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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Act. 523 RESPUESTA Folios: 47

SUPERINTENDENCIA DE INDUSTRIA
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. 10.144.468 ✓

Solicitud de patente a nombre de **REATA PHARMACEUTICALS INC.**

Yo, DILIA MARIA RODRIGUEZ D'ALEMAN, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 86-53, piso 6, obrando como apoderada de la sociedad **REATA PHARMACEUTICALS INC.**, solicitante de la patente de la referencia, en respuesta al oficio No. 22085 notificado por fijación en lista el 4 de diciembre de 2013, y considerando el memorial radicado el 25 de febrero de 2013 en donde se solicitó una prórroga de 30 días para dar respuesta a dicho oficio, me permito manifestar:

1. Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto con este memorial un nuevo capítulo reivindicatorio, el cual consta de 16 reivindicaciones y reemplaza completamente el capítulo presentado anteriormente.

En cuanto a estas modificaciones, me permito decir que las mismas no amplían de ninguna manera la materia objeto de la presente solicitud y se realizaron con el ánimo de superar las objeciones planteadas por el examinador en su concepto técnico.

2. Claridad de la Solicitud

Inicialmente, deseamos poner de presente las modificaciones realizadas, las cuales son las siguientes:

Inicialmente, se aclara que el título de la solicitud se modifica a "**DERIVADOS DE ÁCIDO OLEANÓLICO HOMOLOGADO C-17 CON UN GRUPO CIANO-ENONE EN EL ANILLO-A**"

- Se cancelaron las reivindicaciones 1-14. La antigua reivindicación 15 (ahora reivindicación 1) es ahora la reivindicación independiente más amplia. Como se describe en mayor detalle a continuación, estas modificaciones limitantes abordan las objeciones del examinador que en cuanto a la falta de concisión.

- También la nueva reivindicación 1 no tiene más un grupo R₂. El grupo en esta posición está limitado a ciano, el cual además debe dar por superadas las objeciones del examinador relacionadas con amplitud.
- De modo similar, ninguna de las reivindicaciones modificadas tiene un X₁. Los grupos se han limitado a =O. De esta manera se solicita se tengan superadas las objeciones del examinador relacionadas con amplitud así como claridad.
- La cancelación de las reivindicaciones 1-14 también elimina todas las ocurrencias de la frase "*sustituyente convertible in vivo en hidrógeno*".
- La frase "o una versión sustituida de cualquiera de estos grupos" se ha eliminado de todas las reivindicaciones. Esta se ha reemplazado con ejemplos de grupos sustituidos específicos como se definen en la sección de definiciones químicas (ver páginas 44-57) y con ejemplos por parte de los compuestos divulgados.
- Amablemente se aclara que aunque el solicitante está en desacuerdo con la objeción por falta de claridad, los siguientes grupos se eliminaron para la variable R_a en la reivindicación 15 (nueva reivindicación 1). Estas eliminaciones deben, sin embargo, abordar cualquier objeción que pueda tener el examinador con relación a la amplitud de la reivindicación. Los grupos eliminados son: aralquil(C₁₂), heteroaralquil(C₁₂), heteroariloxi(C₁₂), alquililoxi(C₁₂), alquililamino(C₁₂), heteroarilamino(C₁₂), alqueniltio(C₁₂), alquililtio(C₁₂), aralquiltio(C₁₂), heteroariltio(C₁₂), heteroaralquiltio(C₁₂), aciltio(C₁₂), tioacil(C₁₂), alquenilsulfonil(C₁₂), alquililsulfonil(C₁₂), aralquilsulfonil(C₁₂), heteroarilsulfonil(C₁₂), heteroaralquilsulfonil(C₁₂), alquenilsulfonil(C₁₂), alquililsulfonil(C₁₂), aralquilsulfonil(C₁₂), heteroarilsulfonil(C₁₂), heteroaralquilsulfonil(C₁₂), alquilfosfonil(C₁₂), alquilfosfato(C₁₂), alquilamonio(C₁₂), alquilsulfonio(C₁₂), y alquilsilil(C₁₂). Estas eliminaciones sin embargo deben
- Los siguientes nuevos grupos se adicionaron para la variable R_a en la reivindicación 15 (nueva reivindicación 1): -CO₂H, -CO₂-alquil(C_{≤11}), -C(O)NH₂, -C(O)NH-alquil(C_{≤11}), -C(O)-dialquilamino(C_{≤11}), y -NHCO₂-alquil(C_{≤11}). Los grupos -CO₂H, -CO₂-alquil(C_{≤11}), -C(O)NH₂, -C(O)NH-alquil(C_{≤11}), y -C(O)-dialquilamino(C_{≤11}). Estos grupos están soportados por las definiciones para "acil sustituido" y "amido sustituido". Ver páginas 52, 53 y las reivindicaciones originales PCT.
- Se hicieron los cambios correspondientes a las reivindicaciones que dependen de la reivindicación 15 (nueva reivindicación 1).

