suspended in
 5 300 mL of H₂O and 40 mL of o-phosphoric acid was added. The mixture was
 stirred for 3 h then brought to pH 7 by addition of 3N NaOH. Samples of
 acetone dicarboxylic acid (51 g, 0.15 mol) and (3,4-methylenedioxy)
 phenethylamine (20 g, 0.12 mol) were added and the mixture stirred at 25°C
 for two days. The mixture was made basic by addition of 100 mL of 3N NaOH,
 10 was extracted with EtOAc, washed with brine, dried (K₂CO₃) and concentrated.
 The residue was flash chromatographed using 20% acetone in hexane. The
 product was a crystalline solid. MS *m/z* (MH⁺) 274. ¹H NMR 300 MHz (CDCl₃)
 δ 6.6 (m, 3H), 5.9 (s, 2H), 3.5 (br. m, 2H), 2.85 (s, 4H), 2.65 (dd, 2H), 2.2 (d,
 2H), 2.05 (m, 2H), 1.7 (q, 2H).

Procedure G

Ethyl [[8-(2-benzo[1,3]dioxol-5-ylethyl)-8-azabicyclo[3.2.1]oct-3-ylidene]phenylmethyl]benzoate

Following the protocol of Procedure C and substituting 8-(2-benzo[1,3]dioxol-5-
 20 ylethyl)-8-azabicyclo[3.2.1]octan-3-one for 8-phenethyl-8-
 azabicyclo[3.2.1]octan-3-one, the title compound was obtained. MS *m/z* (MH⁺)
 496.

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Procedure H**[[8-(2-Benzo[1,3]dioxol-5-ylethyl)-8-azabicyclo[3:2:1]
oct-3-ylidene]phenylmethyl]benzoic Acid**

- 5 Following the protocol of Procedure D and substituting ethyl-[[8-(2-benzo[1,3]dioxol-5-ylethyl)-8-azabicyclo[3:2:1]oct-3-ylidene]phenylmethyl]benzoate for ethyl-4-[[8-phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene]phenylmethyl]benzoate, the title compound was obtained. MS *m/z* (MH⁺) 468.

10

Procedure J**[[8-(2-Benzo[1,3]dioxol-5-ylethyl)-8-azabicyclo[3:2:1]
oct-3-ylidene]phenylmethyl]benzoyl Chloride**

- 15 Following the protocol of Procedure E and substituting [[8-(2-benzo[1,3]dioxol-5-ylethyl)-8-azabicyclo[3:2:1]oct-3-ylidene]phenylmethyl]benzoic acid for 4-[[8-phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene]phenylmethyl]benzoic acid, the title compound was obtained.

Example 48

- 20 **N-Ethyl-[[8-(2-Benzo[1,3]dioxol-5-ylethyl)-8-azabicyclo[3:2:1]
oct-3-ylidene]phenylmethyl]benzamide**

- Following the procedure of Example 23 and substituting [[8-(2-benzo[1,3]dioxol-5-ylethyl)-8-azabicyclo[3:2:1]oct-3-ylidene]phenylmethyl]benzoyl chloride for 4-[[8-phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene]phenylmethyl]benzoyl chloride, the title compound was obtained. MS *m/z* (MH⁺) 495.

25

Example 49

- 30 **N,N-Diethyl-[[8-(2-Benzo[1,3]dioxol-5-ylethyl)-8-azabicyclo[3:2:1]
oct-3-ylidene]phenylmethyl]benzamide**

- Following the procedure of Example 23 and substituting [[8-(2-benzo[1,3]dioxol-5-ylethyl)-8-azabicyclo[3:2:1]oct-3-ylidene]phenylmethyl]benzoyl chloride for 4-[[8-phenethyl-8-

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azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoyl chloride and diethyl amine for ethylamine hydrochloride, the title compound was obtained. MS m/z (MH^+) 523.

5

Procedure K

Ethyl 4-[(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoate

Following the protocol of Procedure C and substituting tropinone for 8-phenethyl-8-azabicyclo[3.2.1]octan-3-one, the title compound was obtained.

10 MS m/z (MH^+) 382.

Procedure L

4-[(8-Methyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoic Acid

15 Following the protocol of Procedure D and substituting ethyl 4-[(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoate for ethyl 4-[(8-phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoate, the title compound was obtained. MS m/z (MH^+) 334

20

Procedure M

4-[(8-Methyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoyl Chloride

Following the protocol of Procedure E and substituting 4-[(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoic acid for 4-[(8-phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoic acid, the title compound was obtained.

25

Example 50

N-Ethyl-4-[(8-Methyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide

30

Following the protocol of Example 26 and substituting 4-[(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoyl chloride for 4-[(8-phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoyl chloride, the

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title compound was obtained. MS m/z (MH^+) 361.

Example 51

N-Ethyl-4-[(8-azabicyclo[3.2.1]

5 **oct-3-ylidene)phenylmethyl]benzamide**

Following the protocol of Example 2 and substituting N-ethyl-4-[(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide for N,N-diethyl-4-[(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide, the title compound was obtained. MS m/z (MH^+) 347.

10

Example 52

N-Ethyl-4-[(8-allyl-8-azabicyclo[3.2.1]

oct-3-ylidene)phenylmethyl]benzamide

15 Following the protocol of Example 8 and substituting N-ethyl-4-[(8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide for N,N-diethyl-4-[(8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide, the title compound was obtained. MS m/z (MH^+) 387.

Procedure N

20 **8-[2-(4-Methoxyphenyl)ethyl]-8-azabicyclo[3.2.1]octanone**

Following the protocol of Procedure F and substituting (4-methoxy)phenethylamine for (3,4-methylenedioxy)phenethylamine, the title compound was obtained. MS m/z (MH^+) 260.

25

Procedure Q

Ethyl 4-[[8-[2-(4-methoxyphenyl)ethyl]-8-azabicyclo[3.2.1]

oct-3-ylidene]phenylmethyl]benzoate

Following the protocol of Procedure C and substituting 8-[2-(4-methoxyphenyl)ethyl]-8-azabicyclo[3.2.1]octanone for 8-phenethyl-8-azabicyclo[3.2.1]octan-3-one, the title compound was obtained. MS m/z (MH^+) 482.

30

Procedure P

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4-[[8-[2-(4-Methoxyphenyl)ethyl]-8-azabicyclo[3.2.1]oct-3-ylidene]phenylmethyl]benzoic Acid

Following the protocol of Procedure D and substituting ethyl 4-[[8-[2-(4-methoxyphenyl)ethyl]-8-azabicyclo[3.2.1]oct-3-ylidene]phenylmethyl]benzoate for ethyl 4-[(8-phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoate, the title compound was obtained.

Procedure Q

4-[[8-[2-(4-Methoxyphenyl)ethyl]-8-azabicyclo[3.2.1]oct-3-ylidene]phenylmethyl]benzoyl Chloride

Following the protocol of Procedure E and substituting 4-[[8-[2-(4-methoxyphenyl)ethyl]-8-azabicyclo[3.2.1]oct-3-ylidene]phenylmethyl]benzoic acid for 4-[(8-phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoic acid, the title compound was obtained.

Example 53

N,N-Diethyl-4-[[8-[2-(4-methoxyphenyl)ethyl]-8-azabicyclo[3.2.1]oct-3-ylidene]phenylmethyl]benzamide

Following the protocol of Procedure F and substituting 4-[[8-[2-(4-methoxyphenyl)ethyl]-8-azabicyclo[3.2.1]oct-3-ylidene]phenylmethyl]benzoyl chloride for 4-[(8-phenethyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzoyl chloride, the title compound was obtained. MS *m/z* (MH⁺) 509.

Examples 54-63

N,N-DI-R²,R³-4-[[8-[2-(4-methoxyphenyl)ethyl]-8-azabicyclo[3.2.1]oct-3-ylidene]phenylmethyl]benzamides

Using the method of Example 26 and substituting the material from Procedure Q for the material from Procedure E, the following compounds were prepared:

Ex #	Amine	CIMS (MH ⁺)
54	morpholine	523
55	ethylamine	481

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56	bis(methoxyethyl)amine	569
57	pyrrolidine	507
58	cis-2,6-dimethylpiperidine	549
59	N-ethyl-(N-methylallyl)amine	535
60	di-n-propylamine	537
61	2,2,6,6-tetramethylpiperidine	577
62	di-2-propylamine	537

Procedure R**N-Ethyl-4-(4-methoxybenzoyl)benzamide**

Following the protocol of Procedure A and substituting 4-(4-methoxybenzoyl)benzoic acid for 4-benzoylbenzoic acid and ethylamine hydrochloride for diethylamine, the title compound was obtained. MS m/z (MH^+) 284.

Example 63

N-Ethyl-4-[(4-methoxyphenyl)-(8-methyl-8-azabicyclo[3:2:1]oct-3-ylidene)methyl]benzamide

Following the protocol of Example 1 and substituting N-ethyl-4-(4-methoxybenzoyl)benzamide for N,N-diethyl-4-benzoylbenzamide, the title compound was obtained. MS m/z (MH^+) 391.

Procedure S**2,2,2-Trichloroethyl 3-[(ethylcarbamoylphenyl)-****(4-methoxyphenyl)methylene]-8-azabicyclo[3:2:1]octanecarboxylate**

A solution of 1.95 g (5.0 mmol) of N-ethyl-4-[(4-methoxyphenyl)-(8-methyl-8-azabicyclo[3:2:1]oct-3-ylidene)methyl]benzamide, 1.03 mL (7.5 mmol) of 2,2,2-trichloroethyl chloroformate and 0.43 mL (2.5 mmol) of diisopropylethylamine was stirred in 50 mL of benzene and 1.38 g (10 mmol) of K_2CO_3 added. The mixture was heated at under reflux for 18 h. Another 0.51 mL of (3.75 mmol) of 2,2,2-trichloroethyl chloroformate and 0.21 mL (1.25 mmol) of diisopropylethylamine was added. The mixture was heated under reflux for 3h. The reaction was cooled and poured into H_2O . The organic layer was washed

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with dilute HCl and brine, dried (MgSO₄) and concentrated to give 2.09 g of a yellow gum. MS *m/z* (MH⁺) 553. ¹H NMR 300 MHz (CDCl₃) δ 7.7 (d, 2H), 7.2 (d, 2H), 7.0 (d, 2H), 6.8 (d, 2H), 6.2 br. s, 1H), 4.9 (d, 1H), 4.7 (d, 1H), 4.3 (br. m, 2H), 3.8 (s, 3H), 3.4 (q, 2H), 2.4 (br. m, 4H), 1.9 (m, 2H), 1.7 (m, 2H), 1.2 (t, 3H).

Procedure I

2,2,2-Trichloroethyl 3-[(ethylcarbamoylphenyl)-

(4-hydroxyphenyl)methylene]-8-azabicyclo[3:2:1]octanecarboxylate

10 A solution of 1.03 g (1.82 mmol) of 2,2,2-trichloroethyl 3-[(ethylcarbamoylphenyl)-(4-methoxyphenyl)methylene]-8-azabicyclo[3:2:1]octanecarboxylate in 10 mL of CHCl₃ was cooled to -60°C under N₂ and 9.1 mL of 1M BBr₃ in CH₂Cl₂ was added dropwise. The cooling bath was removed and the mixture stirred at 25°C for 18 h. Saturated aqueous

15 NaHCO₃ was added and the CH₂Cl₂ was evaporated. The solid (1 g) was collected. ¹H NMR 300 MHz (CDCl₃) δ 7.8 (d, 2H), 7.2 (d, 2H), 6.9 (d, 2H), 6.7 (d, 2H), 6.2 (br. s, 1H), 4.9 (d, 1H), 4.7 (d, 1H), 4.4 (br. m, 2H), 3.4 (q, 2H), 2.4 (br. m, 4H), 1.9 (m, 2H), 1.7 (m, 2H), 1.2 (t, 3H).

20

Example 64

4-[(8-Azabicyclo[3:2:1]oct-3-ylidene)-

(4-hydroxyphenyl)methyl]-N-ethylbenzamide

A 0.73 g sample (11 mmol) of zinc dust was added to a solution of 0.89 g (1.61 mmol) of 2,2,2-trichloroethyl 3-[(ethylcarbamoylphenyl)-(4-

25 hydroxyphenyl)methylene]-8-azabicyclo[3:2:1]octanecarboxylate in 9 mL of glacial HOAc. The mixture was heated under reflux for 5 h then cooled and the solid removed by filtration and washed with HOAc. The solvent was evaporated and K₂CO₃ was added. The mixture was extracted six times with 20% EtOH in CHCl₃. The solution was dried (Na₂SO₄) and concentrated. The

30 residue was crystallized from EtOH/2-PrOH to give 0.24 g of a white solid. MS *m/z* (MH⁺) 363. ¹H NMR (DMSO-d₆) δ 8.5 (t, 1H), 7.8 (d, 2H), 7.2 (d, 2H), 6.9 (d, 2H), 6.7 (d, 2H), 3.3 (br. m, 4H), 2.2 (br. m, 4H), 1.5 (m, 4H), 1.1 (t, 3H).

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Procedure U**N-Diethyl-4-(4-methoxybenzoyl)benzamide**

A mixture of 0.75 g (5.5 mmol) of 4-methoxybenzeneboronic acid, 1.5 g (5 mmol) N,N-diethyl-4-iodobenzamide, 0.1 g (0.15 mmol) bis(triphenylphosphine) palladium(II) dichloride and 2.07 g (15 mmol) of K_2CO_3 in 30 mL of anisole was flushed with carbon monoxide then heated at 80°C under a CO atmosphere for 5 h. The mixture was filtered and the solvent evaporated. The residue was flash chromatographed 20% acetone in hexane to give the title compound. MS m/z (MH^+) 312.

Example 65**N,N-Diethyl-4-[(4-methoxyphenyl)-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)methyl]benzamide**

Following the protocol of Example 1 and substituting N,N-diethyl-4-(4-methoxybenzoyl)benzamide for N,N-diethyl-4-benzoylbenzamide, the title compound was obtained. MS m/z (MH^+) 419.

Procedure V**2,2,2-Trichloroethyl 3-[(diethylcarbamoylphenyl)-****(4-methoxyphenyl)methylene]-8-azabicyclo[3.2.1]octanecarboxylate**

Following the protocol of Procedure S and substituting N,N-diethyl-4-[(4-methoxyphenyl)-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)methyl]benzamide for N-ethyl-4-[(4-methoxyphenyl)-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)methyl]benzamide, the title compound was obtained.

Procedure W**2,2,2-Trichloroethyl 3-[(diethylcarbamoylphenyl)-****(4-hydroxyphenyl)methylene]-8-azabicyclo[3.2.1]octanecarboxylate**

Following the protocol of Procedure T and substituting 2,2,2-trichloroethyl 3-[(diethylcarbamoylphenyl)-(4-methoxyphenyl)methylene]-8-azabicyclo[3.2.1]octanecarboxylate for 2,2,2-trichloroethyl 3-[(ethylcarbamoylphenyl)-(4-methoxyphenyl)methylene]-8-azabicyclo[3.2.1]octanecarboxylate, the title compound was obtained.

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Example 66

**4-[(8-Azabicyclo[3:2:1]oct-3-ylidene)-
(4-hydroxyphenyl)methyl]-N-diethylbenzamide**

- 5 Following the protocol for Example 64 and substituting 2,2,2-trichloroethyl 3-
[(diethylcarbamoylphenyl)-(4-hydroxyphenyl)methylene]-8-
azabicyclo[3:2:1]octanecarboxylate for 2,2,2-trichloroethyl 3-
[(ethylcarbamoylphenyl)-(4-hydroxyphenyl)methylene]-8-
azabicyclo[3:2:1]octanecarboxylate, the title compound was obtained. MS *m/z*
10 (MH⁺) 391.

Example 67

**N,N-Diethyl-4-[(4-methoxyphenyl)-[8-[2-(4-methoxyphenyl)ethyl]-
8-azabicyclo[3:2:1]oct-3-ylidene)methyl]benzamide**

- 15 Following the protocol of Example 1 and substituting 8-[2-(4-
methoxyphenyl)ethyl]-8-azabicyclo[3:2:1]octanone for tropinone, the title
compound was obtained. MS *m/z* (MH⁺) 539.

Example 68

- 20 **N,N-Diethyl-4-[(4-hydroxyphenyl)-[8-[2-(4-hydroxyphenyl)ethyl]-
8-azabicyclo[3:2:1]oct-3-ylidene)methyl]benzamide**

- Following the protocol of Example 64 and substituting N,N-diethyl-4-[(4-
methoxyphenyl)-[8-[2-(4-methoxyphenyl)ethyl]-8-azabicyclo[3:2:1]oct-3-
ylidene)methyl]benzamide for 2,2,2-trichloroethyl 3-[(ethylcarbamoylphenyl)-(4-
25 hydroxyphenyl)methylene]-8-azabicyclo[3:2:1]octanecarboxylate, the title
compound was obtained. MS *m/z* (MH⁺) 511.

Example 69

- 30 **N-Ethyl-4-[[8-[2-(4-hydroxyphenyl)ethyl]-8-azabicyclo[3:2:1]
oct-3-ylidene]phenylmethyl]benzamide**

Following the protocol of Procedure T and substituting N-ethyl-4-[[8-[2-(4-
methoxyphenyl)ethyl]-8-azabicyclo[3:2:1]oct-3-ylidene]phenylmethyl]
benzamide for 2,2,2-trichloroethyl 3-[(ethylcarbamoylphenyl)-(4-methoxy

phenyl)methylene]-8-azabicyclo[3.2.1]octanecarboxylate, the title compound was obtained. MS m/z (MH^+) 467.

Example 70

5 **N,N-Diethyl-4-[[8-[2-(4-hydroxyphenyl)ethyl]-8-azabicyclo[3.2.1]oct-3-ylidene]phenylmethyl]benzamide**

Following the protocol of Procedure T and substituting N,N-diethyl-4-[[8-[2-(4-methoxyphenyl)ethyl]-8-azabicyclo[3.2.1]oct-3-ylidene]phenylmethyl]benzamide for 2,2,2-trichloroethyl 3-
10 [(ethylcarbamoylphenyl)-(4-methoxyphenyl)methylene]-8-azabicyclo[3.2.1]octanecarboxylate, the title compound was obtained. MS m/z (MH^+) 495.

Biological Examples

15 **Screening Assay for δ -Opioid and μ -Opioid Receptor Binding**
Rat Brain δ -Opioid Receptor Binding Assay

The activity of the compounds of the invention as analgesics was demonstrated by the rat brain δ -opioid receptor binding assay as described below.

20 **Procedure**

Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, NY) are killed by cervical dislocation, and their brains removed and placed immediately in ice cold Tris HCl buffer (50 mM, pH 7.4). The forebrains are separated from the remainder of the brain by a coronal transection, beginning dorsally at the colliculi and passing ventrally through the midbrain-pontine junction. After dissection, the forebrains are homogenized in Tris buffer in a Teflon®-glass homogenizer. The homogenate is diluted to a concentration of 1 g of forebrain tissue per 100 mL Tris buffer and centrifuged at 39,000 X G for 10 min. The
25 pellet is resuspended in the same volume of Tris buffer with several brief pulses from a Polytron homogenizer. This particulate preparation is used for the δ -opioid binding assays. Following incubation with the δ -selective peptide ligand [^3H]DPDPE at 25°C, the tube contents are filtered through Whatman
30

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GF/B filter sheets on a Brandel cell harvester. The tubes and filters are rinsed three times with 4 mL of 10 mM HEPES (pH 7.4), and the radioactivity associated with the filter circles determined using Formula 989 scintillation fluid (New England Nuclear, Boston, MA) in a scintillation counter.

5

Analysis

The data are used to calculate either the % inhibition compared to control binding (when only a single concentration of test compound is evaluated) or a K_i value (when a range of concentrations is tested).

10

% inhibition was calculated as follows:

$$1 - \left[\frac{(\text{test compound dpm-nonspecific dpm})}{(\text{total dpm-nonspecific dpm})} \right] \times 100\%$$

15

K_i value is calculated using the LIGAND (Munson, P.J. and Rodbard, D., Anal. Biochem. 107: 220-239, 1980) data analysis program.

20

Table 3 shows the biological activity (in K_i value) for 10nM solutions of the present compounds as measured in the rat brain δ -opioid receptor binding assay.