Por consiguiente, se considera que con las modificaciones efectuadas siguiendo las observaciones realizadas por el Señor Examinador se debe tener por superada las objeciones formuladas con base al no cumplimiento de las disposiciones de los artículos 28 y 30.

3. Requisitos de Patentabilidad

El examinador ha rechazado las reivindicaciones, porque considera que se hubieran derivado de manera obvia en vista de los documentos D1 y D2, por lo que respetuosamente nos permitimos decir que no nos encontramos de acuerdo con dichas premisas teniendo en cuenta las siguientes razones:

En primer lugar con respecto a la objeción del Examinador, se pone de presente que el examinador considera que las reivindicaciones actuales carecen de nivel inventivo en vista de los documentos del arte previo D1 y D2, los cuales son considerados como los más cercanos en el estado del arte. En particular, el examinador observa que en contraste con algunos de los compuestos reivindicados, los compuestos divulgados en D1 carecen de un puente metileno en C-17. El examinador luego observa una estructura triterpenoide en D1 que tiene grupo $-\text{CH}_2\text{OAc}$ unido a C-17. A partir de esto el examinador concluye que habría sido obvio para un experto en la materia hacer referencia a las enseñanzas de D2 con el fin de modificar los compuestos de D1 con el fin de obtener los compuestos reivindicados con la expectativa que los compuestos reivindicados "tendrían la misma actividad deseada". El solicitante no está de acuerdo con esta conclusión por varias razones:

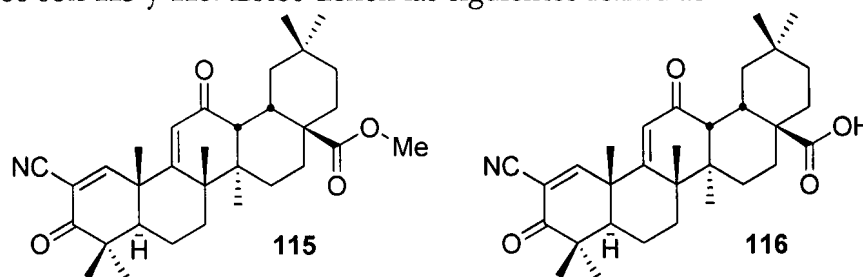
1. Un experto en la materia no tendría expectativa razonable que la inserción de un grupo metileno en la posición C-17 resultaría en un compuesto que tiene "la misma actividad deseada". E introduciendo un grupo metileno en C-17 se esperaría resultar en un compuesto con un ester polar menor en C-17. Así, la principal referencia mencionada por el examinador enseña lo contrario a la modificación.
2. Las reivindicaciones modificadas ahora difieren más de forma significativa de todos los compuestos divulgados en el documento D2. Por lo tanto es menos probable que un experto en la materia llegue a las enseñanzas de D2 cuando esté buscando para hacer candidatos prometedores alternos.
3. D2 tampoco sugiere que un compuesto con un grupo $-\text{CH}_2\text{OAc}$ en C-17 es preferible a cualquier otro grupo en esta posición. De hecho, no se presentan resultados relevantes de actividad biológica en D2. Todos los compuestos divulgados en D2 fueron de hecho reportados para ser inactivos para la actividad biológica para la que se probaron. Así, un experto en la materia no

llegaría a D2 para tener una guía cuando se pretende hacer derivados prometedores.

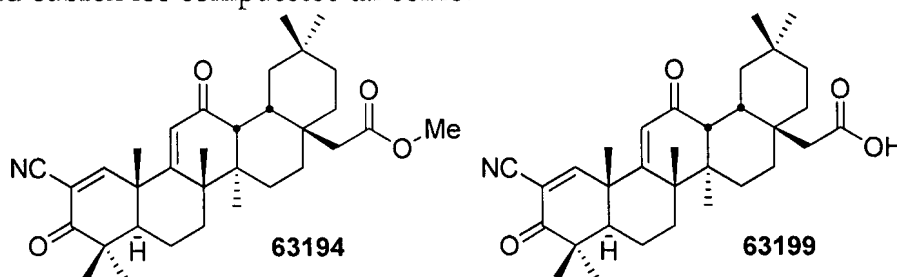
4. El examinador no está apreciando el significado del cambio en la posición C-17 ni los desafíos sintéticos que se necesitan superar para hacer la serie de compuestos reivindicados.