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Table 3

Example #	δK_i (nM)	Example #	δK_i (nM)	Example #	δK_i (nM)
1	1.2	25	9.8	48	48.2
2	0.1	26	7.5	49	4.96
3	0.023	27	46.7	50	8.5
4	0.38	28	4.7	51	5.7
5	0.06	29	35.9	52	0.75
6	0.025	30	35.2	53	2.9
7	2.6	31	49	54	57
8	13	32	16.6	55	225
9	3.5	33	24	56	24
10	1.4	34	11	57	15
11	0.38	35	2.9	58	18
12	18.5	36	7.4	59	3.9
13	6.3	37	352	60	12
14	1.1	38	32	61	15.5
15	6.8	39	49	62	30.7
17	0.23	40	102	64	4.5
18	0.39	41	331	66	0.58
19	0.7	42	924	67	24.7
20	0.01	43	1520	68	0.41
21	0.56	44	178	69	1.08
22	92	45	19.8	70	0.7
23	0.23	46	404		
24	42.1	47	3.2		

Rat Brain μ -Opioid Receptor Binding Assay

- 5 The activity of compounds of the invention as analgesics is demonstrated by the rat brain μ -opioid receptor binding assay as described below.

Procedure

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Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, NY) are killed by cervical dislocation and their brains removed and placed immediately in ice cold Tris HCl buffer (50 mM, pH 7.4). The forebrains are separated from the remainder of the brain by a coronal transection, beginning dorsally at the colliculi and passing ventrally through the midbrain-pontine junction. After dissection, the forebrains are homogenized in Tris buffer in a Teflon®-glass homogenizer. The homogenate is diluted to a concentration of 1 g of forebrain tissue per 100 mL Tris buffer and centrifuged at 39,000 X G for 10 min. The pellet is resuspended in the same volume of Tris buffer with several brief pulses from a Polytron homogenizer. This particulate preparation is used for the μ -opioid binding assays. Following incubation with the m-selective peptide ligand [^{3} H]DAMGO at 25 °C, the tube contents are filtered through Whatman GF/B filter sheets on a Brandel cell harvester. The tubes and filters are rinsed three times with 4 mL of 10 mM HEPES (pH 7.4) and the radioactivity associated with the filter circles determined using Formula 989 scintillation fluid (New England Nuclear, Boston, MA) in a scintillation counter.

Analysis

The data are used to calculate either the % inhibition compared to control binding (when only a single concentration of test compound is evaluated) or a K_i value (when a range of concentrations is tested).

% Inhibition is calculated as follows:

$$1 - \left(\frac{(\text{test compound dpm} - \text{nonspecific dpm})}{(\text{total dpm} - \text{nonspecific dpm})} \right) \times 100\%$$

K_i value is calculated using the LIGAND (Munson, P.J. and Rodbard, D., Anal. Biochem. 107: 220-239, 1980) data analysis program.

Mouse Acetylcholine Bromide-Induced Abdominal Constriction Assay

The activity of compounds of the invention as analgesics was further demonstrated by the mouse acetylcholine bromide-induced abdominal

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constriction assay as described below.

Procedure

The mouse acetylcholine-induced abdominal constriction assay (as described by Collier et al. in *Brit. J. Pharmacol. Chem. Ther.*, 1968, 32: 295-310 with minor modifications) was used to assess analgesic potency of the compounds of formula (I). The test drugs or appropriate vehicles were administered orally (p.o.) and 30 min later the animal received an intraperitoneal (i.p.) injection of 5.5 mg/kg acetylcholine bromide (Matheson, Coleman and Bell, East Rutherford, NJ). The mice were then placed in groups of three into glass bell jars and observed for a ten min observation period for the occurrence of an abdominal constriction response (defined as a wave of constriction and elongation passing caudally along the abdominal wall, accompanied by a twisting of the trunk and followed by extension of the hind limbs). For compounds of the present invention, the percent inhibition of this response to a nociceptive stimulus (equated to % analgesia) was calculated as follows:

% Inhibition of response (i.e., % analgesia) =

$$\frac{(\text{No. of control animal responses} - \text{No. of drug-treated animal responses}) \times 100}{\text{No. of control animals responding.}}$$

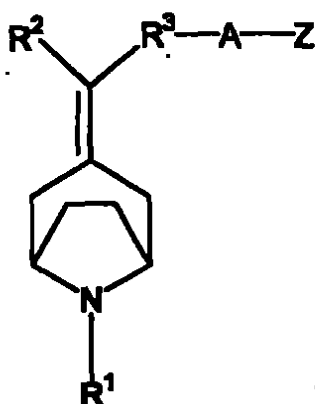
As a result of the mouse acetylcholine bromide-induced abdominal constriction assay, the compound of Example 1 measured an 87% inhibition response at a dose of 150 $\mu\text{mol/kg}$ p.o.

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WHAT IS CLAIMED IS:

1. An oploid receptor modulator compound selected from the group consisting of a δ -oploid and a μ -oploid receptor modulator compound of Formula (I):



(I)

5 wherein:

R¹ is selected from the group consisting of hydrogen, C₁₋₆alkyl, halo₁₋₃(C₁₋₆)alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy(C₂₋₆)alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy(C₂₋₆)alkynyl, cycloalkyl, cycloalkyl(C₁₋₆)alkyl, cycloalkylcarbonyl(C₁₋₆)alkyl, cycloalkyl(C₂₋₆)alkenyl, cycloalkyl(C₂₋₆)alkynyl, heterocyclyl, heterocyclyl(C₁₋₆)alkyl, heterocyclylcarbonyl(C₁₋₆)alkyl, heterocyclyl(C₂₋₆)alkenyl, heterocyclyl(C₂₋₆)alkynyl, aryl, aryl(C₁₋₆)alkyl, arylcarbonyl(C₁₋₆)alkyl, aryl(C₂₋₆)alkenyl, aryl(C₂₋₆)alkynyl, arylaminocarbonyl(C₁₋₆)alkyl, heteroaryl(C₁₋₆)alkyl, heteroarylcarbonyl(C₁₋₆)alkyl, heteroaryl(C₂₋₆)alkenyl, heteroaryl(C₂₋₆)alkynyl, heteroarylaminocarbonyl(C₁₋₆)alkyl, (R^{1a})₂N-(C₁₋₆)alkyl, R^{1a}-O-(C₁₋₆)alkyl, R^{1a}-S-(C₁₋₆)alkyl, R^{1a}-SO-(C₁₋₆)alkyl and R^{1a}-SO₂-(C₁₋₆)alkyl; wherein heterocyclyl is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, oxo, cyano, trifluoromethyl and trifluoromethoxy; and, wherein aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino,

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C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, cyano, trifluoromethyl and trifluoromethoxy;

- 5 R^{1a} is independently selected from the group consisting of hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, halo₁₋₃(C₁₋₆)alkyl, halo₁₋₃(C₁₋₆)alkoxy(C₁₋₆)alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, cycloalkyl, cycloalkyl(C₁₋₆)alkyl, heterocyclyl, heterocyclyl(C₁₋₆)alkyl, heterocyclyl(C₁₋₆)alkenyl, heterocyclyl(C₁₋₆)alkynyl, aryl, aryl(C₁₋₆)alkyl, aryl(C₁₋₆)alkenyl, aryl(C₁₋₆)alkynyl, arylcarbonyl(C₁₋₆)alkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, heteroaryl(C₁₋₆)alkenyl, heteroaryl(C₁₋₆)alkynyl and heteroarylcarbonyl(C₁₋₆)alkyl; wherein heterocyclyl is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, oxo, cyano, trifluoromethyl and trifluoromethoxy; and, wherein aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, cyano, trifluoromethyl and trifluoromethoxy;

- 25 R² is selected from the group consisting of aryl and heteroaryl optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylaminocarbonyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, cyano, trifluoromethyl and trifluoromethoxy; alternatively, when aryl and heteroaryl are substituted with two substituents attached to adjacent carbon atoms, the two substituents can together form a single fused moiety; wherein the moiety is selected from the group consisting of -(CH₂)₂₋₆- and -O(CH₂)₁₋₃O-;

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- R³** is selected from the group consisting of aryl and heteroaryl optionally substituted with one or two substituents in addition to the -A-Z moiety independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylaminocarbonyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, cyano, trifluoromethyl and trifluoromethoxy; alternatively, when aryl and heteroaryl are substituted with two optional substituents attached to adjacent carbon atoms, the two substituents can together form a single fused moiety; wherein the moiety is selected from the group consisting of -(CH₂)₃₋₆- and -O(CH₂)₁₋₃O-;
- A** is selected from the group consisting of -C(=X)- and -SO₂-;
- X** is selected from the group consisting of O and S;
- Z** is selected from the group consisting of -O(R⁴) and -N(R⁵)(R⁶);
- R⁴** is selected from the group consisting of hydrogen, C₁₋₆alkyl (optionally substituted with one to three halogen substituents), C₁₋₆alkoxy(C₁₋₆)alkyl, C₂₋₆alkenyl, cycloalkyl, cycloalkyl(C₁₋₆)alkyl, heterocyclyl, heterocyclyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, amino(C₁₋₆)alkyl, C₁₋₆alkylamino(C₁₋₆)alkyl, di(C₁₋₆)alkylamino(C₁₋₆)alkyl and hydroxy(C₁₋₆)alkyl; wherein heterocyclyl is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, cycloalkyl, trifluoromethyl, halogen, hydroxy, oxo and cyano; and, wherein aryl is optionally substituted with one to four substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, cycloalkyl, -OCH₂O-, -O(CH₂)₂O-, trifluoromethyl, halogen, hydroxy and cyano; and,

R⁵ and **R⁶** are independently selected from the group consisting of hydrogen,

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- C₁₋₆alkyl (optionally substituted with one to three halogen substituents),
 C₁₋₆alkoxy(C₁₋₆)alkyl, C₂₋₆alkenyl, cycloalkyl, cycloalkyl(C₁₋₆)alkyl,
 heterocyclyl, heterocyclyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl,
 heteroaryl(C₁₋₆)alkyl, amino(C₁₋₆)alkyl, C₁₋₆alkylamino(C₁₋₆)alkyl,
 5 dl(C₁₋₆)alkylamino(C₁₋₆)alkyl, aminoimino, aminocarbonyl,
 aminocarbonyl(C₁₋₆)alkyl, aryloxy-carbonylamino(C₁₋₆)alkyl,
 heteroaryloxy-carbonylamino(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl and
 trifluoro(C₁₋₆)alkoxy, wherein heterocyclyl is optionally substituted with one
 to three substituents independently selected from the group consisting of
 10 C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, cycloalkyl, trifluoromethyl, halogen,
 hydroxy, oxo and cyano; and, wherein aryl is optionally substituted with one
 to four substituents independently selected from the group consisting of
 C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, cycloalkyl, -OCH₂O-, -O(CH₂)₂O-,
 trifluoromethyl, halogen, hydroxy and cyano; alternatively, R⁸ and R⁹ may,
 15 together with the nitrogen to which they are attached, form a fused
 heterocyclyl moiety optionally substituted with one to four substituents
 independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy,
 C₂₋₆alkenyl, cycloalkyl, trifluoromethyl, halogen, hydroxy and cyano;
 20 and pharmaceutically acceptable enantiomers, diastereomers and salts
 thereof.

2. The compound of claim 1 wherein R¹ is selected from the group
 consisting of hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, cycloalkyl,
 25 cycloalkyl(C₁₋₆)alkyl, heterocyclyl, heterocyclyl(C₁₋₆)alkyl,
 heterocyclylcarbonyl(C₁₋₆)alkyl, aryl(C₁₋₆)alkyl, arylcarbonyl(C₁₋₆)alkyl,
 aryl(C₂₋₆)alkynyl, arylaminocarbonyl(C₁₋₆)alkyl, heteroaryl(C₁₋₆)alkyl,
 (R^{1a})₂N-(C₁₋₆)alkyl and R^{1a}-O-(C₁₋₆)alkyl; wherein heterocyclyl is
 optionally substituted with one to three substituents independently
 30 selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, halogen,
 hydroxy, oxo and cyano; and, wherein aryl is optionally substituted with
 one to three substituents independently selected from the group
 consisting of C₁₋₆alkyl, C₁₋₆alkoxy, halogen, hydroxy and cyano.

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3. The compound of claim 1 wherein R¹ is selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *n*-hexyl, butenyl, allyl, 3,3-dimethallyl, cyclopropyl, cyclopropyl(C₁₋₃)alkyl, cyclohexyl, cyclohexyl(C₁₋₃)alkyl, pyrrolidinyl, pyrrolidinyl(C₁₋₃)alkyl, 1,3-dioxolanyl(C₁₋₃)alkyl, 2-imidazolynyl, 2-imidazolynyl(C₁₋₃)alkyl, imidazolidinyl, imidazolidinyl(C₁₋₃)alkyl, 2-pyrazolynyl, 2-pyrazolynyl(C₁₋₃)alkyl, pyrazolidinyl, pyrazolidinyl(C₁₋₃)alkyl, piperidinyl, piperidinyl(C₁₋₃)alkyl, morpholinyl, morpholinyl(C₁₋₃)alkyl, thiomorpholinyl, thiomorpholinyl(C₁₋₃)alkyl, piperazinyl, piperazinyl(C₁₋₃)alkyl, [4-(C₁₋₃)alkyl-5-oxo-1,4-dihydropyridazin-1-yl](C₁₋₃)alkyl, piperonyl, (1,3-benzodioxol-5-yl)(C₂₋₃)alkyl, (2,3-dihydro-1,4-benzodioxin-6-yl)carbonyl(C₁₋₃)alkyl, (3,4-dihydro-2H-1,5-benzodioxepin-7-yl)carbonyl(C₁₋₃)alkyl, benzyl, phenyl(C₂₋₃)alkyl, phenyl(C₂₋₃)alkynyl, diphenyl(C₁₋₃)alkyl, phenylcarbonyl(C₁₋₃)alkyl, phenylaminocarbonyl(C₁₋₃)alkyl, furyl(C₁₋₃)alkyl, thienyl(C₁₋₃)alkyl, pyrrolyl(C₁₋₃)alkyl, oxazolyl(C₁₋₃)alkyl, thiazolyl(C₁₋₃)alkyl, imidazolyl(C₁₋₃)alkyl, pyrazolyl(C₁₋₃)alkyl, isoxazolyl(C₁₋₃)alkyl, isothiazolyl(C₁₋₃)alkyl, 1,2,3-oxadiazolyl(C₁₋₃)alkyl, 1,2,3-triazolyl(C₁₋₃)alkyl, 1,3,4-thiadiazolyl(C₁₋₃)alkyl, pyridinyl(C₁₋₃)alkyl, pyridazinyl(C₁₋₃)alkyl, pyrimidinyl(C₁₋₃)alkyl, pyrazinyl(C₁₋₃)alkyl, 1,3,5-triazinyl(C₁₋₃)alkyl, indolyl(C₁₋₃)alkyl, benzo[b]furyl(C₁₋₃)alkyl, benzo[b]thienyl(C₁₋₃)alkyl, (R^{1a})₂N-(C₁₋₃)alkyl and R^{1a}-O-(C₁₋₃)alkyl; wherein pyrrolidinyl, 2-imidazolynyl, imidazolidinyl, 2-pyrazolynyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl and piperazinyl are optionally substituted with one to three substituents selected from oxo; and, wherein phenyl is optionally substituted with one to three substituents independently selected from the group consisting of methyl, ethyl, *n*-propyl, *n*-butyl, methoxy, ethoxy, propoxy, butoxy, chlorine, fluorine, hydroxy and cyano.
4. The compound of claim 1 wherein R¹ is selected from the group consisting of hydrogen, methyl, *n*-propyl, *n*-butyl, allyl, 3,3-dimethallyl, cyclopropylmethyl, cyclohexylethyl, 2-(4-ethyl-5-oxo-1,4-dihydropyridazin-1-yl)ethyl, piperonyl, 2-(1,3-benzodioxol-5-yl)ethyl, 2-(2,3-dihydro-1,4-

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benzodioxin-8-yl)-2-oxoethyl, 2-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)-2-oxoethyl, benzyl, phenethyl, phenylpropyl, phenoxyethyl, phenylcarbonylmethyl, phenylcarbonylethyl, phenylaminocarbonylmethyl, thienylmethyl, thienylethyl, imidazolymethyl, pyridinylmethyl and indolylethyl; wherein phenyl is optionally substituted with one to three substituents independently selected from the group consisting of methoxy, fluorine, hydroxy and cyano.

- 10 5. The compound of claim 1 wherein R^{1a} is independently selected from the group consisting of hydrogen, C₁₋₆alkyl and aryl; wherein aryl is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, 15 C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, cyano, trifluoromethyl and trifluoromethoxy.
- 20 6. The compound of claim 1 wherein R^{1a} is independently selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl and phenyl; wherein phenyl is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, di(C₁₋₆alkyl)amino, halogen, trifluoromethyl and trifluoromethoxy.
- 25 7. The compound of claim 1 wherein R^{1a} is independently selected from the group consisting of methyl, ethyl and phenyl.
- 30 8. The compound of claim 1 wherein R² is selected from the group consisting of phenyl, naphthalenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, indolyl, benzo[b]furyl and benzo[b]thienyl

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optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₃alkyl, C₂₋₃alkenyl, C₁₋₃alkoxy, amino, C₁₋₃alkylamino, di(C₁₋₃alkyl)amino, C₁₋₃alkylcarbonyl, C₁₋₃alkylcarbonyloxy, C₁₋₃alkylcarbonylamino, chlorine, fluorine, hydroxy, trifluoromethyl and trifluoromethoxy.

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9. The compound of claim 1 wherein R² is selected from the group consisting of phenyl, furyl, thienyl, pyridinyl and benzo[b]furyl optionally substituted with one substituent selected from the group consisting of methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, methylcarbonyl, methylcarbonyloxy, methylcarbonylamino, fluorine, hydroxy, trifluoromethyl and trifluoromethoxy.

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10. The compound of claim 1 wherein R² is selected from phenyl optionally substituted with one substituent selected from the group consisting of methoxy and hydroxy.

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11. The compound of claim 1 wherein R³ is selected from the group consisting of phenyl, naphthalenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, indolyl, benzo[b]furyl and benzo[b]thienyl optionally substituted with one or two substituents in addition to the -A-Z moiety independently selected from the group consisting of methyl, ethyl, *n*-propyl, *i*-propyl, allyl, methoxy, ethoxy, amino, C₁₋₃alkylamino, di(C₁₋₃)alkylamino, C₁₋₃alkylcarbonyl, C₁₋₃alkylcarbonyloxy, C₁₋₃alkylcarbonyl, C₁₋₃alkylaminocarbonyl, C₁₋₃alkylcarbonylamino, C₁₋₃alkylthio, C₁₋₃alkylsulfonyl, chloro, fluoro, hydroxy, cyano, trifluoromethyl and trifluoromethoxy; alternatively, when phenyl is substituted with two optional substituents attached to adjacent carbon atoms, the two substituents can together form a single fused moiety; wherein the moiety is selected from the group consisting of -(CH₂)₃₋₅-

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and $-O(CH_2)_{1-3}O-$.