Como resultado de por lo menos una de las razones anteriores, un experto en la materia no haría referencia a las enseñanzas de D2 con el fin de modificar los compuestos de D1 con el fin de obtener los compuestos reivindicados con la expectativa que los compuestos reivindicados “tendrían la misma actividad deseada”. Cada uno de estos puntos se discute en mayor detalle a continuación:

D1 (*Estudios Botánicos*, 2006, 47, 339-368) divulga derivados de ácido oleanólico y sus usos como medicamentos. El solicitante establece que todos los compuestos divulgados en esta referencia que son estructuralmente más similares a los compuestos reivindicados son **115** y **116**. Estos tienen las siguientes fórmulas:



Ver la tabla 6 de D1, página 348. En contraste, las reivindicaciones de la presente solicitud cubren los compuestos tal como:



Como el examinador correctamente establece, la diferencia entre estos compuestos reivindicados y los compuestos anteriores del estado del arte es de hecho un grupo de puente metileno entre C-17 y el grupo carbonilo. Sin embargo, el examinador está completamente equivocado en concluir que un experto en la materia trataría de hacer esta modificación con base en las enseñanzas de D2 o que habría una expectativa razonable que los compuestos resultantes “tendrían la misma actividad deseada”. Ciertamente, ninguna de las referencias D1 ni D2 enseña o sugiere hacer dicha

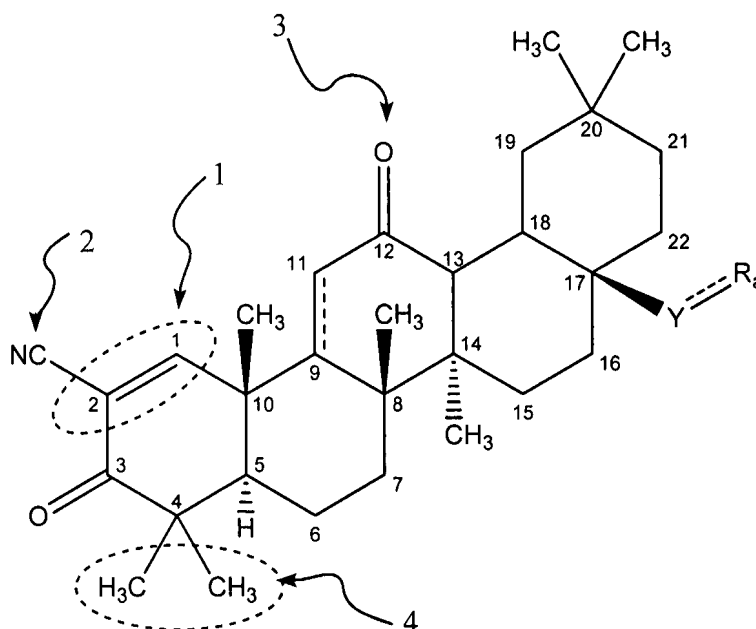
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modificación. En efecto, la mayoría de los compuestos activos presentados en la Tabla 6 son de hecho los compuestos **115** y **116**, y estos compuestos tienen un grupo carbonilo unido a C-17. Así, por qué un experto en la materia descartaría esta característica? Por el contrario, esta característica estructural común puede ser interpretada razonablemente por un experto en la materia para ser por lo menos en parte responsable de las propiedades ventajosas de estos compuestos. De hecho, D1 enseña que "entre menor polar el ester, menor es su potencia". Ver página 347 (parte inferior de la columna de la izquierda hasta la parte superior de la columna de la derecha). Dado que los grupos metileno son no polares, insertar un grupo metileno en C17 se esperaría que resulte en un compuesto con un ester menos polar en C-17, lo cual a su vez se espera que resulte en un compuesto menos potente. Así, D1 de hecho se aleja de hacer esta modificación.

D2 (*Fitoquímica*, 1993, 43, 1111-1116) divulga extractos triterpenoides de *Anamirta cocculus*, así como varios derivados simples de estos extractos. El solicitante establece que las reivindicaciones modificadas difieren significativamente de todos los compuestos divulgados en D2. En particular, ninguno de los triterpenoides divulgados en D2 tiene:

1. Una unión doble entre C1 y C2,
2. Un grupo ciano en C2,
3. Un grupo oxo en C3, o
4. Dos grupos metilo en C4.

Cada una de estas diferencias se resalta en la fórmula reivindicada en la nueva reivindicación 1 (antigua reivindicación 15):



Dadas estas diferencias, un experto en la materia no consultaría esta referencia para guiarse en cómo hacer alternativas prometedoras a los compuestos de D1, especialmente cuando uno también considera que la única actividad biológica reportada por D2 es que los “Compuestos 1-5 son inactivos como moluscicidas y fungicidas”. Ver página 1113, parte superior de la columna derecha. Los compuestos inactivos ciertamente no suministran mucho en vía de motivación. Además, D2 no sugiere que un compuesto con un grupo $-\text{CH}_2\text{OAc}$ en C-17 es preferible a cualquier otro grupo en esta posición. Así, no hay ninguna sugerencia en D2 que un compuesto que tiene un grupo metileno unido a C-17 sea prometedor o “tiene la misma actividad deseada” como cualquiera de los compuestos **115** y **116** de D1.

De forma importante, los documentos del arte previo citados por el examinador claramente muestran que uno no puede simplemente hacer cualquier cambio en C-17 de estos compuestos y esperar retener la actividad. Considere por ejemplo la Tabla 7 de D1. Las actividades de estos compuestos mostradas en esta tabla varían por varios órdenes de magnitud, aún cuando uno sólo se enfoca en estos compuestos con diferentes tipos de grupos carbonilo en C-17. Una expectativa que la inserción de un grupo metileno entre C-17 y el carbonilo resultaría en compuestos que “tendrían la misma actividad deseada” es por lo tanto no razonable. Esto se confirma por un tratado estándar en el campo, *Química Medicinal de Burger y Descubrimiento de Droga*, 6^a ed.:

El cambio en tamaño o derivación de una cadena alquilo en una molécula bioactiva *puede tener profundos (y algunas veces impredecibles)* efectos en propiedades físicas y farmacológicas. La alteración del tamaño y/o forma de un sustituyente alquilo puede afectar la preferencia de conformación de una

molécula flexible y puede alterar las relaciones espaciales de los componentes del farmacóforo, el cual se puede reflejar en la capacidad de la molécula de lograr complementariamente con su receptor o con la superficie catalítica de una enzima de metabolización. El grupo alquilo como tal puede representar un sitio de unión con el receptor (a través de interacciones hidrofóbicas), y la alteración de la cadena puede alterar su capacidad de unión.

Capítulo 16, en la página 699 (énfasis adicionado) (Anexo 1). En vista de estos “profundos (y algunas veces impredecibles) efectos” esperados cuando se cambia el tamaño o derivación de un grupo alquilo, las objeciones de la Acción Oficial que un experto en la materia habría tenido una expectativa de éxito razonable cuando hace un mayor cambio, especialmente al insertar un grupo metileno entre un sistema de anillo y un grupo carbonilo está claramente en desacuerdo con las enseñanzas en este campo. De hecho, en vista de las enormes diferencias en la actividad de los compuestos de la Tabla 7 de D1, es el mejor motivo para suponer que el efecto de un grupo metileno unido directamente a C-17 simplemente podría no ser predicho.

Finalmente, el solicitante establece que ninguno de D1 o D2 enseña las metodologías sintéticas requeridas para insertar un grupo $-CH_2-$ entre el carbono C-17 y por ejemplo los grupos carbonilo de los compuestos 115 y 116. Y esta caracterización representa una simplificación que no hace justicia al significado del cambio, dado que uno no puede simplemente reorganizar los átomos y moléculas sin tener en cuenta las limitaciones sintéticas y sin tener en cuenta la imprevisibilidad reconocida de este campo del arte. En este sentido, el solicitante manifiesta que ninguno de D1 o D2 suministra o sugiere una ruta sintética a cualquiera de los compuestos reivindicados, incluye aquellos que tienen el grupo $-CH_2-$ en el átomo de carbono C-17. En contraste, los métodos de múltiples pasos que superan exitosamente los desafíos sintéticos y resultan en los compuestos reivindicados se describen en detalle en las páginas 108-158 de la descripción. En resumen, no se ha identificado ninguna razón que llevaría a un químico a seleccionar y luego hacer las modificaciones particulares requeridas, por ejemplo, la inserción de un grupo $-CH_2-$ entre el carbono C-17 y un grupo cetona, con el fin de llegar a cualquiera de los compuestos de las nuevas reivindicaciones.

En vista de lo anterior, los compuestos **definidos en las nuevas reivindicaciones no son obvios y por lo tanto son inventivos sobre el estado del arte, incluyendo D1 y D2.** Por lo tanto, se le solicita respetuosamente al examinador retire la objeción de nivel inventivo.

Por consiguiente, teniendo en cuenta los argumentos presentados, se concluye que las enseñanzas de la anterioridad citada por su Despacho no lleva a un técnico versado en la materia a obtener la presente invención ya que no revelan o enseñan las

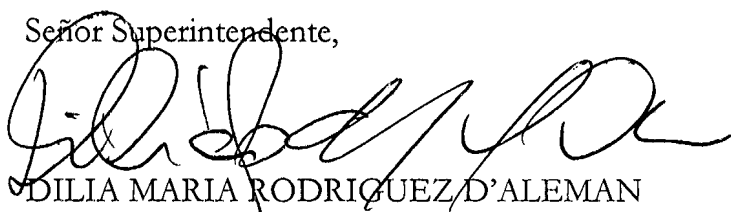
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características técnicas esenciales relacionadas con la misma, de manera tal acá es reivindicada. Lo anterior si se tiene en cuenta que para el estudio de nivel inventivo el Examinador no puede adoptar la posición de un inventor y que además no puede partir de la solución dada sino simplemente de lo que expresamente revelen el o los documentos más cercanos del estado del arte.