12. The compound of claim 1 wherein R^2 is phenyl substituted with the moiety $-A-Z$ at the 3 or 4 position.
13. The compound of claim 1 wherein A is $-C(=X)-$.
14. The compound of claim 1 wherein Z is $-N(R^5)(R^6)$.
15. The compound of claim 1 wherein R^4 is selected from the group consisting of C_{1-3} alkyl (optionally substituted with one to three halogen substituents), C_{2-3} alkenyl, aryl and aryl(C_{1-3})alkyl; wherein aryl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3} alkyl, $-OCH_2O-$, $-O(CH_2)_2O-$ and halogen.
16. The compound of claim 1 wherein R^4 is selected from the group consisting of C_{1-3} alkyl (optionally substituted with one or three fluorine substituents), C_{2-3} alkenyl, phenyl and benzyl; wherein phenyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3} alkyl, $-OCH_2O-$, $-O(CH_2)_2O-$ and fluorine.
17. The compound of claim 1 wherein R^4 is selected from the group consisting of methyl, ethyl, 3-methyl, phenyl and benzyl; wherein phenyl is optionally substituted with one substituent selected from the group consisting of methyl and fluorine.
18. The compound of claim 1 wherein R^5 and R^6 are independently selected from the group consisting of hydrogen, C_{1-3} alkyl, fluoro(C_{1-3})alkyl, trifluoro(C_{1-3})alkyl, C_{1-3} alkoxy(C_{1-3})alkyl, C_{2-3} alkenyl, cyclopropyl, cyclopropyl(C_{1-3})alkyl, cyclopentyl, cyclopentyl(C_{1-3})alkyl, cyclohexyl, cyclohexyl(C_{1-3})alkyl, pyrrolidinyl, pyrrolidinyl(C_{1-3})alkyl, 1,3-dioxolanyl,

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1,3-dioxolanyl(C₁₋₃)alkyl, 2-imidazoliny, 2-imidazolnlyl(C₁₋₃)alkyl,
imidazolidinyl, imidazolidinyl(C₁₋₃)alkyl, 2-pyrazolnlyl,
2-pyrazolnlyl(C₁₋₃)alkyl, pyrazolidinyl(C₁₋₃)alkyl, piperidinyl,
piperidinyl(C₁₋₃)alkyl, morpholnlyl, morpholnlyl(C₁₋₃)alkyl, thiomorpholnlyl,
thiomorpholnlyl(C₁₋₃)alkyl, piperaznlyl, piperaznlyl(C₁₋₃)alkyl, piperonyl,
5 phenyl, benzyl, phenyl(C₂₋₃)alkyl, furyl, furyl(C₁₋₃)alkyl, thienyl,
thienyl(C₁₋₃)alkyl, pyrrolyl(C₁₋₃)alkyl, oxazolyl, oxazolyl(C₁₋₃)alkyl, thiazolyl,
thiazolyl(C₁₋₃)alkyl, imidazolyl, imidazolyl(C₁₋₃)alkyl, pyrazolyl,
pyrazolyl(C₁₋₃)alkyl, isoxazolyl, isoxazolyl(C₁₋₃)alkyl, isothiazolyl,
10 isothiazolyl(C₁₋₃)alkyl, 1,2,3-oxadiazolyl, 1,2,3-oxadiazolyl(C₁₋₃)alkyl,
1,2,3-triazolyl, 1,2,3-triazolyl(C₁₋₃)alkyl, 1,3,4-thiadiazolyl,
1,3,4-thiadiazolyl(C₁₋₃)alkyl, pyridinyl, pyridinyl(C₁₋₃)alkyl, pyridaznlyl,
pyridaznlyl(C₁₋₃)alkyl, pyrimidinyl, pyrimidinyl(C₁₋₃)alkyl, pyraznlyl,
pyraznlyl(C₁₋₃)alkyl, 1,3,5-triaznlyl, 1,3,5-triaznlyl(C₁₋₃)alkyl,
15 indolyl(C₁₋₃)alkyl, benzo[b]furyl, benzo[b]furyl(C₁₋₃)alkyl, benzo[b]thienyl,
benzo[b]thienyl(C₁₋₃)alkyl, benzimidazolyl, benzimidazolyl(C₁₋₃)alkyl,
amino(C₁₋₃)alkyl, C₁₋₃alkylamino(C₁₋₃)alkyl, di(C₁₋₃)alkylamino(C₁₋₃)alkyl,
aminoimino, hydroxy(C₁₋₃)alkyl and trifluoro(C₁₋₄)alkoxy; wherein
pyrrolidinyl, 1,3-dioxolanyl, 2-imidazolnlyl, imidazolidinyl, 2-pyrazolnlyl,
20 pyrazolidinyl, piperidinyl, morpholnlyl, thiomorpholnlyl, piperaznlyl are
optionally substituted with one to three substituents independently
selected from the group consisting of C₁₋₄alkyl and oxo; and, wherein
phenyl is optionally substituted with one to four substituents
independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄alkoxy,
25 -OCH₂O-, -O(CH₂)₂O-, halogen, hydroxy and cyano; alternatively, R⁵ and
R⁶ may, together with the nitrogen to which they are attached, form a
fused heterocyclyl moiety selected from the group consisting of
pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholnlyl,
thiomorpholnlyl and piperaznlyl optionally substituted with one to four
30 substituents independently selected from C₁₋₄alkyl.

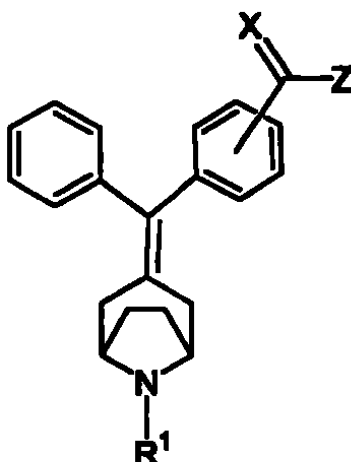
19. The compound of claim 1 wherein R⁵ and R⁶ are independently selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl,

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5 *t*-butyl, fluoro(C₁₋₃)alkyl, methoxy(C₁₋₃)alkyl, methallyl, cyclopropyl, cyclohexyl, phenyl, thiazolyl, imidazolyl(C₁₋₃)alkyl, benzimidazolyl(C₁₋₃)alkyl, dimethylamino(C₁₋₃)alkyl and hydroxy(C₁₋₃)alkyl; wherein phenyl is optionally substituted with one to three substituents selected from fluorine; alternatively, R⁵ and R⁶ may, together with the nitrogen to which they are attached, form a fused heterocyclyl moiety selected from the group consisting of pyrrolidinyl, piperidinyl and morpholinyl optionally substituted with one to four substituents independently selected from the group consisting of methyl, ethyl, *n*-propyl and *n*-butyl.

15 20. The compound of claim 1 wherein R⁵ and R⁶ are independently selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *t*-propyl, *t*-butyl, 2-fluoroethyl, methoxyethyl, methallyl, cyclopropyl, cyclohexyl, phenyl, thiazolyl, 2-(2-imidazolyl)ethyl, benzimidazolylmethyl, dimethylaminopropyl and hydroxyethyl; wherein phenyl is optionally substituted with fluorine; alternatively, R⁵ and R⁶ may, together with the nitrogen to which they are attached, form a fused heterocyclyl moiety selected from the group consisting of pyrrolidinyl, piperidinyl and morpholinyl; wherein piperidinyl is substituted with two or four substituents selected from methyl.

21. The compound of claim 1 of the formula:



wherein the moiety -C(=X)- is substituted on phenyl at the 3 or 4 position and

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R', -C(=X)- and Z are dependently selected from the group consisting of:

R'	-C(=X)-	Z
methyl	-4-C(=O)-	N,N-diethylamino;
H	-4-C(=O)-	N,N-diethylamino;
allyl	-4-C(=O)-	N,N-diethylamino;
2-(4-fluorophenyl)ethyl	-4-C(=O)-	N,N-diethylamino;
2-(2-thienyl)ethyl	-4-C(=O)-	N,N-diethylamino;
2-(3-indolyl)ethyl	-4-C(=O)-	N,N-diethylamino;
2-cyclohexylethyl	-4-C(=O)-	N,N-diethylamino;
2-phenoxyethyl	-4-C(=O)-	N,N-diethylamino;
2-(4-ethyl-5-oxo-1,4-dihydro-1H-tetrazol-1-yl)ethyl	-4-C(=O)-	N,N-diethylamino;
2-phenyl-2-oxoethyl	-4-C(=O)-	N,N-diethylamino;
2-(4-methoxyphenyl)-2-oxoethyl	-4-C(=O)-	N,N-diethylamino;
2-(3-cyanophenyl)-2-oxoethyl	-4-C(=O)-	N,N-diethylamino;
2-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-oxoethyl	-4-C(=O)-	N,N-diethylamino;
2-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)-2-oxoethyl	-4-C(=O)-	N,N-diethylamino;
propyl	-4-C(=O)-	N,N-diethylamino;
2-phenylethyl	-4-C(=O)-	N,N-diethylamino;
piperonyl	-4-C(=O)-	N,N-diethylamino;
3-phenylpropyl	-4-C(=O)-	N,N-diethylamino;
methyl	-3-C(=O)-	N-methyl-N-(3-fluorophenyl)amino;
2-phenylethyl	-4-C(=S)-	N,N-diethylamino;
2-phenylethyl	-4-C(=O)-	N-ethylamino;
2-phenylethyl	-4-C(=O)-	amino;
2-phenylethyl	-4-C(=O)-	4-morpholinyl;
2-phenylethyl	-4-C(=O)-	N,N-diisopropylamino;
2-phenylethyl	-4-C(=O)-	N,N-bis(methoxyethyl)amino;
2-phenylethyl	-4-C(=O)-	1-pyrrolidinyl;
2-phenylethyl	-4-C(=O)-	2,6-dimethyl-1-piperidinyl;

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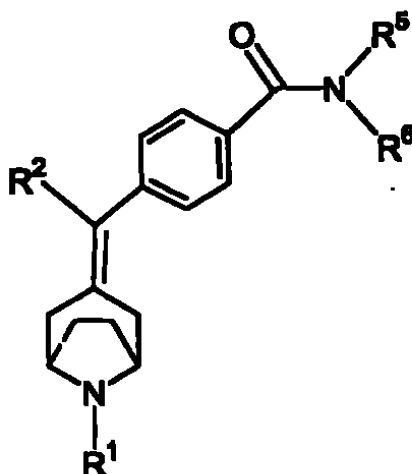
2-phenylethyl	-4-C(=O)-	N-ethyl-N-(methylallyl)amino;
2-phenylethyl	-4-C(=O)-	N,N-dipropylamino;
2-phenylethyl	-4-C(=O)-	N-t-butylamino;
2-phenylethyl	-4-C(=O)-	N-(2-fluoroethyl)amino;
2-phenylethyl	-4-C(=O)-	N-(2-thiazolyl)amino;
2-phenylethyl	-4-C(=O)-	N-(2-methoxyethyl)amino;
2-phenylethyl	-4-C(=O)-	N-(1H-benzimidazol-2-ylmethyl)amino;
2-phenylethyl	-4-C(=O)-	N-cyclohexylamino;
2-phenylethyl	-4-C(=O)-	N-phenylamino;
2-phenylethyl	-4-C(=O)-	N-[2-(2-imidazolyl)ethyl]amino;
2-phenylethyl	-4-C(=O)-	N-cyclopropylamino;
2-phenylethyl	-4-C(=O)-	N,N-(dimethylaminopropyl)amino;
2-phenylethyl	-4-C(=O)-	N-ethyl-N-(hydroxyethyl)amino;
2-(1,3-benzodioxol-5-yl)ethyl	-4-C(=O)-	N-ethylamino;
2-(1,3-benzodioxol-5-yl)ethyl	-4-C(=O)-	N,N-diethylamino;
methyl	-4-C(=O)-	N-ethylamino;
H	-4-C(=O)-	N-ethylamino;
allyl	-4-C(=O)-	N-ethylamino;
2-(4-methoxyphenyl)ethyl	-4-C(=O)-	N,N-diethylamino;
2-(4-methoxyphenyl)ethyl	-4-C(=O)-	4-morpholinyl;
2-(4-methoxyphenyl)ethyl	-4-C(=O)-	N-ethylamino;
2-(4-methoxyphenyl)ethyl	-4-C(=O)-	N,N-bis(2-methoxyethyl)amino;
2-(4-methoxyphenyl)ethyl	-4-C(=O)-	1-pyrrolidinyl;
2-(4-methoxyphenyl)ethyl	-4-C(=O)-	2,6-dimethyl-1-piperidinyl;
2-(4-methoxyphenyl)ethyl	-4-C(=O)-	N-ethyl-N-(methylallyl)amino;
2-(4-methoxyphenyl)ethyl	-4-C(=O)-	N,N-(di-n-propyl)amino;
2-(4-methoxyphenyl)ethyl	-4-C(=O)-	2,2,6,6-tetramethyl-1-piperidinyl;
2-(4-methoxyphenyl)ethyl	-4-C(=O)-	N,N-(di-2-propyl)amino;
2-(4-hydroxyphenyl)ethyl	-4-C(=O)-	N-ethylamino; and,

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2-(4-hydroxyphenyl)ethyl -4-C(=O)- N,N-diethylamine

and pharmaceutically acceptable enantiomers, diastereomers and salts thereof.

5 22. The compound of claim 1 of the formula:



wherein R¹, R², R⁵ and R⁶ are dependently selected from the group consisting of:

R¹	R²	(R⁵)(R⁶)
methyl	4-MeOPh	(H)(Et);
H	4-HOPh	(H)(Et);
methyl	4-MeOPh	Et₂;
H	4-HOPh	Et₂;
2-(4-MeOPh)ethyl	4-MeOPh	Et₂; and,
2-(4-HOPh)ethyl	4-HOPh	Et₂;

10 and pharmaceutically acceptable enantiomers, diastereomers and salts thereof.

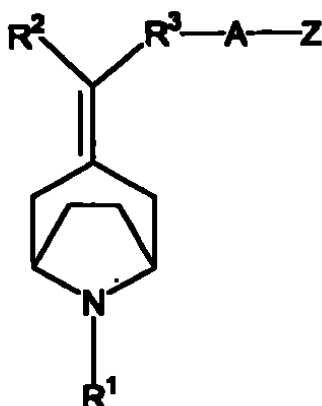
23. The compound of claim 1 which is an effective analgesic.

15 24. The compound of claim 1 which is an effective immunosuppressant, antinflammatory agent, agent for the treatment of neurological and psychiatric conditions, medicament for drug and alcohol abuse, agent

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for treating gastritis and diarrhea, cardiovascular agent or agent for the treatment of respiratory diseases.

25. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.
26. A method for the treatment of a pharmacological condition in a subject in need thereof comprising administering to the subject a therapeutically effective amount of an opioid receptor modulator compound selected from the group consisting of a δ -opioid and a μ -opioid receptor modulator compound of Formula (I):



(I)

wherein:

R¹ is selected from the group consisting of hydrogen, C₁₋₆alkyl, halo₁₋₃(C₁₋₆)alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy(C₂₋₆)alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy(C₂₋₆)alkynyl, cycloalkyl, cycloalkyl(C₁₋₆)alkyl, cycloalkylcarbonyl(C₁₋₆)alkyl, cycloalkyl(C₂₋₆)alkenyl, cycloalkyl(C₂₋₆)alkynyl, heterocyclyl, heterocyclyl(C₁₋₆)alkyl, heterocyclylcarbonyl(C₁₋₆)alkyl, heterocyclyl(C₂₋₆)alkenyl, heterocyclyl(C₂₋₆)alkynyl, aryl, aryl(C₁₋₆)alkyl, arylcarbonyl(C₁₋₆)alkyl, aryl(C₂₋₆)alkenyl, aryl(C₂₋₆)alkynyl, arylaminocarbonyl(C₁₋₆)alkyl, heteroaryl(C₁₋₆)alkyl, heteroarylcarbonyl(C₁₋₆)alkyl, heteroaryl(C₂₋₆)alkenyl, heteroaryl(C₂₋₆)alkynyl, heteroarylaminocarbonyl(C₁₋₆)alkyl, (R^{1a})₂N-(C₁₋₆)alkyl, R^{1a}-O-(C₁₋₆)alkyl, R^{1a}-S-(C₁₋₆)alkyl, R^{1a}-SO-(C₁₋₆)alkyl and R^{1a}-SO₂-(C₁₋₆)alkyl; wherein heterocyclyl is optionally substituted with one to three substituents

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independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, oxo, cyano, trifluoromethyl and trifluoromethoxy; and, wherein aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, cyano, trifluoromethyl and trifluoromethoxy;

R¹ is independently selected from the group consisting of hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, halo₁₋₃(C₁₋₆)alkyl, halo₁₋₃(C₁₋₆)alkoxy(C₁₋₆)alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, cycloalkyl, cycloalkyl(C₁₋₆)alkyl, heterocyclyl, heterocyclyl(C₁₋₆)alkyl, heterocyclyl(C₁₋₆)alkenyl, heterocyclyl(C₁₋₆)alkynyl, aryl, aryl(C₁₋₆)alkyl, aryl(C₁₋₆)alkenyl, aryl(C₁₋₆)alkynyl, arylcarbonyl(C₁₋₆)alkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, heteroaryl(C₁₋₆)alkenyl, heteroaryl(C₁₋₆)alkynyl and heteroarylcarbonyl(C₁₋₆)alkyl; wherein heterocyclyl is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, oxo, cyano, trifluoromethyl and trifluoromethoxy; and, wherein aryl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, cyano, trifluoromethyl and trifluoromethoxy;

R² is selected from the group consisting of aryl and heteroaryl optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino,

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di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylaminocarbonyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, cyano, trifluoromethyl and trifluoromethoxy; alternatively, when aryl and heteroaryl are substituted with two substituents attached to adjacent carbon atoms, the two substituents can together form a single fused moiety, wherein the moiety is selected from the group consisting of -(CH₂)₃₋₅- and -O(CH₂)₁₋₃O-;

R³ is selected from the group consisting of aryl and heteroaryl optionally substituted with one or two substituents in addition to the -A-Z moiety independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylaminocarbonyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, cyano, trifluoromethyl and trifluoromethoxy; alternatively, when aryl and heteroaryl are substituted with two optional substituents attached to adjacent carbon atoms, the two substituents can together form a single fused moiety; wherein the moiety is selected from the group consisting of -(CH₂)₃₋₅- and -O(CH₂)₁₋₃O-;

A is selected from the group consisting of -C(=X)- and -SO₂-;

X is selected from the group consisting of O and S;

Z is selected from the group consisting of -O(R⁴) and -N(R⁴)(R⁵);

R⁴ is selected from the group consisting of hydrogen, C₁₋₆alkyl (optionally substituted with one to three halogen substituents), C₁₋₆alkoxy(C₁₋₆alkyl, C₂₋₆alkenyl, cycloalkyl, cycloalkyl(C₁₋₆alkyl, heterocyclyl, heterocyclyl(C₁₋₆alkyl, aryl, aryl(C₁₋₆alkyl, heteroaryl, heteroaryl(C₁₋₆alkyl, amino(C₁₋₆alkyl, C₁₋₆alkylamino(C₁₋₆alkyl, di(C₁₋₆alkylamino(C₁₋₆alkyl and hydroxy(C₁₋₆alkyl; wherein heterocyclyl is optionally substituted with one to three substituents independently selected from the group consisting of

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C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, cycloalkyl, trifluoromethyl, halogen, hydroxy, oxo and cyano; and, wherein aryl is optionally substituted with one to four substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, cycloalkyl, -OCH₂O-, -O(CH₂)₂O-, trifluoromethyl, halogen, hydroxy and cyano; and,

R⁵ and R⁶ are independently selected from the group consisting of hydrogen, C₁₋₆alkyl (optionally substituted with one to three halogen substituents), C₁₋₆alkoxy(C₁₋₆)alkyl, C₂₋₆alkenyl, cycloalkyl, cycloalkyl(C₁₋₆)alkyl, heterocyclyl, heterocyclyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, amino(C₁₋₆)alkyl, C₁₋₆alkylamino(C₁₋₆)alkyl, di(C₁₋₆)alkylamino(C₁₋₆)alkyl, aminolmino, aminocarbonyl, aminocarbonyl(C₁₋₆)alkyl, aryloxy carbonylamino(C₁₋₆)alkyl, heteroaryloxy carbonylamino(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl and trifluoro(C₁₋₆)alkoxy; wherein heterocyclyl is optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, cycloalkyl, trifluoromethyl, halogen, hydroxy, oxo and cyano; and, wherein aryl is optionally substituted with one to four substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, cycloalkyl, -OCH₂O-, -O(CH₂)₂O-, trifluoromethyl, halogen, hydroxy and cyano; alternatively, R⁵ and R⁶ may, together with the nitrogen to which they are attached, form a fused heterocyclyl moiety optionally substituted with one to four substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, cycloalkyl, trifluoromethyl, halogen, hydroxy and cyano;

and pharmaceutically acceptable enantiomers, diastereomers and salts thereof.

27. The method of claim 26 wherein the therapeutically effective amount is from about 0.01 mg/day to about 15,000 mg/day.

28. The method of claim 26 wherein the δ -opioid or μ -opioid receptor

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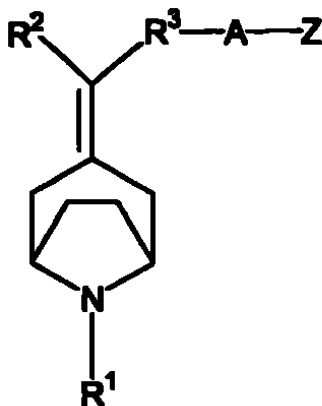
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modulator compound is an effective analgesic.

29. The method of claim 26 wherein the δ -opioid or μ -opioid receptor modulator compound is an effective immunosuppressant, antinflammatory agent, agent for the treatment of neurological and psychiatric conditions, medicament for drug and alcohol abuse, agent for treating gastritis and diarrhea, cardiovascular agent or agent for the treatment of respiratory diseases.