Habiendo atendido cabalmente las objeciones presentadas por ese despacho, atentamente solicitamos se conceda el privilegio de patente de invención a la solicitud en estudio o si el examinador considera que subsisten razones para objetar la presente invención rogamos expedir otro examen de fondo con los debidos motivos y razones que sustenten su objeción con el fin de que nuestro mandante tenga la posibilidad de exponer sus argumentos con base en la interpretación de los artículos 45 de la Decisión 486 -el cual otorga la facultad al examinador para emitir los exámenes de fondo-, 35 y 59 del Código Contencioso Administrativo que señala que: *"habiéndose dado oportunidad a los interesados para expresar sus opiniones, y con base en las pruebas e informes disponibles, se tomará la decisión que será motivada al menos en forma sumaria si afecta a particulares"* y *"(.) deberá proferirse la decisión definitiva. Esta se motivará en sus aspectos de hecho y de derecho, y en los de conveniencia si es el caso"*, respectivamente (El subrayado es nuestro).

En consecuencia, solicitamos a ese despacho pronunciarse en relación con todos los argumentos presentados en este memorial dando estricta aplicación al principio del debido proceso consagrado en el artículo 29 de la Constitución Nacional.

Señor Superintendente,



DILIA MARIA RODRIGUEZ D'ALEMAN

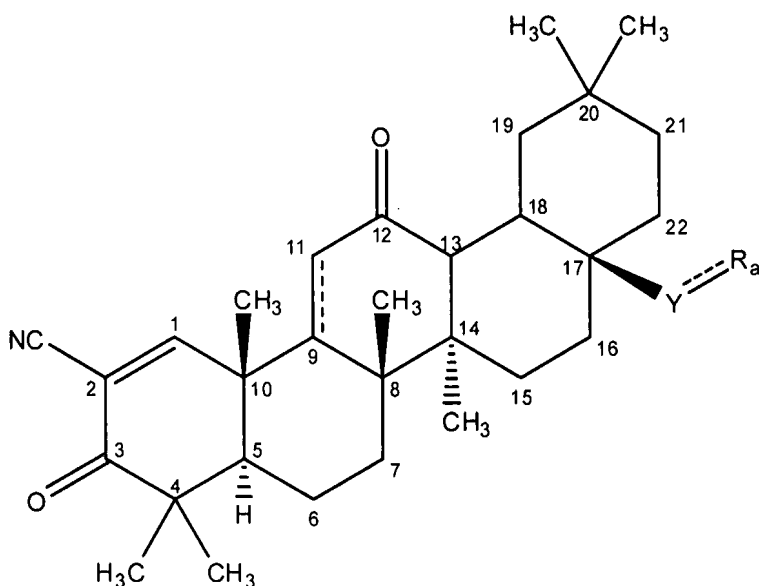
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notificaciones@clarkemodet.com.co

REIVINDICACIONES

1. Un compuesto de fórmula:



en donde:

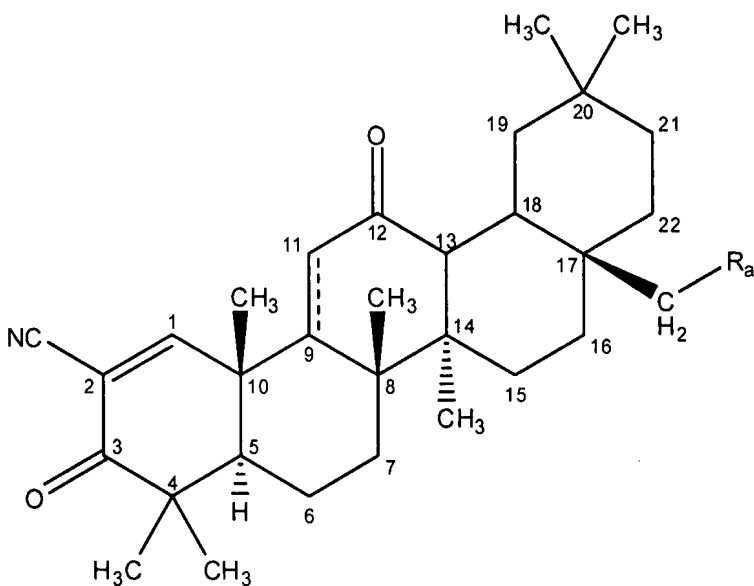
Y es alcanodiil_(C≤8), alquenodiil_(C≤8),
alquinodiil_(C≤8), o una versión de estos grupos
en donde un hidrógeno cualquiera o más se
reemplaza con un halo, hidroxilo o ciano;

R_a es:

hidrógeno, hidróxilo, halo, amino, nitro,
ciano, azido, fosfato, 1,3-
dioxoisindolin-2-il, mercapto o sililo; o
alquil_(C≤12), alquenil_(C≤12), alquinil_(C≤12),
aril_(C≤12), heteroaril_(C≤12), acil_(C≤12),
alcoxi_(C≤12), alqueniloxi_(C≤12), ariloxi_(C≤12),
aralcoxi_(C≤12), aciloxi_(C≤12), alquil-
amino_(C≤12), dialquilamino_(C≤12),
alquenilamino_(C≤12), arilamino_(C≤12),

- aralquilamino_(C≤12),
 heteroaralquilamino_(C≤12),
 alquilsulfonilamino_(C≤12), amido_(C≤12),
 alquiltio_(C≤12), ariltio_(C≤12),
 5 alquilsulfonil_(C≤12), arilsulfonil_(C≤12),
 alquilsulfinil_(C≤12), arilsulfinil_(C≤12),
 alquilfosfato_(C≤12), dialquilfosfato_(C≤12),
 -CO₂H, -CO₂-alquil_(C≤11), -C(O)NH₂,
 -C(O)NH-alquil_(C≤11),
 10 -C(O)-dialquilamino_(C≤11), y
 -NHCO₂-alquil_(C≤11), o una versión de estos
 grupos en donde un hidrógeno cualquiera o
 más se reemplaza con un halo, hidróxi o
 ciano; o
 15 Y y R_a forman un anillo de tres a siete miembros,
 tal que Y y R_a además se conectan el uno al
 otro a través de uno o más de -O- y
 alcanodiil_(C1-5), en donde además Y es -CH- y R_a
 es -CH₂-;
 20 O una sal farmacéuticamente aceptable o tautómero de
 éstos.

2. El compuesto de la reivindicación 1, además definido como:



en donde R_a es:

5 hidrógeno , hidróxi , halo, amino, fosfato, 1,3-
 dioxoisindolin-2-il, o ciano; o

$$\text{alquil}_{(c \leq 12)}, \quad \text{alguenil}_{(c \leq 12)}, \quad \text{alquinil}_{(c \leq 12)},$$

aryl_(c≤12), heteroaryl_(c≤12), acyl_(c≤12),

alcoxi_(C≤12), alqueniloxi_(C≤12), ariloxi_(C≤12),

10 aralcoxi_(C≤12), aciloxi_(C≤12),

alquilamino_(c≤12), dialquilamino_(c≤12),

alquenilamino_(c≤12), arilamino_(c≤12),

aralquilamino_(c≤12),

heteroaralquilamino_(c≤12), amido_(c≤12),

15 arilsulfonil_(C≤12), arilsulfinil_(C≤12),

alquilfosfato_(C≤12), dialquilfosfato_(C≤12),

$$-\text{CO}_2\text{H}, \quad -\text{CO}_2\text{-alquil}_{(c \leq 11)}, \quad -\text{C}(\text{O})\text{NH}_2,$$
$$-C(O)NH-\text{alquil}_{(c \leq 11)},$$

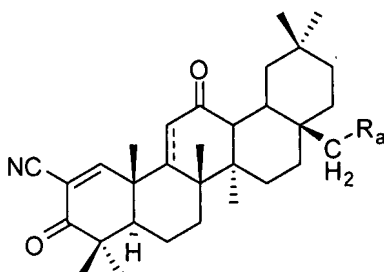
-C(=O)-dialkylamino_(C≤11),

 y

-NHCO₂-alquil_(C≤11), o una versión de estos grupos en donde un hidrógeno cualquiera o más se reemplaza con un halo, hidroxilo o ciano; o

5 una sal farmacéuticamente aceptable o tautómero de éstos.

3. El compuesto de la reivindicación 16, además definido como:



en donde R_a es hidróxi, amino, acil_(C≤8), -CO₂H, -CO₂-alquil_(C≤11), -C(O)NH₂, -C(O)NH-alquil_(C≤11), -C(O)-dialquilamino_(C≤11), -NHCO₂-alquil_(C≤11), amido_(C≤8), o una versión de estos grupos en donde un hidrógeno cualquiera o más se reemplaza con un flúor;