30. The method of claim 26 wherein the pharmacological condition is pain.

31. A pharmaceutical composition comprising a combination of a μ -opioid receptor modulator compound and an opioid receptor modulator compound selected from the group consisting of a δ -opioid and a μ -opioid receptor modulator compound of Formula (I):



(I)

wherein:

R¹ is selected from the group consisting of hydrogen, C₁₋₈alkyl, halo₁₋₃(C₁₋₈)alkyl, C₂₋₈alkenyl, C₁₋₈alkoxy(C₂₋₈)alkenyl, C₂₋₈alkynyl, C₁₋₈alkoxy(C₂₋₈)alkynyl, cycloalkyl, cycloalkyl(C₁₋₈)alkyl, cycloalkylcarbonyl(C₁₋₈)alkyl, cycloalkyl(C₂₋₈)alkenyl, cycloalkyl(C₂₋₈)alkynyl, heterocyclyl, heterocyclyl(C₁₋₈)alkyl, heterocyclylcarbonyl(C₁₋₈)alkyl, heterocyclyl(C₂₋₈)alkenyl, heterocyclyl(C₂₋₈)alkynyl, aryl, aryl(C₁₋₈)alkyl, arylcarbonyl(C₁₋₈)alkyl, aryl(C₂₋₈)alkenyl, aryl(C₂₋₈)alkynyl.

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arylaminoalkyl(C₁₋₆)alkyl, heteroaryl(C₁₋₆)alkyl,
heteroarylcarbonyl(C₁₋₆)alkyl, heteroaryl(C₂₋₆)alkenyl, heteroaryl(C₂₋₆)alkynyl,
heteroarylaminoalkyl(C₁₋₆)alkyl, (R^{1a})₂N-(C₁₋₆)alkyl, R^{1a}-O-(C₁₋₆)alkyl,
R^{1a}-S-(C₁₋₆)alkyl, R^{1a}-SO-(C₁₋₆)alkyl and R^{1a}-SO₂-(C₁₋₆)alkyl; wherein

5 heterocyclyl is optionally substituted with one to three substituents
independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl,
C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl,
C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl,
halogen, hydroxy, oxo, cyano, trifluoromethyl and trifluoromethoxy; and,
10 wherein aryl and heteroaryl are optionally substituted with one to three
substituents independently selected from the group consisting of C₁₋₆alkyl,
C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino,
C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio,
C₁₋₆alkylsulfonyl, halogen, hydroxy, cyano, trifluoromethyl and
15 trifluoromethoxy;

R^{1a} is independently selected from the group consisting of hydrogen, C₁₋₆alkyl,
C₁₋₆alkoxy(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, halo₁₋₃(C₁₋₆)alkyl,
halo₁₋₃(C₁₋₆)alkoxy(C₁₋₆)alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, cycloalkyl,
20 cycloalkyl(C₁₋₆)alkyl, heterocyclyl, heterocyclyl(C₁₋₆)alkyl,
heterocyclyl(C₁₋₆)alkenyl, heterocyclyl(C₁₋₆)alkynyl, aryl, aryl(C₁₋₆)alkyl,
aryl(C₁₋₆)alkenyl, aryl(C₁₋₆)alkynyl, arylcarbonyl(C₁₋₆)alkyl, heteroaryl,
heteroaryl(C₁₋₆)alkyl, heteroaryl(C₁₋₆)alkenyl, heteroaryl(C₁₋₆)alkynyl and
heteroarylcarbonyl(C₁₋₆)alkyl; wherein heterocyclyl is optionally substituted
25 with one to three substituents independently selected from the group
consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino,
di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy,
C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy,
oxo, cyano, trifluoromethyl and trifluoromethoxy; and, wherein aryl and
30 heteroaryl are optionally substituted with one to three substituents
independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl,
C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl,
C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl,

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halogen, hydroxy, cyano, trifluoromethyl and trifluoromethoxy;

R² is selected from the group consisting of aryl and heteroaryl optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylaminocarbonyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, cyano, trifluoromethyl and trifluoromethoxy; alternatively, when aryl and heteroaryl are substituted with two substituents attached to adjacent carbon atoms, the two substituents can together form a single fused moiety; wherein the moiety is selected from the group consisting of $-(CH_2)_{3-6}-$ and $-O(CH_2)_{1-3}O-$;

R³ is selected from the group consisting of aryl and heteroaryl optionally substituted with one or two substituents in addition to the -A-Z moiety independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, C₁₋₆alkylamino, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylaminocarbonyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkylthio, C₁₋₆alkylsulfonyl, halogen, hydroxy, cyano, trifluoromethyl and trifluoromethoxy; alternatively, when aryl and heteroaryl are substituted with two optional substituents attached to adjacent carbon atoms, the two substituents can together form a single fused moiety; wherein the moiety is selected from the group consisting of $-(CH_2)_{3-6}-$ and $-O(CH_2)_{1-3}O-$;

A is selected from the group consisting of $-C(=X)-$ and $-SO_2-$;

X is selected from the group consisting of O and S;

Z is selected from the group consisting of $-O(R^4)$ and $-N(R^4)(R^4)$;

R⁴ is selected from the group consisting of hydrogen, C₁₋₆alkyl (optionally substituted with one to three halogen substituents), C₁₋₆alkoxy(C₁₋₆)alkyl,

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C₂₋₆alkenyl, cycloalkyl, cycloalkyl(C₁₋₆)alkyl, heterocyclyl,
heterocyclyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl,
amino(C₁₋₆)alkyl, C₁₋₆alkylamino(C₁₋₆)alkyl, di(C₁₋₆)alkylamino(C₁₋₆)alkyl and
hydroxy(C₁₋₆)alkyl; wherein heterocyclyl is optionally substituted with one to
5 three substituents independently selected from the group consisting of
C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, cycloalkyl, trifluoromethyl, halogen,
hydroxy, oxo and cyano; and, wherein aryl is optionally substituted with one
to four substituents independently selected from the group consisting of
C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, cycloalkyl, -OCH₂O-, -O(CH₂)₂O-,
10 trifluoromethyl, halogen, hydroxy and cyano; and,

R^a and R^b are independently selected from the group consisting of hydrogen,
C₁₋₆alkyl (optionally substituted with one to three halogen substituents),
C₁₋₆alkoxy(C₁₋₆)alkyl, C₂₋₆alkenyl, cycloalkyl, cycloalkyl(C₁₋₆)alkyl,
15 heterocyclyl, heterocyclyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl,
heteroaryl(C₁₋₆)alkyl, amino(C₁₋₆)alkyl, C₁₋₆alkylamino(C₁₋₆)alkyl,
di(C₁₋₆)alkylamino(C₁₋₆)alkyl, aminolmino, aminocarbonyl,
aminocarbonyl(C₁₋₆)alkyl, aryloxy carbonylamino(C₁₋₆)alkyl,
heteroaryloxy carbonylamino(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl and
20 trifluoro(C₁₋₆)alkoxy; wherein heterocyclyl is optionally substituted with one
to three substituents independently selected from the group consisting of
C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, cycloalkyl, trifluoromethyl, halogen,
hydroxy, oxo and cyano; and, wherein aryl is optionally substituted with one
to four substituents independently selected from the group consisting of
25 C₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, cycloalkyl, -OCH₂O-, -O(CH₂)₂O-,
trifluoromethyl, halogen, hydroxy and cyano; alternatively, R^a and R^b may,
together with the nitrogen to which they are attached, form a fused
heterocyclyl moiety optionally substituted with one to four substituents
independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy,
30 C₂₋₆alkenyl, cycloalkyl, trifluoromethyl, halogen, hydroxy and cyano;

and pharmaceutically acceptable enantiomers, diastereomers and salts thereof.

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32. The pharmaceutical composition of claim 31 wherein the μ -opioid receptor modulator compound is selected from alfentanil, allylprodine, alphaprodine, anileridine, bezitramide; buprenorphine, clonitazene, cyciazocine, dextromoramide, dihydrocodeine, dihydromorphine, ethoheptazine, ethylmorphine, etonitazene, fentanyl, heroin, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, lofentanil, meperidine, meptazinol, metazocine, methadone, morphine, nalbuphine, norlevorphanol, normethadone, nalorphine, normorphine, opium, oxycodone, oxymorphone, phensazocine, piritramide, propiram, propoxyphene, sufentanil, tramadol or diastereomers, salts, complexes and mixtures thereof of any of the foregoing.
33. A method for the treatment of a pharmacological condition in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of claim 31.
34. The method of claim 33 wherein the therapeutically effective amount is from about 0.01 mg/day to about 15,000 mg/day.
35. The method of claim 33 wherein the pharmaceutical composition is an effective analgesic.
36. The method of claim 33 wherein the pharmaceutical composition is an effective immunosuppressant, antiinflammatory agent, agent for the treatment of neurological and psychiatric conditions, medicament for drug and alcohol abuse, agent for treating gastritis and diarrhea, cardiovascular agent or agent for the treatment of respiratory diseases.
37. The method of claim 33 wherein the pharmacological condition is pain.

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ABSTRACT OF THE INVENTION

This invention is directed to 3-(diarylmethylene)-8-azabicyclo[3.2.1]octane derivatives useful as δ -opioid or μ -opioid receptor modulators. Depending on
5 their agonist or antagonist effect, the compounds are useful analgesics, immunosuppressants, antiinflammatory agents, agents for the treatment of neurological and psychiatric conditions, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents and agents for the treatment of respiratory diseases.

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PTO/SB/01 (10-05)
Approved for use through 10/31/2002, OMB 0551-0032
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Under the Paperwork Reduction Act of 1995, no person is required to respond to a collection of information unless it contains a valid OMB control number.

DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.83) ☒ Declaration Submitted with Initial Filing ☐ Declaration Submitted after Initial Filing OR Initial Filing (Surcharge (37 CFR 1.16(e)) required)	Attorney Docket Number	ORT-1375			
	First Names Inventor	Boyd et al			
	COMPLETE IF KNOWN				
	Application Number				
	Filing Date	February 22, 2001			
	Group Art Unit				
	Examiner Name				
As a below named inventor, I hereby declare that: My residence, mailing address, and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:					
3-(DIARYLMETHYLENE)-8-AZABICYCLO[3.2.1]OCTANE DERIVATIVES (Title of the Invention)					
the specification of which ☒ is attached hereto OR ☐ was filed on (MM/DD/YYYY) as United States Application Number or PCT International Application Number and was amended on (MM/DD/YYYY) I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT International filing date of the continuation-in-part application. I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(e) of any PCT International application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or any PCT International application having a filing date before that of the application on which priority is claimed.					
Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES NO	
			☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐
☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:					

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DECLARATION - Utility or Design Patent Application		
I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.		
Application Number(s)	Filing Date (MM/DD/YYYY)	☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB02B attached hereto.
60/186,778	03/03/2000	
I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT International filing date of this application:		
Application Serial No.	Filing Date	Status
		Patented Patented Patented
I hereby appoint:		
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as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.		
Address all telephone calls to John W Harbour at telephone number (732) 524-2186.		
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NAME OF SOLE OR FIRST INVENTOR:		☐ A petition has been filed for this unsigned inventor	
Given Name (first and middle (if any)) Robert E.		Family Name or Surname Boyd	
Inventor's Signature		Date	
Residence: CityHorsham	State PA	Country USA	Citizenship USA
Mailing Address 84 Wymore Drive			
City Horsham	State PA	ZIP 19044	Country USA
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NAME OF SECOND INVENTOR:		☐ A petition has been filed for this unsigned inventor	
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Inventor's Signature		Date	
Residence: CityNorristown	State PA	Country USA	Citizenship USA
Mailing Address 551 Rittenhouse Blvd.,			
City Norristown	State PA	ZIP 19003	Country USA
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NAME OF THIRD INVENTOR:		☐ A petition has been filed for this unsigned inventor	
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Inventor's Signature		Date	
Residence: CityQuakertown	State PA	Country USA	Citizenship USA
Mailing Address 1029 Bryton Ct.,			
City Quakertown	State PA	ZIP 18951	Country USA

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NAME OF SOLE OR FIRST INVENTOR:		☐ A petition has been filed for this unsigned inventor	
Given Name (first and middle (if any)) Lou Anne		Family Name or Surname Nelson	
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Mailing Address 1210 Diamond Street,			
City Sellersville	State PA	ZIP 18860	Country USA
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.			
NAME OF SECOND INVENTOR:		☐ A petition has been filed for this unsigned inventor	
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Inventor's Signature		Date	
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City North Wales	State PA	ZIP 19454	Country USA
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.			
NAME OF THIRD INVENTOR:		☐ A petition has been filed for this unsigned inventor	
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Inventor's Signature		Date	
Residence: City Lansdale	State PA	Country USA	Citizenship USA
Mailing Address 2043 Spring Valley Road			
City Lansdale	State PA	ZIP 19446	Country USA

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**ESTADOS UNIDOS DE AMERICA
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LLEGUE:**

**DEPARTAMENTO DE COMERCIO DE LOS ESTADOS
UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos**

marzo 14, 2001

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con 35 USC 111.

Número de Solicitud: 60/186,778

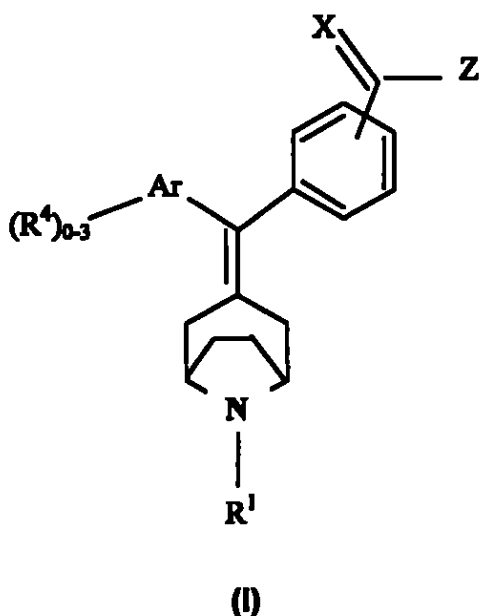
Fecha de Presentación: marzo 3, 2000

Por la autoridad del
Comisionado de Patentes y Marca

(fdo) M.K. HAWKINS
Oficial Certificador
Sello oficial de la Oficina de Patentes y Marcas de los
Estados Unidos de América

LO QUE SE REIVINDICA ES:

1. Un compuesto representado por la siguiente formula (I):



En donde:

X se selecciona del grupo formado por S y O;

Z se selecciona del grupo formado por $N(R^2)(R^3)$ y $O(R^2)$;

La porción $-C(=X)-$ esta sustituida con fenil en la 3 o 4 posición;

R^1 es un sustituyente seleccionado del grupo formado por hidrógeno, C_{1-8} alquil, C_{2-8} alquenil, C_{3-7} cicloalquil, C_{3-8} cicloalquil C_{1-3} alquil, C_{1-8} alcoxi C_{1-3} alquil, 4- C_{1-4} alquil - 4,5 - dihidro - 5 - oxo- 1H- tetrazol - 1 - il C_{1-4} alquil, tien - 2 - il C_{1-4} alquil, tien - 3 - il C_{1-4} alquil, furan - 2 - il C_{1-4} alquil, furan - 3 - il C_{1-4} alquil, pirrol - 2 - il C_{1-4} alquil, pirrol - 3 -il C_{1-4} alquil, piridin - 2 - il C_{1-4} alquil, piridin - 3 - il C_{1-4} alquil, piridin - 4 -il C_{1-4} alquil, pirazinil C_{1-4} alquil,

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pirimidin - 2 - il C₁₋₄ alquil, pirimidin - 4 - il C₁₋₄ alquil, pirimidin - 5 - il C₁₋₄ alquil, tiazol - 2 - il C₁₋₄ alquil, tiazol - 4 - il C₁₋₄ alquil, tiazol - 5 - il C₁₋₄ alquil, oxazol - 2 - il C₁₋₄ alquil, oxazol - 4 - il C₁₋₄ alquil, oxazol - 5 - il C₁₋₄ alquil, fenil C₁₋₄ alquil, fenil C₂₋₄ alquenil y bencil; en donde los anteriores sustituyentes tienil, furanil, pirrolil, tiazolil y oxazolil están opcionalmente mono-, di- o tri - sustituidos con un sustituyente seleccionado del grupo formado por hidroxil, halógeno, C₁₋₃ alquil, C₂₋₃ alquenil, C₁₋₃ alcoxi, C₁₋₃ acil, C₁₋₁₀ aciloxi, ciano, amino, C₁₋₃ acilamino, C₁₋₃ alquilamino, di (C₁₋₃ alquil) amino, C₁₋₃ alquilitio, C₁₋₃ alquilsulfonil, - OCH₂O-, -O(CH₂)₂O-, trifluorometil y trifluorometoxi; y en donde los anteriores sustituyentes piridinil, pirazinil, pirimidinil, fenil y bencil están opcionalmente sustituidos con un sustituyente seleccionado del grupo formado por hidroxil, halógeno, C₁₋₃ alquil, C₂₋₃ alquenil, C₁₋₃ alcoxi, C₁₋₃ acil, C₁₋₁₀ aciloxi, ciano, amino, C₁₋₃ acilamino, C₁₋₃ alquilamino, di(C₁₋₃alquil)amino, C₁₋₃ alquilitio, C₁₋₃ alquilsulfonil, -OCH₂O-, -O(CH₂)₂O-, trifluorometil y trifluorometoxi;

R² y R³ son seleccionados independientemente del grupo formado por hidrógeno, C₁₋₈ alquil, C₂₋₈ alquenil, C₃₋₇ cicloalquil, fenil y bencil, en donde el anterior sustituyente fenil esta opcionalmente mono- , di o tri sustituido con un sustituyente seleccionado del grupo formado por halógeno, C₁₋₈ alquil, C₂₋₈ alquenil, C₃₋₇cicloalquil y trifluorometil; y en donde el anterior sustituyente bencil esta opcionalmente mono- , di- o tri- sustituido con un sustituyente seleccionado del grupo formado por halógeno, C₁₋₈ alquil, C₂₋₈ alquenil, C₁₋₈ alcoxi, C₃₋₇ cicloalquil, trifluorometil, metilendioxi y etilendioxi;

R² y R³ alternativamente, cuando ambos están presentes, pueden formar combinadamente una porción única fusionada con N; en donde R² y R³ son seleccionados del grupo formado por 1,4 - butileno, 1-5 pentileno, 1,5 - (3-oxapentileno) y 1,5 - (3 - azapentileno) y en donde la porción única fusionada puede estar opcionalmente sustituida con, desde 1 hasta 4 sustituyentes seleccionados del grupo formado por C₁₋₈ alquil C₂₋₈ alquenil y C₃₋₇ cicloalquil;

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Ar se selecciona del grupo formado por fenil, 1-naftil y 2-naftil opcionalmente sustituidos con, desde 0 hasta 3 sustituyentes seleccionados de R⁴;

R⁴ se selecciona opcionalmente e independientemente del grupo formado por hidroxil, halógeno, C₁₋₃ alquil, C₂₋₃ alquenil, C₁₋₃ alcoxi, C₁₋₃ acil, C₁₋₁₀ aciloxi, ciano, amino, C₁₋₃acilamino, C₁₋₃ alquilamino, di(C₁₋₃alquil)amino, C₁₋₃ alquilitio, C₁₋₃ alquilsulfonil, -OCH₂O-, -O(CH₂)₂O-, trifluorometil y trifluorometoxi; y,

R⁴ alternativamente, cuando dos grupos R⁴ están presentes, pueden formar combinadamente una porción única; en donde la porción se selecciona del grupo formado por -(CH₂)₃₋₆ - y -O(CH₂)₁₋₃O- unida a un átomo de carbono adyacente a Ar,

Y aquellos enantiómeros, diastómeros y sus sales, farmacéuticamente aceptables.

2. El compuesto de la reivindicación 1 en donde:

X es O;

Z es N(R²)(R³);

R¹ se selecciona del grupo formado por hidrógeno, metil, etil, n-propil, n-butil, n-hexil, 3-etilbutil, alil, dimetalil, ciclopropilmetil, ciclohexilmetil, ciclohexil, tien - 2 - il etil, piperonil, 2 - furilmetil, fenetil, difeniletil, fenilpropil, 3,4 - dimetoxifenetil, 4 - fluorofenetil y 3,4 - metilendioxi-bencil;

R² y R³ son seleccionados del grupo formado por metil, etil, n-propil, isopropil, t-butil, metalil, 3-fluorofenil y 4 - metilbencil;

R^2 y R^3 alternativamente, cuando ambos están presentes, pueden formar combinadamente una porción única fusionada con N; en donde la porción es pirrolidinil opcionalmente sustituida con, desde 1 hasta 4 sustituyentes seleccionados del grupo formado por C_{1-6} alquil, C_{2-6} alquenil y C_{3-7} cicloalquil;

Ar es fenil; y,

R^4 se selecciona opcional e independientemente del grupo formado por hidroxil, cloro, bromo, flúor, metil, etil, metoxi, etoxi, metilamino, N, N-dimetilamino, metiltio, metilsulfonil, trifluorometoxi y trifluorometil;

Y aquellos enantiómeros, diastómeros y sus sales, farmacéuticamente aceptables.

3. El compuesto de la reivindicación 1 en donde:

R^1 se selecciona del grupo formado por hidrógeno, metil, etil, n-propil, n-butil, alil, ciclopropilmetil, tien – 2 – il etil, fenetil, fenilpropil y 3,4 – metilendioxbencil;

R^2 y R^3 se seleccionan independientemente del grupo formado por metil, etil, n-propil, metalil, y 3 – fluorofenil; y

R^4 es metoxi;

Y aquellos enantiómeros, diastómeros y sus sales, farmacéuticamente aceptables.

4. El compuesto de la reivindicación 1 en donde:

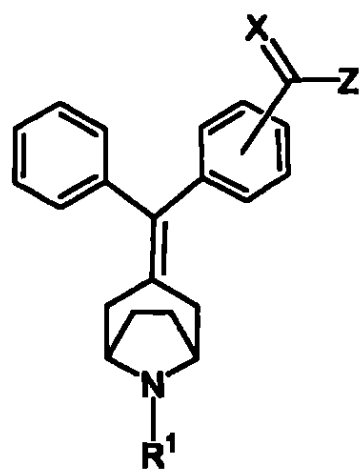
R^1 se secciona del grupo formado por hidrógeno, metil, etil, n-propil, alil, fenetil, fenilpropil y 3,4 – metilendioxbencil;

R^2 y R^3 se seleccionan independientemente del grupo formado por metil, etil y 3 – fluorofenil; y,

R^4 es inexistente

Y aquellos enantiómeros, diastómeros y sus sales, farmacéuticamente aceptables.

5. El compuesto de la reivindicación 1 que presenta la siguiente estructura



en donde R^1 , X y Z se seleccionan dependientemente del grupo formado por:

R^1	$-C(=X)-$	Z
CH_3	4- $C(=O)-$	$N(CH_2CH_3)_2$
H	4- $C(=O)-$	$N(CH_2CH_3)_2$
$CH_2CH=CH_2$	4- $C(=O)-$	$N(CH_2CH_3)_2$
$(CH_2)_2CH_3$	4- $C(=O)-$	$N(CH_2CH_3)_2$
$(CH_2)_2Ph$	4- $C(=O)-$	$N(CH_2CH_3)_2$

	C(=O)-	
3,4 – metilendioxi-benzil	-4- C(=O)-	N(CH ₂ CH ₃) ₂
(CH ₂) ₃ Ph y	-4- C(=O)-	N(CH ₂ CH ₃) ₂
CH ₃	-3- C(=O)-	NCH ₃ (3-F-Ph)

6. El compuesto de la reivindicación 1 los cuales son analgésicos efectivos
7. El compuesto de la reivindicación 1 los cuales son inmunosupresores efectivos, agentes antiinflamatorios, agentes para el tratamiento de condiciones siquiátricas y neurológicas, medicamentos para el tratamiento del abuso de drogas y alcohol, agentes para el tratamiento de gastritis y diarrea, agentes cardiovasculares y agentes para el tratamiento de afecciones respiratorias.
8. Una composición farmacéutica que incluye un compuesto de la reivindicación 1 y un vehículo farmacéuticamente aceptable.
9. Una composición farmacéutica obtenida por la mezcla de un compuesto de la reivindicación 1 y un vehículo farmacéuticamente aceptable.
10. Una composición farmacéutica que incluye una combinación de un compuesto de la reivindicación 1 y un compuesto efectivo como un modulador mu-opiáceo
11. Una composición farmacéutica de la reivindicación 10 en donde el compuesto útil como un modulador mu- opiáceo se selecciona del grupo formado por alfentanil, alilprodina, alfaprodina, anileridina, bencil morfina, bezitramida, buprenorfina, butorfanol, clonitazene, ciclazocine, desomorfina, dextromoramida, dezocina, diampromida, diamorfona,

dihidrocodeína, dihidromorfina, dimenoxadol, dimefeptanol, dimetiltiambuteno, dioxafetilbutirato, dipipanona, eptazocina, etoheptazina, etilmetiltiambuteno, etilmorfina, etonitazeno, fentanil, heroína, hidromorfona, hidroxipetidina, isometadona, ketobemidona, levallorfan, levorfanol, levofenacilmorfano, lofentanil, meperidina, meptazinol, metazocina, metadona, metopona, morfina, mirofina, nalbufina, narceína, nicomorfina, norlevorfanol, normetadona, nalorfina, normorfina, norpipanona, opio, oxiconona, oximorfona, papaveretum, pentazocina, fenadoxona, fenomorfano, fenazocina, fenoperidina, piminodina, piritramida, profeptazina, promedol, properidina, propiram, propoxifeno, sufentanil, tilidina, tramadol, sales, complejos y las mezclas de cualquiera de los anteriores.

12. Un método para el tratamiento de una condición farmacológica en un sujeto que necesite de este, comprendiendo la administración al sujeto de una cantidad terapéuticamente efectiva de la composición farmacéutica de la reivindicación 1
13. El método de la reivindicación 12 donde la condición farmacológica es dolor
14. El método de la reivindicación 13 en donde la cantidad terapéuticamente efectiva del compuesto de la reivindicación 1 es desde aproximadamente 0.1 Mg / día hasta aproximadamente 300 MG / día
15. El método de la reivindicación 12 donde la cantidad terapéuticamente efectiva del compuesto de la reivindicación 1 es efectiva como agente inmunosupresor, antiinflamatorio, agente para el tratamiento de condiciones neurológicas y psiquiátricas, medicamento para casos de abuso de droga y alcohol, agente para el tratamiento de gastritis y

diarrea, agente cardiovascular o agente para el tratamiento de enfermedades respiratorias

16.El método de la reivindicación 12 en donde el método incluye la administración a un individuo de una cantidad terapéuticamente efectiva de la composición farmacéutica de la reivindicación 8.

17.El método de la reivindicación 12 en donde la cantidad terapéuticamente efectiva de la composición farmacéutica de la reivindicación 8 es desde aproximadamente 0.1 Mg. / día hasta aproximadamente 300 Mg. /día

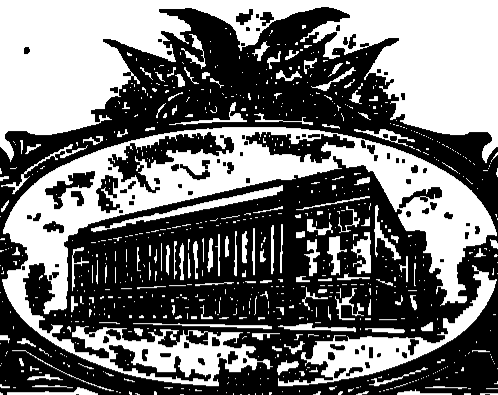
18.El método de la reivindicación 12 en donde el método incluye la administración a un individuo de una cantidad terapéuticamente efectiva de la composición farmacéutica de la reivindicación 9.

19.El método de la reivindicación 12 en donde la cantidad terapéuticamente efectiva de la composición farmacéutica de la reivindicación 9 es desde aproximadamente 0.1 Mg. / día hasta aproximadamente 300 Mg. /día

20.El método de la reivindicación 12 en donde el método incluye la administración a un individuo de una cantidad terapéuticamente efectiva de la composición farmacéutica de la reivindicación 10

21.El método de la reivindicación 12 en donde la cantidad terapéuticamente efectiva de la composición farmacéutica de la reivindicación 10 es desde aproximadamente 0.1 Mg / día hasta aproximadamente 300 Mg /día

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THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

March 14, 2001

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/186,778

FILING DATE: March 03, 2000



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

M. K. Hawkins

M. K. HAWKINS
Certifying Officer

03/03/00
14700 U.S. P.O.

3-6-00
PROVISIONAL APPLICATION COVER SHEET

APPROV
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This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53 (c).

DOCKET NUMBER		ORT-1196		TYPE A PLUS SIGN (+) INSIDE THIS BOX →		+	
INVENTOR(S) / APPLICANT(S)							
LAST NAME		FIRST NAME		MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)		
Carson		John		R.	551 Rittenhouse Blvd., Norristown, PA, 19403		
Neilson		Lou Anne			1210 Diamond Street, Sellersville, PA, 18960		
TITLE OF THE INVENTION (240 characters max)							
[(8-AZABICYCLO[3.2.1]OCT-3-YLIDENE)ARYLMETHYL] BENZOIC ACID DERIVATIVES							
CORRESPONDENCE ADDRESS							
Andloy A. Champoreau, Jr., Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick							
STATE		New Jersey		ZIP CODE		08933-7003	
COUNTRY		USA					
ENCLOSED APPLICATION PARTS (check all that apply)							
☒ Specification		Number of Pages		36		☐ Small Entity Statement	
☒ Claims		Number of Claims		21		☐ Other (specify)	
☐ Drawing(s)		Number of Sheets					
METHOD OF PAYMENT (check one)							
☐ A check or money order is enclosed to cover the Provisional filing fees.					Provisional Filing Fee Amount (\$)		\$ 150.00
☒ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. 10-0750							

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE		Date: March 3, 2000	
TYPED or PRINTED NAME		REGISTRATION NO.	
John W. Harbour		31,365	

☐ Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

Telephone No. (732) 524-2169

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DOCKET NO. ORT-1196

IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

Applicant: John R. Carson and Lou Anne Neilson

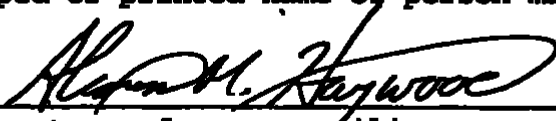
For : [(8-AZABICYCLO[3.2.1]OCT-3-YLIDENE)ARYLMETHYL]
BENZOIC ACID DERIVATIVES

Express Mail Certificate

"Express Mail" mailing number: EL327261246US

Date of Deposit: March 3, 2000

I hereby certify that this complete Provisional application, including specification pages, and claims, 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 Assistant Commissioner for Patents, Washington, D.C. 20231.

Alwin M. Haywood
(Typed or printed name of person mailing paper or fee)

(Signature of person mailing paper or fee)

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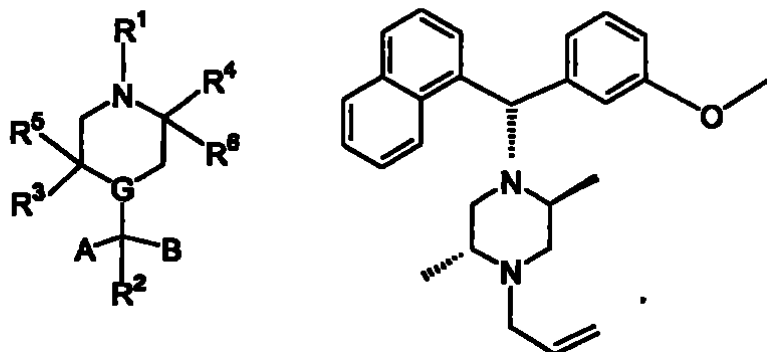
**[(8-AZABICYCLO[3.2.1]OCT-3-YLIDENE)ARYLMETHYL] BENZOIC ACID
DERIVATIVES**

FIELD OF THE INVENTION

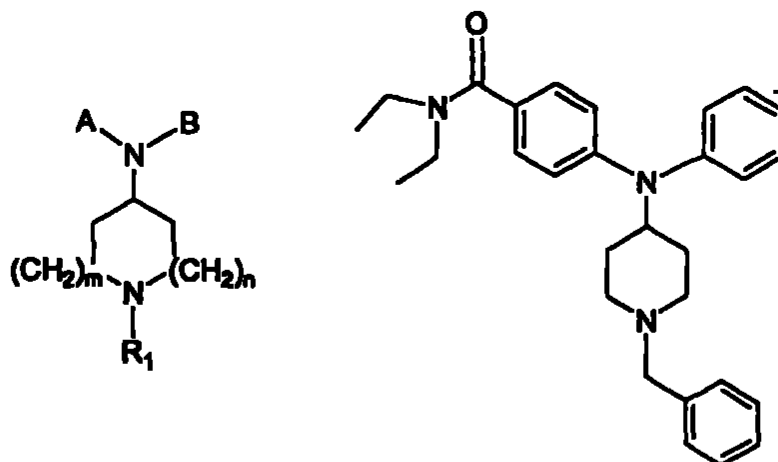
The present invention is directed to delta-opioid receptor modulators.
5 More particularly, the present invention is directed to [(8-azabicyclo[3.2.1]oct-3-ylidene)arylmethyl] benzoic acid derivatives which are delta-opioid receptor modulators useful as effective analgesics.

BACKGROUND OF THE INVENTION

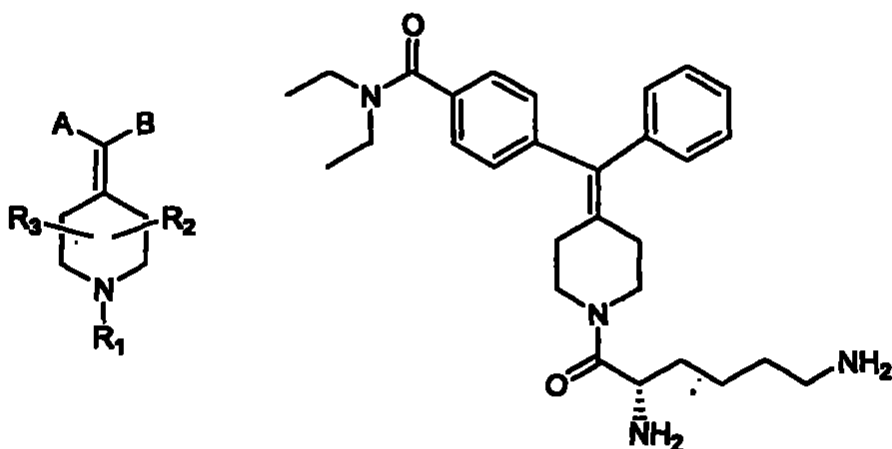
10 WO 97/23466 discloses compounds described as having an analgesic effect, having a general and a typical preferred formula:



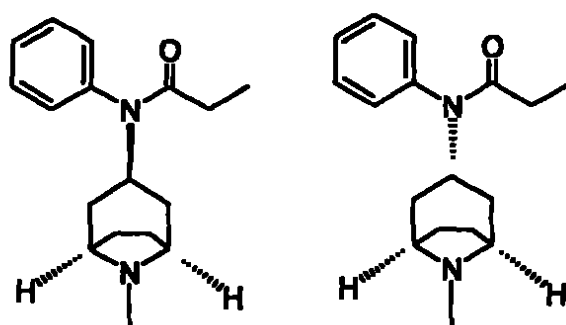
WO 98/28270 also discloses compounds described as having an analgesic effect, having a general and a typical preferred formula:



WO 98/28275 further discloses compounds described as having an analgesic effect, having a general and a typical preferred formula:

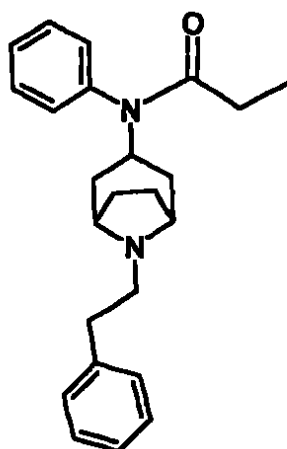


- 5 Isomeric 3-propananilidotropans are used as intermediates herein and have been published in Bagley, J. R., et al., *J. Heterocycl. Chem.*, 1977, 14(4), 599-602, having the following formulae:

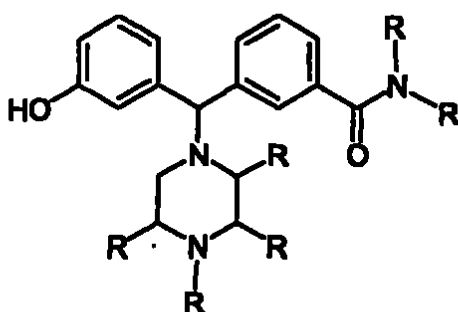


Amide derivatives of 3-aminotropane are also used as intermediates herein and have been prepared and described as having potential pharmacological activity, Gutkowska, B., et al., *Acta Pol. Pharm.*, 1984, 41(6).

5 613-617, having the formula:



WO 93/15062 discloses compounds which have been described as delta-opioid and mu-opioid receptor agonists, having (approximately) the formula:



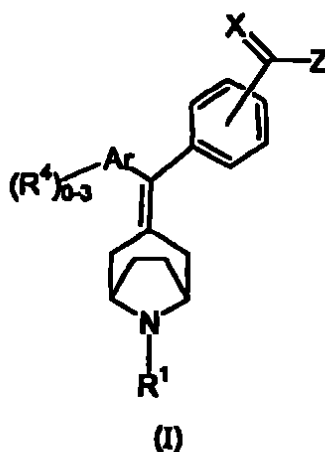
The foregoing reference compounds have been described as either delta- or mu-opioid receptor agonists or antagonists.

It is an object of the present invention to provide delta-opioid receptor modulators as analgesics. It is another object of the present invention to provide delta-opioid receptor selective agonists as analgesics having reduced side-effects. It is also another object of the present invention to provide delta-opioid receptor antagonists as immunosuppressants, antiinflammatory agents, agents for the treatment of neurological and psychiatric conditions, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents and agents for the treatment of respiratory diseases, having reduced side-effects. It is a further object of the present invention to provide a useful pharmaceutical composition comprising a compound of the present invention useful as delta-opioid receptor modulators. It is also a further object of the present invention to provide a useful pharmaceutical composition comprising a delta-opioid receptor modulator of the present invention in combination with mu-opioid receptor modulators having a synergistic analgesic effect.

SUMMARY OF THE INVENTION

There are provided by the present invention delta-opioid receptor modulators having the general formula (I):

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wherein:

X is selected from the group consisting of S and O;

- 5 Z is selected from the group consisting of O(R²) and N(R²)(R³);

the moiety -C(=X)- is substituted on phenyl at the 3 or 4 position;

R¹ is a substituent selected from the group consisting of hydrogen, C₁₋₈alkyl,

C₂₋₈alkenyl, C₃₋₇cycloalkyl, C₃₋₆cycloalkylC₁₋₃alkyl, C₁₋₈alkoxyC₁₋₃alkyl,

4-C₁₋₄alkyl-4,5-dihydro-5-oxo-1H-tetrazol-1-ylC₁₋₄alkyl, thien-2-ylC₁₋₄alkyl,

- 10 thien-3-ylC₁₋₄alkyl, furan-2-ylC₁₋₄alkyl, furan-3-ylC₁₋₄alkyl, pyrrol-2-ylC₁₋₄alkyl,

pyrrol-3-ylC₁₋₄alkyl, pyridin-2-ylC₁₋₄alkyl, pyridin-3-ylC₁₋₄alkyl,

pyridin-4-ylC₁₋₄alkyl, pyrazinylC₁₋₄alkyl, pyrimidin-2-ylC₁₋₄alkyl,

pyrimidin-4-ylC₁₋₄alkyl, pyrimidin-5-ylC₁₋₄alkyl, thiazol-2-ylC₁₋₄alkyl,

thiazol-4-ylC₁₋₄alkyl, thiazol-5-ylC₁₋₄alkyl, oxazol-2-ylC₁₋₄alkyl,

- 15 oxazol-4-ylC₁₋₄alkyl, oxazol-5-ylC₁₋₄alkyl, phenylC₁₋₄alkyl, phenylC₂₋₄alkenyl

and benzyl; wherein the foregoing thienyl, furanyl, pyrrolyl, thiazolyl and

oxazolyl substituents are optionally mono-, di- or tri-substituted with a

substituent selected from the group consisting of hydroxy, halogen,

C₁₋₃alkyl, C₂₋₃alkenyl, C₁₋₃alkoxy, C₁₋₃acyl, C₁₋₁₀acyloxy, cyano, amino,

- 20 C₁₋₃acylamino, C₁₋₃alkylamino, di(C₁₋₃alkyl)amino, C₁₋₃alkylthio,

C₁₋₃alkylsulfonyl, -OCH₂O-, -O(CH₂)₂O-, trifluoromethyl and trifluoromethoxy;

and wherein the foregoing pyridinyl, pyrazinyl, pyrimidinyl, phenyl and

benzyl substituents are optionally mono-, di- or tri-substituted with a

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substituent selected from the group consisting of hydroxy, halogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₁₋₃alkoxy, C₁₋₃acyl, C₁₋₁₀acyloxy, cyano, amino, C₁₋₃acylamino, C₁₋₃alkylamino, di(C₁₋₃alkyl)amino, C₁₋₃alkylthio, C₁₋₃alkylsulfonyl, -OCH₂O-, -O(CH₂)₂O-, trifluoromethyl and trifluoromethoxy;

- 5 R² and R³ are independently selected from the group consisting of hydrogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₃₋₇cycloalkyl, phenyl and benzyl; wherein the foregoing phenyl substituent is optionally mono-, di- or tri-substituted with a substituent selected from the group consisting of halogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₃₋₇cycloalkyl and trifluoromethyl; and wherein the foregoing
- 10 benzyl substituent is optionally mono-, di- or tri-substituted with a substituent selected from the group consisting of halogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₁₋₃alkoxy, C₃₋₇cycloalkyl, trifluoromethyl, methylenedioxy and ethylenedioxy;

- 15 R² and R³ alternatively, when both are present, can together form a single fused moiety with N; wherein R² and R³ are selected from the group consisting of 1,4-butylene, 1,5-pentylene, 1,5-(3-oxapentylene) and 1,5-(3-azapentylene) and wherein the single fused moiety may be optionally substituted with from 1 to 4 substituents selected from the group consisting of C₁₋₃alkyl, C₂₋₃alkenyl and C₃₋₇cycloalkyl;

- 20 Ar is selected from the group consisting of phenyl, 1-naphthyl and 2-naphthyl optionally substituted with from 0 to 3 substituents selected from R⁴;

- R⁴ is optionally and independently selected from the group consisting of hydroxy, halogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₁₋₃alkoxy, C₁₋₃acyl, C₁₋₁₀acyloxy, cyano, amino, C₁₋₃acylamino, C₁₋₃alkylamino, di(C₁₋₃alkyl)amino, C₁₋₃alkylthio,
- 25 C₁₋₃alkylsulfonyl, -OCH₂O-, -O(CH₂)₂O-, trifluoromethyl and trifluoromethoxy; and,

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R^4 alternatively, when two R^4 groups are present, can together form a single fused moiety; wherein the moiety is selected from the group consisting of $-(CH_2)_{3-6}$ and $-O(CH_2)_{1-3}O-$ attached to adjacent carbon atoms of Ar;

and pharmaceutically acceptable enantiomers, diastereomers and salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Relative to the above generic description, certain compounds of the general formula (I) are preferred. Preferred embodiments are those compounds wherein:

10 X is O;

Z is $N(R^2)(R^3)$;

15 R^1 is selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *n*-butyl, *n*-hexyl, 3-ethylbutyl, allyl, dimethylallyl, cyclopropylmethyl, cyclohexylmethyl, cyclohexyl, thien-2-ylethyl, piperonyl, 2-furylmethyl, phenethyl, diphenylethyl, phenylpropyl, 3,4-dimethoxyphenethyl, 4-fluorophenethyl and 3,4-methylenedioxybenzyl;

R^2 and R^3 are independently selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, *t*-butyl, methallyl, 3-fluorophenyl and 4-methylbenzyl;

20 R^2 and R^3 , alternatively, when both are present, can together form a single fused moiety with N; wherein the moiety is pyrrolidinyl optionally substituted with from 1 to 4 substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl and C_{3-7} cycloalkyl;

Ar is phenyl; and,

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R⁴ is optionally and independently selected from the group consisting of hydroxy, chloro, bromo, fluoro, methyl, ethyl, methoxy, ethoxy, methylamino, N,N-dimethylamino, methylthio, methylsulfonyl, trifluoromethoxy and trifluoromethyl;

- 5 and pharmaceutically acceptable enantiomers, diastereomers and salts thereof.

Particularly preferred embodiments are those compounds wherein:

- 10 R¹ is selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *n*-butyl, allyl, cyclopropylmethyl, thien-2-ylethyl, phenethyl, phenylpropyl and 3,4-methylenedioxybenzyl; preferably, R¹ is selected from the group consisting of hydrogen, methyl, *n*-propyl, allyl, phenethyl, phenylpropyl and 3,4-methylenedioxybenzyl;

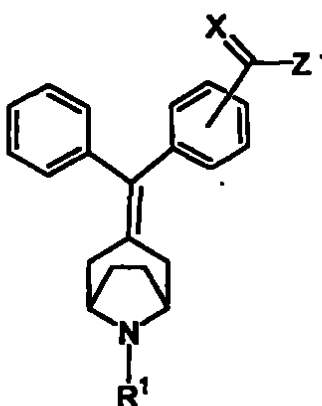
- 15 R² and R³ are independently selected from the group consisting of methyl, ethyl, *n*-propyl, methallyl and 3-fluorophenyl; preferably, R² and R³ are independently selected from the group consisting of methyl, ethyl and 3-fluorophenyl; and,

R⁴ is optionally methoxy; preferably, R⁴ is nonexistent;

and pharmaceutically acceptable enantiomers, diastereomers and salts thereof.

- 20 Particular compounds of the present invention are listed in Table 1 and have the general structure:

Table 1



wherein R¹, X and Z are dependently selected from the group consisting of:

Ex #	R ¹	-C(=X)-	Z
1	CH ₃	-4-C(=O)-	N(CH ₂ CH ₃) ₂
2	H	-4-C(=O)-	N(CH ₂ CH ₃) ₂
3	CH ₂ CH=CH ₂	-4-C(=O)-	N(CH ₂ CH ₃) ₂
4	(CH ₂) ₂ CH ₃	-4-C(=O)-	N(CH ₂ CH ₃) ₂
5	(CH ₂) ₂ Ph	-4-C(=O)-	N(CH ₂ CH ₃) ₂
6	3,4-methylenedioxybenzyl	-4-C(=O)-	N(CH ₂ CH ₃) ₂
7	(CH ₂) ₃ Ph	-4-C(=O)-	N(CH ₂ CH ₃) ₂
8	CH ₃	-3-C(=O)-	NCH ₃ (3-F-Ph)

Instant compounds of the invention may also be present in the form of a
 5 pharmaceutically acceptable salt. The pharmaceutically acceptable salt
 generally takes a form in which the basic nitrogen is protonated with an
 inorganic or organic acid. Representative organic or inorganic acids include
 hydrochloric, hydrobromic, hydroiodic, perchloric, sulfuric, nitric, phosphoric,
 acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric,
 10 benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benzenesulfonic,
 oxalic, pantoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic,
 salicylic, saccharic or trifluoroacetic.

It is intended that the definition of any substituent or variable at a
 particular location in a molecule be independent of its definitions elsewhere in

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that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth
5 herein.

The compounds of this invention are chiral and, thus, may exist as enantiomers. In addition, the compounds may exist as diastereomers. It is to be understood that all such enantiomers and diastereomers, as well as all mixtures thereof, are encompassed within the scope of the present invention.

10 Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention.

In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are also intended to
15 be encompassed within the scope of this invention.

The present invention also contemplates a pharmaceutical composition comprising a combination of a delta-opioid receptor modulator compound of the present invention and mu-opioid receptor modulator compounds having a synergistic analgesic effect.

20 Suitable mu-opioid receptor modulator compounds for use in such a combination include, without limitation, the compounds alfentanil, allylprodine, alphaprodine, anileridine, benzyl-morphine, bezitramide, buprenorphine, butorphanol, clonitazene, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, diamorphine, dihydrocodeine, dihydromorphine,
25 dimenoxadol, dimepheptanol dimethylthiambutene, dioxaphetylbutyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol,

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levophenacymorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, pirtramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, diastereomers thereof, salts thereof, complexes thereof; and mixtures of any of the foregoing.

The terms used in describing the invention are commonly used and known to those skilled in the art. However, the terms that could have other meanings are hereinafter defined. These definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

The term "alkyl" refers to straight or branched chain unsubstituted hydrocarbon groups of 1 to 10 carbon atoms, preferably 1 to 8 carbon atoms and, most preferably, 1 to 6 carbon atoms. The term "aryl" refers to an unsubstituted or substituted aromatic group such as phenyl or naphthyl. The term "aralkyl" refers to an aryl group bonded directly through an alkyl group, such as benzyl. As well, whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., aralkyl, dialkylamino) it shall be interpreted as including the limitations for the "alkyl" and "aryl" groups.

An "independently" selected substituent refers to a group of substituents, wherein the substituents may be different. Therefore, designated numbers of carbon atoms (e.g., C₁₋₈) shall refer independently to the number of carbon atoms in an alkyl or cycloalkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

For example, alkyl radicals are those 1 to 8 carbon branched or straight chains including, but not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *t*-butyl, *n*-pentyl, 3-(2-methyl)butyl, 2-pentyl, 2-methylbutyl,

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neopentyl, *n*-hexyl, 2-hexyl and 2-methylpentyl. Alkoxy radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups having the formula: alkyl-O-. Acyl radicals are those 1 to 6 carbon branched or straight chains derived from an organic acid by removal of the hydroxyl group having the formula: alkyl-C(=O)-. Acyloxy radicals are those 1 to 6 carbon branched or straight chains derived from an organic acid by removal of the hydrogen having the formula alkyl-C(=O)O-.

Cycloalkyl groups contain 3 to 8 ring carbons and preferably 5 to 7 carbons. Similarly, alkenyl and alkynyl groups include straight and branched chain alkenes and alkynes having 1 to 8 carbon atoms, or any number within this range.

When a particular group is "substituted," that group may have one or more substituents, preferably from one to five substituents, more preferably from one to three substituents, most preferably from one to two substituents, independently selected from the list of substituents.

As well, where the aryl is "substituted," the aryl group may be substituted with, for example, one to four substituents such as hydroxy, halogen, alkyl, substituted alkyl, trifluoromethoxy, trifluoromethyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, acyl, acyloxy, alkanoyl, alkanoyloxy, carboxy, carbamyl, nitro, cyano, amino, ureido, thiol, carboxyalkyl, alkoxy carbonyl, alkylamino, dialkylamino, acylamino, alkanoylamino, alkylthio, alkylsulfonyl, sulfonamido, cycloalkyl, cycloalkyloxy, cycloalkylamino, cycloalkylthio, aryloxy, aralkylamino, furyl and the like. The foregoing alkyl or aryl substituents may be further substituted by hydroxy, halogen, alkyl, substituted alkyl, alkoxy, cyano, alkoxy carbonyl, aryl, substituted aryl, substituted aralkyl or aryloxy carbonyl.

Exemplary substituents include one or more alkyl groups as described above or one or more groups described above as substituted alkyl.

The term "carbonyl" refers to the group C=O. Therefore, the term "aroyl" refers to an aryl group bonded directly to the carbonyl group, such as phenyl-C(=O)-, hereinafter referred to as benzoyl.

5 The term "halogen" or "halo" shall include iodine, bromine, chlorine and fluorine.

Where the compounds according to this invention are chiral, they may accordingly exist as enantiomers. In addition, the compounds may exist as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

10 The terms used in describing the invention are commonly used and known to those skilled in the art. As used herein, the following abbreviations have the indicated meanings:

DCE	1,2-dichloroethane
Et ₂ O	Diethyl ether
15 EtOH	Ethanol
h	Hour
K ₂ CO ₃	Potassium carbonate
MeOH	Methanol
NaBH ₄	Sodium borohydride
20 NaBH(OAc) ₃	Sodium triacetoxyborohydride
min	Minute
2-PrOH	2-Propanol
rt	Room temperature
TiCl ₄	Titanium(IV) tetrachloride

25 General Synthetic Methods

Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below and are illustrated in the schemes that follows. Since the schemes are an illustration, the invention should not be construed as being limited by the chemical

reactions and conditions expressed. The preparation of the various starting materials used in the schemes is well within the skill of persons versed in the art.

As described below in Scheme 1, certain target benzoic acid derivative
5 compounds of the invention were prepared using synthetic methods whereby
an aroyl Compound 1a, having a benzoic acid moiety, was converted to the
aroyl Compound 1b, having a benzamide moiety, by displacement of the
activated acid with the appropriate amine compound. Compound 1b thus
produced was then coupled with 8-methyl-8-azabicyclo[3:2:1]octanone
10 Compound 1c using titanium mediated coupling to produce the intermediate
benzamide Compound 1d.

The particular X, Z, R¹, R², R³, Ar and R⁴ functions desired in the target
benzoic acid derivative may be added in later steps. For example, the
synthetic sequence may be carried out starting with an aroylbenzoic acid
15 compound wherein the Ar variable is a phenyl group. Other variable Ar groups
known to one skilled in the art may also be used in the starting materials to
produce other compounds intended to be within the scope of the present
invention. Similarly, the synthetic sequence may be carried out starting with a
removable R¹ group such as methyl or BOC on the 8-position. At the
20 conclusion of the sequence shown in Scheme 1, the blocking group may be
removed and replaced with the desired R¹ substituent.

After titanium mediated coupling, compounds of the present invention
wherein X is O may also be further treated with a suitable thionating agent
such as P₂S₅ or Lawesson's Reagent to prepare compounds of the invention
25 wherein X is S. Similarly, target compounds wherein Z is O(R²) and R² is
hydrogen may be conveniently produced by conventional hydrolysis of the
N(R²)(R³) group; further, such compounds wherein Z is O(R²) and R² is
hydrogen may be esterified by conventional methods to produce other target
compounds wherein R² is C₁₋₈alkyl.

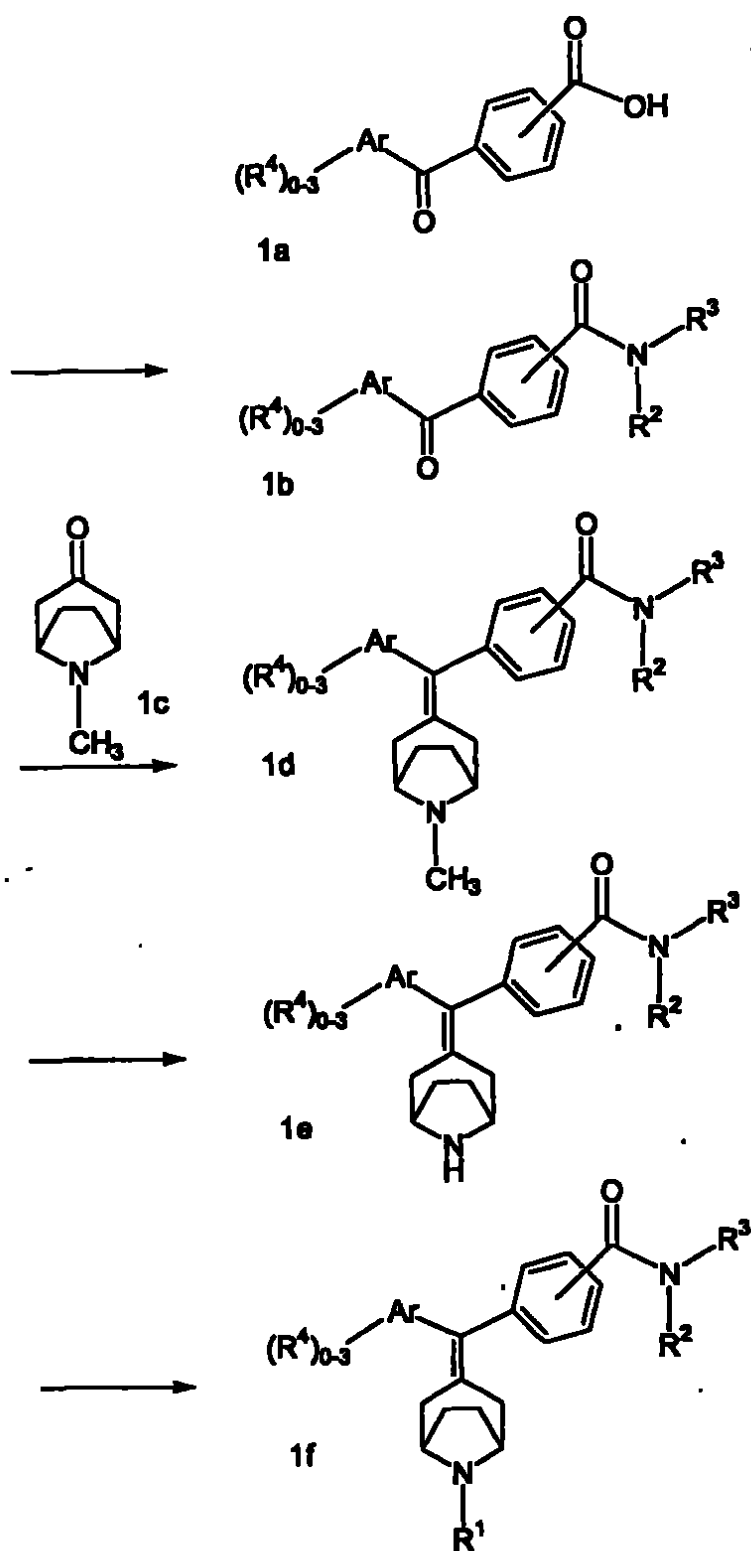
Scheme 1 describes the general scheme for the preparation of certain [(8-azabicyclo[3.2.1]oct-3-ylidene)arylmethyl] benzoic acid derivatives.

Scheme 1

Certain aroylbenzoic acid derivative compounds of the invention were prepared using synthetic methods wherein the aroyl Compound 1a, having a benzoic acid moiety, was activated with thionyl chloride and then converted to the aroyl Compound 1b, having a benzamide moiety, by reaction with the appropriate amine compound. Titanium mediated coupling of Compound 1b with the 8-methyl-8-azabicyclo[3.2.1]octanone Compound 1c produced the Intermediate Compound 1d. Upon treatment of Compound 1d with 2,2,2-trichloroethyl chloroformate followed by reflux with zinc powder in MeOH, the N-demethylated Compound 1e was obtained. Compound 1e was then converted by alkylation with alkyl halides or reductive alkylation with sodium triacetoxyborohydride and carbonyl compounds to produce the derivative [(8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl] benzamide Compound 1f.

Scheme 1 illustrates the scheme described above.

Scheme 1



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5 The compounds of the present invention may be used to treat mild to moderately severe pain in warm-blooded animals, such as, humans by administration of an analgesically effective dose. The dosage range would be from about 1 mg to about 3000 mg, in particular from about 10 mg to about 1000 mg or, more particularly from about 25 mg to about 500 mg of active ingredient in a regimen of about 1 to 4 times per day for an average (70 kg) human; although, it is apparent to one skilled in the art that the therapeutically effective amount for active compounds of the invention will vary as will the types of pain being treated. Examples of pain intended to be within the scope of the present invention include, but are not limited to, centrally mediated pain, peripherally mediated pain, structural or soft tissue injury related pain, progressive disease related pain, neuropathic pain and acute pain such as caused by acute injury, trauma or surgery and chronic pain such as caused by neuropathic conditions, diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, post-stroke pain syndromes or cluster or migraine headaches.

20 In regard to the use of the present compounds as immunosuppressants, antiinflammatory agents, agents for the treatment of neurological and psychiatric conditions, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents and agents for the treatment of respiratory diseases, a therapeutically effective dose can be determined by persons skilled in the art by the use of established animal models. Such a dose would likely fall in the range of from about 1 mg to about 3000 mg of active ingredient administered 1 to 4 times per day for an average (70 kg) human.

30 Pharmaceutical compositions of the invention comprise the formula (I) compounds as defined above, particularly in admixture with a pharmaceutically acceptable carrier. Illustrative of the invention, therefore, is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and any of the compounds described above. Another illustration of the invention is a pharmaceutical composition made by mixing any of the compounds described

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The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

Specific Synthetic Methods

Specific compounds which are representative of this invention may be prepared as per the following examples offered by way of illustration and not by way of limitation. For the sake of clarity, bracketed numbers following compound names indicate the stoichiometric salt associated with the compound, which is further exemplified by the calculated analytical data. Also, examples specifically used to prepare intermediates for the further synthesis of compounds of the invention are designated by "Procedure." As well, instant compounds may also be used in subsequent examples to produce additional compounds of the present invention. No attempt has been made to optimize the yields obtained in any of the reactions. One skilled in the art would know how to increase such yields through routine variations in reaction times, temperatures, solvents and/or reagents.

Example 1

N,N-Diethyl-4-[(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide Hydrochloride [1:1]

A 100 mL dry THF slurry of 18.6 g (284 mmol) zinc powder and 15.6 mL (142 mmol) TiCl_4 was stirred and allowed to reflux for 2 h under Ar. The reaction was allowed to cool then a 20 mL THF solution of 10 g (35.5 mmol) N,N-diethyl-4-benzoylbenzamide and 5 g (35.5 mmol) tropinone was added slowly. Once the addition was complete, the reaction was allowed to reflux for 3 h, cooled, then quenched with 100 mL 10% K_2CO_3 in H_2O . The resulting slurry was partitioned between water and Et_2O . The organic fraction was washed with brine, dried over MgSO_4 , filtered, and concentrated. The remaining yellow

oil was absorbed onto silica gel then purified by flash chromatography eluted with 10% 0.5 M NH_3 in MeOH 90% CH_2Cl_2 to produce the product N,N-Diethyl-4-[(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide (4.27g, 11 mmol, 31%). The HCl salt was precipitated from Et_2O after the addition of etheral HCl; mp 145-147°C. MS m/z (MH^+) 389. ^1H NMR 300 MHz ($\text{DMSO}-d_6$) δ 7.2-7.45 (m, 9H), 3.8-3.9 (m, 2H), 3.15-3.25 (m, 2H), 2.75-2.95 (m, 4H), 2.65 (s, 3H), 2.25-2.4 (m, 2H), 2.15-2.25 (m, 2H), 1.75-1.9 (m, 2H), 0.95-1.2 (m, 6H). Anal calc $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}\cdot\text{HCl}$ (3% H_2O): C, 71.21; H, 7.93; N, 6.39. Found: C, 71.16; H, 7.95; N, 6.27.

10

Procedure A

A solution of 25 g (110 mmol) 4-benzoylbenzoic acid [611-95-0] and 20 mL SOCl_2 was allowed to reflux for 2 h then allowed to cool. The excess SOCl_2 was evaporated off and the resulting clear oil was dissolved in 10 mL CH_2Cl_2 then slowly added to 12 mL (116 mmol) diethylamine in a mixture of 10 mL 3N NaOH and 50 mL CH_2Cl_2 . The mixture was allowed to stir for 30 min then partitioned between H_2O and CH_2Cl_2 . The organic layer was washed with brine, dried over K_2CO_3 , filtered and concentrated. The product precipitated from EtOAc /hexane to give 29.6 g (105 mmol) white crystals, MS m/z (MH^+) 282.

20

Example 2

N,N-Diethyl-4-[(8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide Hydrochloride [1:1]

A 100 mL benzene suspension of 3.1 g (5.6 mmol) N,N-Diethyl-4-[(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide, 3.45 g (25 mmol) K_2CO_3 , and 1.5 mL (10 mmol) 2,2,2-trichloroethyl chloroformate was allowed to reflux for 2 h. The reaction was cooled, filtered, and the solvent evaporated. The residual oil was dissolved in MeOH then stirred at reflux with 2.6 g (40 mmol) zinc powder for 1h. After cooling, the reaction was filtered through celite and partitioned between 3N NaOH and CH_2Cl_2 . The organic layer was washed with brine, dried over K_2CO_3 , filtered, and concentrated (2.1 g, 5.6 mmol). The resulting clear oil was dissolved in Et_2O , filtered, and the product precipitated

after the addition of ethereal HCl; mp 128-132°C. MS m/z (MH^+) 375. ^1H NMR 300 MHz (DMSO- d_6) δ 7.15-7.4 (m, 9H), 3.9-4.0 (m, 2H), 3.15-3.3 (m, 2H), 2.55-2.65 (m, 2H), 2.25-2.35 (m, 4H), 1.9-2.0 (m, 2H), 1.75-1.85 (m, 2H), 1.0-1.2 (m, 6H). Anal calc $C_{22}H_{30}N_2O \cdot HCl$ (3% H_2O): C, 70.89; H, 7.71; N, 6.61.

5 Found: C, 70.52; H, 7.41; N, 6.24.

Example 3

N,N-Diethyl-4-[(8-allyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide Hydrochloride [1:1]

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10 A 20 mL acetonitrile suspension of 0.4 g (1.0 mmol) N,N-Diethyl-4-[(8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide, 0.4 g (3.0 mmol) K_2CO_3 , and 0.09 mL allyl bromide was allowed to stir for 3 h. The reaction was filtered and concentrated. The remaining oil was absorbed onto silica gel then purified by flash chromatography eluted with 5% 0.5 M NH_3 in MeOH 95% CH_2Cl_2 . The pure product (0.2 g, 0.4 mmol) was taken up in Et_2O , filtered, and
15 precipitated after the addition of ethereal HCl; MS m/z (MH^+) 415. ^1H NMR 300 MHz (DMSO- d_6) δ 7.15-7.45 (m, 9H), 5.95-6.10 (m, 1H), 5.4-5.55 (m, 2H), 3.85-3.95 (m, 2H), 3.55-3.65 (t, 2H), 3.35-3.45 (m, 2H), 3.1-3.25 (m, 2H), 2.75-2.85 (t, 2H), 2.2-2.3 (m, 2H), 2.1-2.25 (m, 2H), 1.75-1.9 (m, 2H), 1.0-1.2 (m, 6H).

20

Example 4

N,N-Diethyl-4-[(8-propyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide Hydrochloride [1:1]

A slurry of 0.4 g (1.0 mmol) N,N-Diethyl-4-[(8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide, 0.11 mL (1.5 mmol) propionaldehyde, 0.1 mL
25 (1.7 mmol) HOAc, and 0.5 g (2.3 mmol) $NaBH(OAc)_2$ in 20 mL DCE was allowed to stir for 16 h. The reaction was made strongly basic with 3N NaOH and diluted with CH_2Cl_2 . The organic layer was separated, washed with brine, dried over K_2CO_3 , filtered, and concentrated. The remaining oil was absorbed onto silica gel and purified by flash chromatography eluted with 5% 0.5 M NH_3
30 in MeOH 95% CH_2Cl_2 . The pure product (0.25 g, 0.6 mmol) was taken up in Et_2O , filtered, and precipitated after the addition of ethereal HCl; mp 184-

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184°C. MS m/z (MH^+) 417. ^1H NMR 300 MHz (CD_3OD) δ 7.2-7.45 (m, 9H), 3.95-4.05 (m, 2H), 3.45-3.6 (m, 2H), 3.2-3.3 (m, 2H), 2.95-3.05 (m, 2H), 2.55-2.7 (m, 4H), 2.2-2.3 (m, 2H), 1.95-2.05 (m, 2H), 1.7-1.85 (m, 2H), 1.0-1.35 (br m, 9H). Anal calc $C_{28}H_{38}N_2O \cdot HCl \cdot 0.5H_2O$: C, 72.78; H, 8.29; N, 6.06. Found: C, 73.01; H, 7.94; N, 5.85.

Examples 5-7

Following the procedure of Example 4 and substituting the appropriate carbonyl compound for propionaldehyde the following compounds were prepared:

Ex#	Carbonyl Compound	R'	MS m/z (MH^+)
5	Phenylacetaldehyde	phenethyl	479
6	Piperonal	piperonyl	509
7	Hydrocinnamaldehyde	phenylpropyl	493

Procedure B

N-(3-Fluorophenyl)-N-methyl-3-benzoylbenzamide

Following Procedure A with the substitution of 20 g (88 mmol) 3-benzoylbenzoic acid [579-18-0] and 8.5 mL (88 mmol) 3-fluoroaniline for 4-benzoylbenzoic acid and diethyl amine, the product N-(3-fluorophenyl)-3-benzoylbenzamide was generated (28 g, 88 mmol) as a clear oil. The oil was dissolved in 50 mL dry THF to which a 10 mL THF slurry of 2.1 g (90 mmol) NaH was slowly added. The mixture was allowed to stir for 5 min then 5.6 mL (90 mmol) of MeI was added and continued stirring for 16 h. The reaction was carefully quenched with water and partitioned between water and CH_2Cl_2 . The organic layer was washed with brine, dried over K_2CO_3 , filtered, and concentrated to yield 29.3 g (88 mmol) product. MS m/z (MH^+) 334.

Example 8

N-(3-Fluorophenyl)-N-methyl-3-[(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide Fumarate [1:1]

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Following the procedure of Example 1 with the substitution of N-(3-Fluorophenyl)-N-methyl-3-benzoylbenzamide obtained in Procedure B for N,N-diethyl-4-benzoylbenzamide, the product N-(3-Fluorophenyl)-N-methyl-3-[(8-methyl-8-azabicyclo[3.2.1]oct-3-ylidene)phenylmethyl]benzamide was produced. The fumarate salt was precipitated from 2-PrOH/hexane, mp 122-125°C. MS m/z (MH⁺) 441. ¹H NMR 300 MHz (DMSO-d₆) δ 6.85-7.35 (m, 13H), 3.4 (s, 3H), 3.3-3.5 (m, 1H), 3.15-3.2 (m, 1H), 3.4-3.55 (m, 2H), 2.35 (s, 3H), 2.15-2.25 (m, 1H), 2.05-2.15 (m, 1H), 1.9-2.05 (m, 2H), 1.55-1.65 (m, 1H), 1.35-1.55 (br m, 1H). Anal calc C₂₈H₂₈FN₂O·C₄H₄O₄: C, 71.21; H, 5.98; N, 5.03. Found: C, 71.50; H, 6.20; N, 4.92.

Biological Examples

Screening Assay for Delta- and Mu-Opioid Receptor Binding

Rat Brain δ-Opioid Receptor Binding Assay

The activity of the compounds of the invention as analgesics was demonstrated by the rat brain δ-opioid receptor binding assay as described below.

Procedure

Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, NY) are killed by cervical dislocation, and their brains removed and placed immediately in ice cold Tris HCl buffer (50 mM, pH 7.4). The forebrains are separated from the remainder of the brain by a coronal transection, beginning dorsally at the colliculi and passing ventrally through the midbrain-pontine junction. After dissection, the forebrains are homogenized in Tris buffer in a Teflon®-glass homogenizer. The homogenate is diluted to a concentration of 1 g of forebrain tissue per 100 mL Tris buffer and centrifuged at 39,000 X G for 10 min. The pellet is resuspended in the same volume of Tris buffer with several brief pulses from a Polytron homogenizer. This particulate preparation is used for the δ-opioid binding assays. Following incubation with the δ-selective peptide ligand [³H]DPDPE at 25°C, the tube contents are filtered through Whatman GF/B filter sheets on a Brandel cell harvester. The tubes

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and filters are rinsed three times with 4 mL of 10 mM HEPES (pH 7.4), and the radioactivity associated with the filter circles determined using Formula 989 scintillation fluid (New England Nuclear, Boston, MA) in a scintillation counter.

Analysis

- 5 The data are used to calculate either the % inhibition compared to control binding (when only a single concentration of test compound is evaluated) or a K_i value (when a range of concentrations is tested).

% Inhibition was calculated as:

$$1 - \left[\frac{(\text{test compound dpm-nonspecific dpm})}{(\text{total dpm-nonspecific dpm})} \right] \times 100\%$$

- 10 K_i value is calculated using the LIGAND (Munson, P.J. and Rodbard, D., Anal. Biochem. 107: 220-239, 1980) data analysis program.

Table 2 shows the biological activity in % inhibition for 10nM solutions of the present compounds as measured in the rat brain δ -opioid receptor binding assay.

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Table 2

Compound #	% Inhibition
1	95
2	99
3	98
4	100
5	96
6	99
7	99
8	20

Rat Brain μ -Opioid Receptor Binding Assay

The activity of compounds of the invention as analgesics is demonstrated by the rat brain μ -opioid receptor binding assay as described below.

5 Procedure

Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, NY) are killed by cervical dislocation and their brains removed and placed immediately in ice cold Tris HCl buffer (50 mM, pH 7.4). The forebrains are separated from the remainder of the brain by a coronal transection, beginning dorsally at the
10 colliculi and passing ventrally through the midbrain-pontine junction. After dissection, the forebrains are homogenized in Tris buffer in a Teflon®-glass homogenizer. The homogenate is diluted to a concentration of 1 g of forebrain tissue per 100 mL Tris buffer and centrifuged at 39,000 X G for 10 min. The pellet is resuspended in the same volume of Tris buffer with several brief
15 pulses from a Polytron homogenizer. This particulate preparation is used for the μ -opioid binding assays. Following incubation with the m-selective peptide ligand [^{3} H]DAMGO at 25°C, the tube contents are filtered through Whatman GF/B filter sheets on a Brandel cell harvester. The tubes and filters are rinsed three times with 4 mL of 10 mM HEPES (pH 7.4) and the radioactivity
20 associated with the filter circles determined using Formula 989 scintillation fluid (New England Nuclear, Boston, MA) in a scintillation counter.

Analysis

The data are used to calculate either the % inhibition compared to control binding (when only a single concentration of test compound is evaluated) or a K_i value (when a range of concentrations is tested).

5

% Inhibition is calculated as:

$$1 - \left[\frac{(\text{test compound dpm-nonspecific dpm})}{(\text{total dpm-nonspecific dpm})} \right] \times 100\%$$

K_i value is calculated using the LIGAND (Munson, P.J. and Rodbard, D., Anal. Biochem. 107: 220-239, 1980) data analysis program.

Mouse Acetylcholine Bromide-Induced Abdominal Constriction Assay

- 10 The activity of compounds of the invention as analgesics was further demonstrated by the mouse acetylcholine bromide-induced abdominal constriction assay as described below.

Procedure

- The mouse acetylcholine-induced abdominal constriction assay, as described by Collier et al. in *Brit. J. Pharmacol. Chem. Ther.*, 32: 295-310, 1968 with minor modifications, was used to assess analgesic potency of the compounds of formula (I). The test drugs or appropriate vehicles were administered orally (p.o.) and 30 min later the animal received an intraperitoneal (i.p.) injection of 5.5 mg/kg acetylcholine bromide (Matheson, Coleman and Bell, East Rutherford, NJ). The mice were then placed in groups of three into glass bell jars and observed for a ten min observation period for the occurrence of an abdominal constriction response (defined as a wave of constriction and elongation passing caudally along the abdominal wall, accompanied by a twisting of the trunk and followed by extension of the hind limbs). For compounds of the present invention, the percent inhibition of this

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response to a nociceptive stimulus (equated to % analgesia) was calculated as follows:

% Inhibition of response (i.e., % analgesia) =

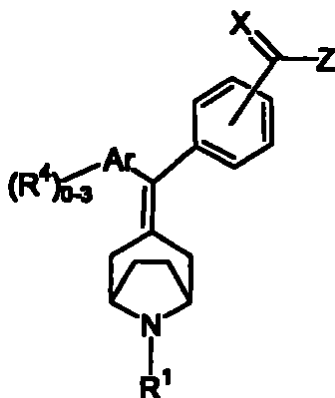
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$$\frac{(\text{No. of control animal responses} - \text{No. of drug-treated animal responses}) \times 100}{\text{No. of control animals responding.}}$$

As a result of the mouse acetylcholine bromide-induced abdominal constriction assay, the compound of Example 1 measured an 87% inhibition response at a dose of 150- μ mole/Kg p.o.

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WHAT IS CLAIMED IS:

1. A compound of the formula (I):



(I)

- 5 wherein:

X is selected from the group consisting of S and O;

Z is selected from the group consisting of $N(R^2)(R^3)$ and $O(R^2)$;

the moiety $-C(=X)-$ is substituted on phenyl at the 3 or 4 position;

R^1 is a substituent selected from the group consisting of hydrogen, C_{1-6} alkyl,

- 10 C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{3-6} cycloalkyl C_{1-3} alkyl, C_{1-6} alkoxy C_{1-3} alkyl, 4- C_{1-4} alkyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl C_{1-4} alkyl, thien-2-yl C_{1-4} alkyl, thien-3-yl C_{1-4} alkyl, furan-2-yl C_{1-4} alkyl, furan-3-yl C_{1-4} alkyl, pyrrol-2-yl C_{1-4} alkyl, pyrrol-3-yl C_{1-4} alkyl, pyridin-2-yl C_{1-4} alkyl, pyridin-3-yl C_{1-4} alkyl, pyridin-4-yl C_{1-4} alkyl, pyrazinyl C_{1-4} alkyl, pyrimidin-2-yl C_{1-4} alkyl, 15 pyrimidin-4-yl C_{1-4} alkyl, pyrimidin-5-yl C_{1-4} alkyl, thiazol-2-yl C_{1-4} alkyl, thiazol-4-yl C_{1-4} alkyl, thiazol-5-yl C_{1-4} alkyl, oxazol-2-yl C_{1-4} alkyl, oxazol-4-yl C_{1-4} alkyl, oxazol-5-yl C_{1-4} alkyl, phenyl C_{1-4} alkyl, phenyl C_{2-4} alkenyl and benzyl; wherein the foregoing thienyl, furanyl, pyrrolyl, thiazolyl and oxazolyl substituents are optionally mono-, di- or tri-substituted with a 20 substituent selected from the group consisting of hydroxy, halogen, C_{1-3} alkyl, C_{2-3} alkenyl, C_{1-3} alkoxy, C_{1-3} acyl, C_{1-6} acyloxy, cyano, amino, C_{1-3} acylamino, C_{1-3} alkylamino, di(C_{1-3} alkyl)amino, C_{1-3} alkylthio, C_{1-3} alkylsulfonyl, $-OCH_2O-$, $-O(CH_2)_2O-$, trifluoromethyl and trifluoromethoxy;

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and wherein the foregoing pyridinyl, pyrazinyl, pyrimidinyl, phenyl and benzyl substituents are optionally mono-, di- or tri-substituted with a substituent selected from the group consisting of hydroxy, halogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₁₋₃alkoxy, C₁₋₃acyl, C₁₋₁₀acyloxy, cyano, amino, C₁₋₃acylamino, C₁₋₃alkylamino, di(C₁₋₃alkyl)amino, C₁₋₃alkylthio, C₁₋₃alkylsulfonyl, -OCH₂O-, -O(CH₂)₂O-, trifluoromethyl and trifluoromethoxy;

R² and R³ are independently selected from the group consisting of hydrogen, C₁₋₄alkyl, C₂₋₄alkenyl, C₃₋₇cycloalkyl, phenyl and benzyl; wherein the foregoing phenyl substituent is optionally mono-, di- or tri-substituted with a substituent selected from the group consisting of halogen, C₁₋₄alkyl, C₂₋₄alkenyl, C₃₋₇cycloalkyl and trifluoromethyl; and wherein the foregoing benzyl substituent is optionally mono-, di- or tri-substituted with a substituent selected from the group consisting of halogen, C₁₋₄alkyl, C₂₋₄alkenyl, C₁₋₄alkoxy, C₃₋₇cycloalkyl, trifluoromethyl, methylenedioxy and ethylenedioxy;

R² and R³ alternatively, when both are present, can together form a single fused moiety with N; wherein R² and R³ are selected from the group consisting of 1,4-butylene, 1,5-pentylene, 1,5-(3-oxapentylene) and 1,5-(3-azapentylene) and wherein the single fused moiety may be optionally substituted with from 1 to 4 substituents selected from the group consisting of C₁₋₄alkyl, C₂₋₄alkenyl and C₃₋₇cycloalkyl;

Ar is selected from the group consisting of phenyl, 1-naphthyl and 2-naphthyl optionally substituted with from 0 to 3 substituents selected from R⁴;

R⁴ is optionally and independently selected from the group consisting of hydroxy, halogen, C₁₋₃alkyl, C₂₋₃alkenyl, C₁₋₃alkoxy, C₁₋₃acyl, C₁₋₁₀acyloxy, cyano, amino, C₁₋₃acylamino, C₁₋₃alkylamino, di(C₁₋₃alkyl)amino, C₁₋₃alkylthio, C₁₋₃alkylsulfonyl, -OCH₂O-, -O(CH₂)₂O-, trifluoromethyl and trifluoromethoxy; and,

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R^4 alternatively, when two R^4 groups are present, can together form a single moiety; wherein the moiety is selected from the group consisting of $-(CH_2)_{2-6}-$ and $-O(CH_2)_{1-3}O-$ attached to adjacent carbon atoms of Ar;

and pharmaceutically acceptable enantiomers, diastereomers and salts thereof.

2. The compound of claim 1 wherein:

X is O;

Z is $N(R^2)(R^3)$;

R^1 is selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *n*-butyl, *n*-hexyl, 3-ethylbutyl, allyl, dimethylallyl, cyclopropylmethyl, cyclohexylmethyl, cyclohexyl, thien-2-ylethyl, piperonyl, 2-furylmethyl, phenethyl, diphenylethyl, phenylpropyl, 3,4-dimethoxyphenethyl, 4-fluorophenethyl and 3,4-methylenedioxybenzyl;

R^2 and R^3 are independently selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, *t*-butyl, methylallyl, 3-fluorophenyl and 4-methylbenzyl;

R^2 and R^3 , alternatively, when both are present, can together form a single fused moiety with N; wherein the moiety is pyrrolidinyl optionally substituted with from 1 to 4 substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl and C_{3-7} cycloalkyl;

Ar is phenyl; and,

R^4 is optionally and independently selected from the group consisting of hydroxy, chloro, bromo, fluoro, methyl, ethyl, methoxy, ethoxy,

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methylamino, N,N-dimethylamino, methylthio, methylsulfonyl, trifluoromethoxy and trifluoromethyl;

and pharmaceutically acceptable enantiomers, diastereomers and salts thereof.

5 3. The compound of claim 1 wherein:

R¹ is selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *n*-butyl, allyl, cyclopropylmethyl, thien-2-ylethyl, phenethyl, phenylpropyl and 3,4-methylenedioxybenzyl;

10 R² and R³ are independently selected from the group consisting of methyl, ethyl, *n*-propyl, methallyl and 3-fluorophenyl; and,

R⁴ is methoxy;

and pharmaceutically acceptable enantiomers, diastereomers and salts thereof.

4. The compound of claim 1 wherein:

15 R¹ is selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, allyl, phenethyl, phenylpropyl and 3,4-methylenedioxybenzyl;

R² and R³ are independently selected from the group consisting of methyl, ethyl and 3-fluorophenyl; and,

R⁴ is nonexistent;

20 and pharmaceutically acceptable enantiomers, diastereomers and salts thereof.

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9. A pharmaceutical composition made by mixing a compound of claim 1 and a pharmaceutically acceptable carrier.
10. A pharmaceutical composition comprising a combination of a compound of claim 1 and a compound effective as a mu-opioid modulator.
- 5 11. The pharmaceutical composition of claim 10 wherein the compound effective as a mu-opioid modulator is selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzyl-morphine, bezitramide, buprenorphine, butorphanol, clonitazene, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, diamorphine, 10 dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol dimethylthiambutene, dioxaphetylbutyrate, dipipanone, eptazocine, ethoheptazine, ethylmethythiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacymorphan, 15 lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, 20 plimnodine, pirtramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, salts thereof, complexes thereof; and mixtures of any of the foregoing.
12. A method for the treatment of a pharmacological condition in a subject in need thereof comprising administering to the subject a therapeutically 25 effective amount of a compound of claim 1.
13. The method of claim 12 wherein the pharmacological condition is pain.

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251

14. The method of claim 13 wherein the therapeutically effective amount of the compound of claim 1 is from about 0.1 mg/day to about 300 mg/day.
15. The method of claim 12 wherein the therapeutically effective amount the compound of claim 1 is effective as an immunosuppressant,
5 antiinflammatory agent, agent for the treatment of neurological and psychiatric conditions, medicament for drug and alcohol abuse, agent for treating gastritis and diarrhea, cardiovascular agent and agent for the treatment of respiratory diseases.
16. The method of claim 12 wherein the method comprises administering to
10 the subject a therapeutically effective amount of the pharmaceutical composition of claim 8.
17. The method of claim 12 wherein the therapeutically effective amount of the pharmaceutical composition of claim 8 is from about 0.1 mg/day to about 300 mg/day.
18. The method of claim 12 wherein the method comprises administering to
15 the subject a therapeutically effective amount of the pharmaceutical composition of claim 9.
19. The method of claim 12 wherein the therapeutically effective amount of the pharmaceutical composition of claim 9 is from about 0.1 mg/day to
20 about 300 mg/day.
20. The method of claim 12 wherein the method comprises administering to the subject a therapeutically effective amount of the pharmaceutical composition of claim 10.

6018578.030300

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ABSTRACT OF THE INVENTION

- [(8-azabicyclo[3.2.1]oct-3-ylidene)arylmethyl] benzoic acid derivatives are delta-opioid receptor modulators. As delta-opioid receptor agonists, such compounds are useful as analgesics. Depending on their antagonist effect,
- 5 such compounds may also be useful immunosuppressants, antiinflammatory agents, agents for the treatment of neurological and psychiatric conditions, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents and agents for the treatment of respiratory diseases.

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ESCOBAR - URIBE ASOCIADOS

A B O G A D O S

Carrera 11A No. 94-76 Of. 305 - P.O. Box 94948, Bogotá, Colombia, S.A.
Tels.: (571) 6162051 - 6162061 - 6161859 - 6161869
Fax: (571) 6161889

2439/P

SUPERINDUSTRIA Y COMERCIO
Radicación: 01017369 00000003 Folios 6
Fecha (CD): 2001-05-20 16:05:18
Trámite: 002 PATENTES D 1 REGISTRADO/ 444 REPUESTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES

E. S. D.

Ref.: Expediente No. 01.017.369
Solicitud de Patente a nombre de
Ortho-McNeil Pharmaceutical, Inc.

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en la Carrera 11 A No. 94-76, of. 305-306, obrando como apoderada de la sociedad Ortho-McNeil Pharmaceutical, Inc, domiciliada en Raritan, New Jersey, Estados Unidos de América, solicitante de la patente de la referencia, en respuesta su oficio No. 1334 notificado por fijación en lista el día 3 de mayo de 2001, me permito manifestar lo siguiente:

1. Anexo los documentos de cesión suscritos por los inventores a favor de mi mandante.

De conformidad con las normas legales vigentes, artículo 1 de la Resolución 210 de 2001, expedida por el Superintendente de Industria y Comercio y artículo 2 de la Convención de la Haya, los documentos en inglés que se pretendan aportar como parte de los trámites de propiedad industrial ante la Superintendencia de Industria y Comercio no requieren traducción. Por otro lado, la legalización consular y/o diplomática de los documentos expedidos en el extranjero no es necesaria. Por lo tanto, los documentos de cesión anexos a este memorial son válidamente presentados en idioma inglés y con la correspondiente Apostilla.

2. Las copias certificadas de las solicitudes extranjeras base de las prioridades reivindicadas en la presente solicitud fueron presentadas ante ese despacho el día 18 de mayo de 2001.

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Espero con esto haber dado cabal cumplimiento a lo solicitado por ese despacho y de conformidad con lo indicado en los artículos 3º., inciso 3, 35 inciso 2 y 59 inciso 2 del CCA, al analizar este memorial, atentamente solicito se traten todas las cuestiones planteadas con motivo del mismo.

Señor Superintendente,



JIMENA ESCOBAR URIBE

C.C.39.779.452 de usaquén

T.P. 68228

Cód. 5376

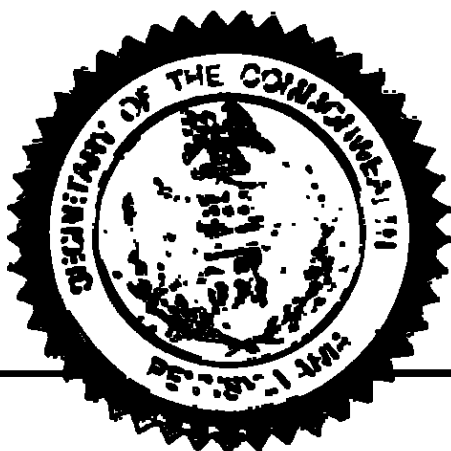
APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: United States of America
2. This public document has been signed by Brenda Myers
3. acting in the capacity of Notary Public, Montgomery County
4. bears the seal/stamp Brenda Myers, Notary Public, Commonwealth of Pennsylvania

Certified

5. at Harrisburg, Pennsylvania
6. The 14th day of June, 2001
7. by Kim Pizzigrilli, Secretary of the Commonwealth of Pennsylvania
8. No. 6114271
9. Seal/Stamp
10. Signature:



Kim Pizzigrilli

Kim Pizzigrilli

ASSIGNMENT

TRASPASO

The undersigned
NAME OF INVENTOR(S)

Abajo firmado

**ROBERT E. BOYD, JOHN R. CARSON,
STEVEN J. COATS, LOU ANNE NEILSON,
PHILIP M. PITIS, WU-NAN-WU**

Domiciled in
ADDRESS OF INVENTOR(S)
**24 WYNMERE DRIVE, HORSHAM,
PENNSYLVANIA 19044
351 BITTENHOUSE BLVD., NORRISTOWN,
PENNSYLVANIA 19403
1839 BRAYTON COURT, QUAKERTOWN,
PENNSYLVANIA 18951
1210 DIAMOND STREET, SELLERSVILLE,
PENNSYLVANIA 18969
188 SUNRISE DRIVE, NORTH WALES,
PENNSYLVANIA 19454
2943 SPRING VALLEY ROAD, LANSDALE,
PENNSYLVANIA 19446**

domiciliado en

Hereby state under oath to be the sole and true
inventor of
**3-(DIARYLMETHYLENE)-8-AZABICYCLO
[3.2.1] OCTANE DERIVATIVES**

decla bajo juramento ser unico y verdadero inventor
de

State as well that he/she/they assign, without
reservations or limitation, in favor of
ORTHO-MCNEIL PHARMACEUTICAL, INC.

declar asimismo que ced y transf sin reserva ni
limitacion, a favor de

a corporation organized and existing under the laws
of **DELAWARE**

la sociedad organizada y existente de conformidad
con las leyes de

domiciliada en

Domiciled in
**U.S. ROUTE #282, P.O. BOX 300
BARITAN, NJ 08869-0602, USA**

todos los derechos inherentes a dicha invencion y
que la citada sociedad queda facultada para solicitar
en su nombre la patente correspondiente en la
Republica de Colombia.

all rights inherent to said invention, and that the
above mentioned corporation hereby is enabled to
apply, in its name, for the corresponding patent in
the Republic of Colombia.

ROBERT E. BOYD

JOHN R. CARSON

STEVEN J. COATS

Lou Anne Neilson
LOU ANNE NEILSON

PHILIP M. PITIS

WU-NAN-WU

CERTIFICADO NOTARIAL (INDIVIDUO)

A los días del mes de
de 19 , comparecí personalmente ante mi,
Notario Publico,

a quien doy fe de conocer y me consta que
la persona descrita y firmante del documento que
precede, declarando ante mi que otorga el
mismo para los fines y propósitos que en el se
expresan.

NOTARIO PUBLICO

NOTARIAL CERTIFICATE (INDIVIDUAL)

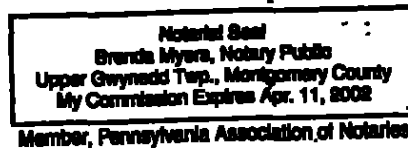
On this 18-May-2001, personally appeared before me, a
Notary Public, *Low Anne Neilson*

to me known and known to me to be the person
described in and who executed the foregoing
document, and he/she duly acknowledged to me
that he/she executed the same for the uses and
purposes therein expressed.

Brenda Myers

NOTARY PUBLIC
STATE OF
COUNTY OF
My commission expires:

NOTARY SEAL



CERTIFICADO NOTARIAL (INDIVIDUO)

A los días del mes de
de 19 , comparecí personalmente ante mi,
Notario Publico,

a quien doy fe de conocer y me consta que
la persona descrita y firmante del documento que
precede, declarando ante mi que otorga el
mismo para los fines y propósitos que en el se
expresan.

NOTARIO PUBLICO

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this , personally appeared before
me, a Notary Public,

to me known and known to me to be the person
described in and who executed the foregoing
document, and he/she duly acknowledged to me
that he/she executed the same for the uses and
purposes therein expressed.

NOTARY PUBLIC
COUNTY OF
STATE OF
My commission expires:

NOTARY SEAL

Commonwealth of Pennsylvania

267
258

Department of State

BRENDA MYERS

OF THE COUNTY OF

MONTGOMERY

GREETINGS:

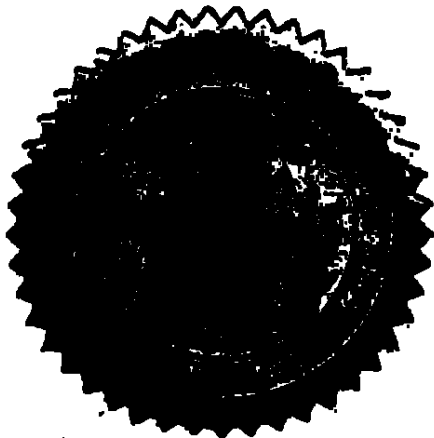
WHEREAS, UNDER THE PROVISIONS OF THE NOTARY PUBLIC LAW, APPROVED THE 21ST DAY OF AUGUST, ANNO DOMINI ONE THOUSAND NINE HUNDRED FIFTY-THREE, THE SECRETARY OF THE COMMONWEALTH IS AUTHORIZED TO APPOINT AND COMMISSION NOTARIES PUBLIC IN AND FOR THE COMMONWEALTH OF PENNSYLVANIA.

THEREFORE, KNOW YE, THAT I HAVE APPOINTED AND DO BY THESE PRESENTS COMMISSION YOU TO BE A

NOTARY PUBLIC FOR THE COMMONWEALTH OF PENNSYLVANIA

TO HAVE AND TO HOLD THE SAID OFFICE, TOGETHER WITH ALL RIGHTS, POWERS AND EMOLUMENTS THEREUNTO PERTAINING, OR BY LAW IN ANYWISE APPERTAINING, FOR THE PERIOD OF FOUR YEARS, IF YOU SHALL SO LONG BEHAVE YOURSELF WELL.

THIS APPOINTMENT TO COMPUTE FROM: APRIL 11, 1998.



0724611

GIVEN UNDER MY HAND AND THE SEAL OF MY OFFICE AT THE CITY OF HARRISBURG, THIS EIGHTEENTH DAY OF MARCH IN THE YEAR OF OUR LORD ONE THOUSAND NINE HUNDRED AND NINETY-EIGHT AND OF THE COMMONWEALTH THE TWO HUNDRED AND TWENTY-SECOND.

Shirley L. Lander
SECRETARY OF THE COMMONWEALTH

PCOK -183 PAGE 0546

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259

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: United States of America
2. This public document has been signed by **Marla I. Shchuka**
3. acting in the capacity of **Notary Public, Montgomery County**
4. bears the seal/stamp **Marla I. Shchuka, Notary Public, Commonwealth of Pennsylvania**

Certified

5. at **Harrisburg, Pennsylvania**
6. The **13th** day of **June, 2001**
7. by **Kim Pizzigrilli, Secretary of the Commonwealth of Pennsylvania**
8. No. **0113989**
9. Seal/Stamp
10. Signature:



Kim Pizzigrilli

Kim Pizzigrilli

Colombia²⁶⁴
260

RT 1196/1375 COL(L)

ASSIGNMENT

TRESPASO

The undersigned
NAME OF INVENTOR(S)

Abajo firmado

ROBERT E. BOYD, JOHN R. CARSON,
STEVEN J. COATS, LOU ANNE NEILSON,
PHILIP M. FITTS, WU-NAN-WU

Domiciled in
ADDRESS OF INVENTOR(S)
84 WYNMERE DRIVE, HORSHAM,
PENNSYLVANIA 19044
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PENNSYLVANIA 18369
108 SUNRISE DRIVE, NORTH WALES,
PENNSYLVANIA 19454
2043 SPRING VALLEY ROAD, LANSDALE,
PENNSYLVANIA 19446

domiciliado en

Hereby state under oath to be the sole and true
inventor of
**3-(DIARYLMETHYLENE)-8-AZABICYCLO
[3.2.1] OCTANE DERIVATIVES**

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Domiciled in
U.S. ROUTE #282, P.O. BOX 300
RARITAN, NJ 08869-0602, USA

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en su nombre la patente correspondiente en la
Republica de Colombia.

all rights inherent to said invention, and that the
above mentioned corporation hereby is enabled to
apply, in its name, for the corresponding patent in
the Republic of Colombia.

Robert E. Boyd
ROBERT E. BOYD

John R. Carson
JOHN R. CARSON

Steven J. Coats
STEVEN J. COATS

Lou Anne Neilson
LOU ANNE NEILSON

Philip M. Fitts
PHILIP M. FITTS

Wu-Nan-Wu
WU-NAN-WU

CERTIFICADO NOTARIAL (INDIVIDUO)

A los días del mes de
de 19 , comparecí personalmente ante mí,
Notario Público,

a quien doy fe de conocer y me consta que
la persona descrita y firmante del documento que
precede, declarando ante mí que otorga el
mismo para los fines y propositos que en el se
expresan.

NOTARIO PUBLICO

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this 5th day of April, 2001
, personally appeared before me, a
Notary Public,
ROBERT E. BOYD, STEVEN S. COATS,
PHILIP M. PITTS, JOHN R. CARSON
AND WU-NAN WU

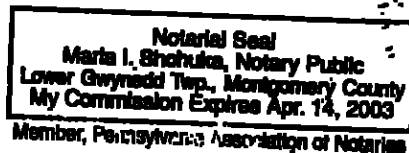
to me known and known to me to be the person
described in and who executed the foregoing
document, and he/she duly acknowledged to me
that he/she executed the same for the uses and
purposes therein expressed.

Maria I. Shchuka

NOTARY PUBLIC
STATE OF Pennsy/Vania
COUNTY OF Montgomery
My commission expires:

April 14, 2003

NOTARY SEAL



CERTIFICADO NOTARIAL (INDIVIDUO)

A los días del mes de
de 19 , comparecí personalmente ante mí,
Notario Público,

a quien doy fe de conocer y me consta que
la persona descrita y firmante del documento que
precede, declarando ante mí que otorga el
mismo para los fines y propositos que en el se
expresan.

NOTARIO PUBLICO

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this , personally appeared before
me, a Notary Public,

to me known and known to me to be the person
described in and who executed the foregoing
document, and he/she duly acknowledged to me
that he/she executed the same for the uses and
purposes therein expressed.

NOTARY PUBLIC
COUNTY OF
STATE OF
My commission expires:

NOTARY SEAL



261

Industria y Comercio
SUPERINTENDENCIA

2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio-265

Radicación no 01-17369

Concepto Técnico no 1891

Clasificación Internacional de Patentes: A 61 K 31/439

Practicado el examen de acuerdo a lo establecido en el Art. 38 de la Decisión 486 se determinó que esta solicitud de Patente de Invención:

- SI [☒] NO [☐] Contiene un resumen de la invención (Art.26-e).
- SI [☒] NO [☐] Contiene el título o nombre de la invención (Art.27-d).
- SI [☒] NO [☐] Contiene la descripción de la invención (Art.26-b).
- SI [☒] NO [☐] NO ES APLICABLE [☐] Contiene los dibujos necesarios para comprender la invención (Art.26-d)
- SI [☒] NO [☐] Contiene una o más reivindicaciones. (Art.26-c).
- SI [☐] NO [☐] NO ES APLICABLE [☒] Han sido desarrollados los productos y/o procedimientos a partir de recursos genéticos o de sus productos derivados de los que cualquiera de los Países Miembros es país de origen. (Art. 26- h).
- SI [☐] NO [☐] NO ES APLICABLE [☒] Los productos y/o procedimientos han sido obtenidos o desarrollados a partir de los conocimientos tradicionales de las comunidades indígenas, afroamericanas, o locales de los países miembros, de acuerdo a lo establecido en la Decisión 391 y sus modificaciones y reglamentaciones vigentes.(Art.26-I).
- SI [☐] NO [☒] La invención se refiere a un producto relativo a un material biológico. (Art.26-J).
- SI [☒] NO [☐] La prioridad coincide con la materia reivindicada.
- SI [☒] NO [☐] **CUMPLE LOS REQUISITOS TÉCNICOS**

OBSERVACIONES Y OTROS: SI [☐] NO [☒] ver hoja(s) anexa(s)

EXAMINADOR TÉCNICO
202049

Bogotá D. C., 26 de Diciembre de 2002

Carrera 13 No. 27-00 Pto 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 31 26 e-mail: info@dic.gov.co
Santa Fe de Bogotá D.C. - Colombia



262

Industria y Comercio
SUPERINTENDENCIA

Folio: 266

2020
Bogotá DC

Doctora
JIMENA ESCOBAR URIBE
Apoderado

REFERENCIA:	Radicación No.	01-17389
	Trámite	002
	Evento	001
	Actuación	416
	Oficio No.	2377
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la misma Decisión.

Cúmplase
Dado en Bogotá DC, a los 23 ENE. 2003


CLARA DE JAIMES
Jefe (E) de la División de Nuevas Creaciones

202049



Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 261 31 25 e-mail: info@ic.gov.co
Santa Fe de Bogotá D.C. - Colombia

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 01-17369

**EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION
FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 528, DE
FECHA 30 DE MAYO DE 2003, EL TERMINO HABIL SEÑALADO POR LA LEY
EXPIRA EL 20 DE AGOSTO DE 2003.**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud calga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO ☒ _____

264

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: 1-17389

EDICTO No. 12881

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia proferió Resolución No. 21010 de 15-AGO-2006. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Declarar abandonada la solicitud de privilegio de patente de invención contenida en el expediente de la referencia.

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución a la doctora Jimena Escobar Uribe, o a quien haga sus veces, en su calidad de apoderada de Ortho - McNeil Pharmaceutical, Inc. entregándole copia de la misma; advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CÚPLASE
Dada en Bogotá, D.C., a los

18 AGO. 2006

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JIMENA ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc 30-AGO-2006
Secretaría General Ad-Hoc
EDICTO No. 12881

Este edicto se desfiya hoy 12-SEP-2006 a las cinco (5:00 p.m.)