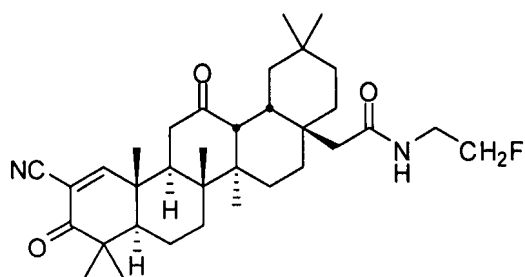
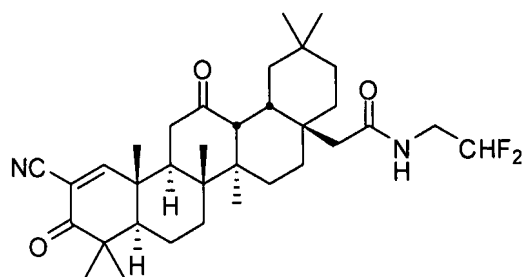
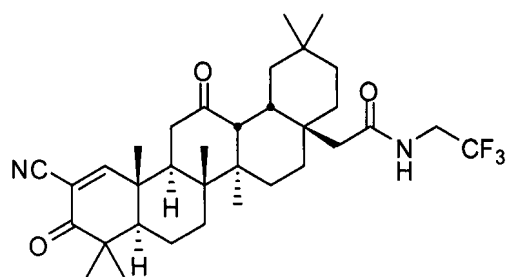
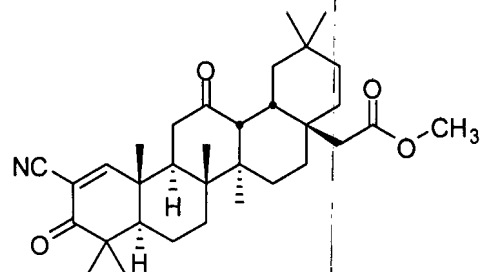
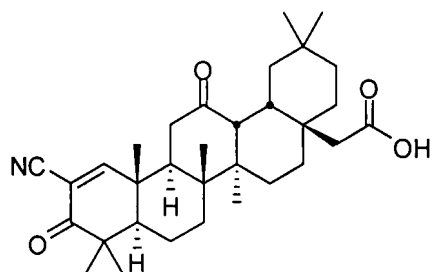
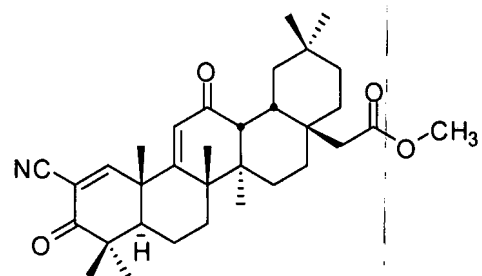
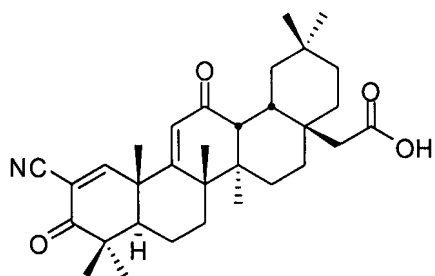
o una sal farmacéuticamente aceptable o tautómero de éstos.

20 4. El compuesto de la reivindicación 1, en donde Y es
-C(OH)HCH₂-.

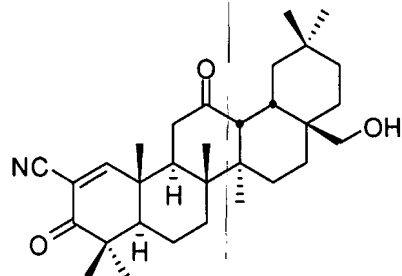
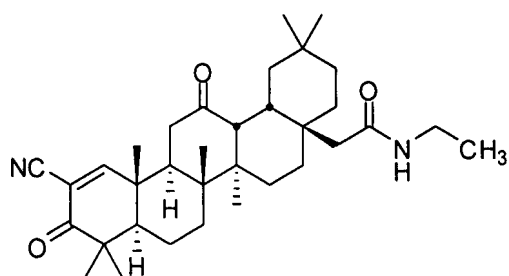
5. El compuesto de la reivindicación 1, en donde R_a es -OH.

6. El compuesto de la reivindicación 1, en donde R_a es $-\text{Cl}$.
7. El compuesto de la reivindicación 1, en donde R_a es $-\text{Br}$.
- 5 8. El compuesto de la reivindicación 1, en donde R_a es $-\text{H}$.
9. El compuesto de la reivindicación 1, en donde R_a es
 $\text{acil}_{(\text{C}1-3)}$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{-alquil}_{(\text{C}\leq 11)}$, $-\text{C}(\text{O})\text{NH}_2$,
 $-\text{C}(\text{O})\text{NH-alquil}_{(\text{C}\leq 11)}$, $-\text{C}(\text{O})\text{-dialquilamino}_{(\text{C}\leq 11)}$,
10 $-\text{NHCO}_2\text{-alquil}_{(\text{C}\leq 11)}$, o una versión de estos grupos en
donde un hidrógeno cualquiera o más se reemplaza con un
flúor.
10. El compuesto de la reivindicación 1, en donde R_a es
15 $\text{aciloxi}_{(\text{C}1-8)}$ o una versión de este grupo en donde un
hidrógeno cualquiera o más se reemplaza con un flúor.
11. El compuesto de la reivindicación 1, en donde R_a es
 $\text{alquilamino}_{(\text{C}\leq 12)}$, $\text{dialquilamino}_{(\text{C}\leq 12)}$, $\text{alquenilamino}_{(\text{C}\leq 12)}$,
20 $\text{arilamino}_{(\text{C}\leq 12)}$, $\text{aralquilamino}_{(\text{C}\leq 12)}$,
 $\text{heteroaralquilamino}_{(\text{C}\leq 12)}$, $\text{alquilsulfonilamino}_{(\text{C}\leq 12)}$,
 $\text{amido}_{(\text{C}\leq 12)}$, o $-\text{NHCO}_2\text{-alquil}_{(\text{C}\leq 11)}$, o una versión de estos
grupos en donde un hidrógeno cualquiera o más se
reemplaza con un flúor o grupo ciano.
25
12. El compuesto de la reivindicación 1 además definido
como:

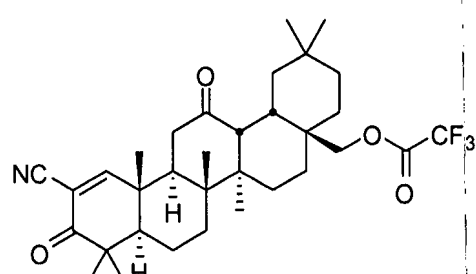
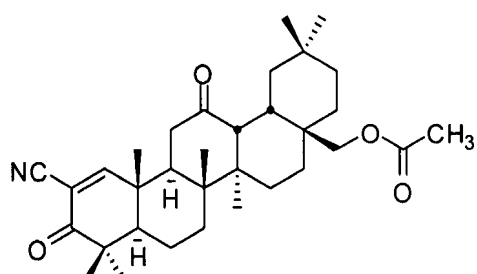
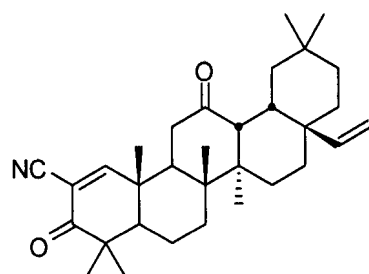
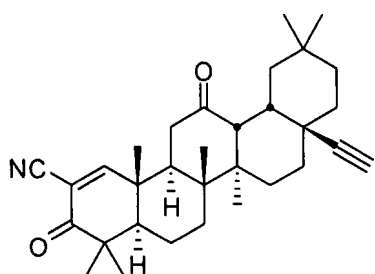
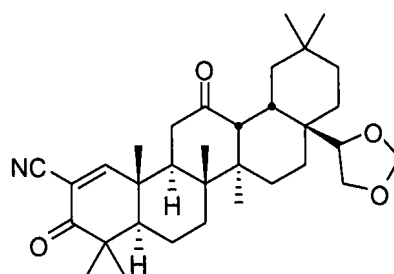
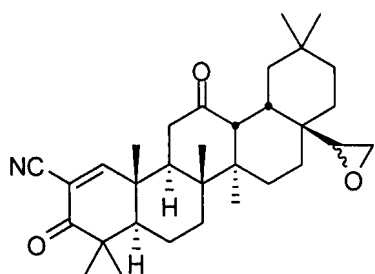
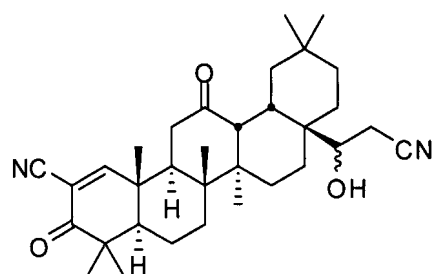
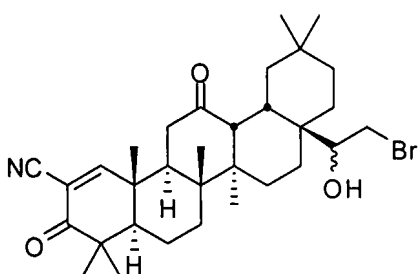
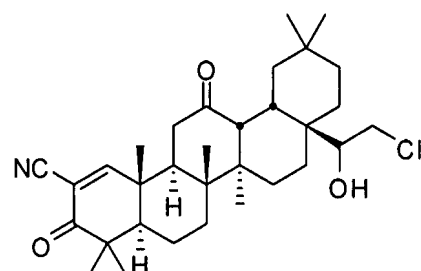
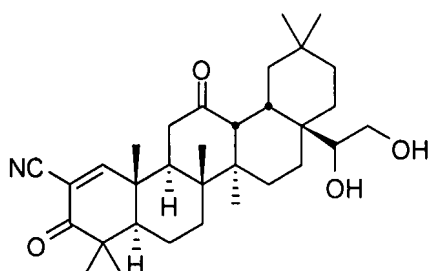
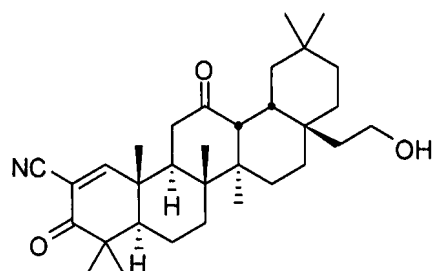
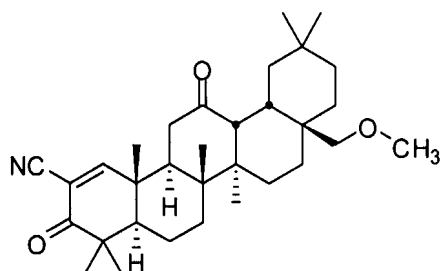
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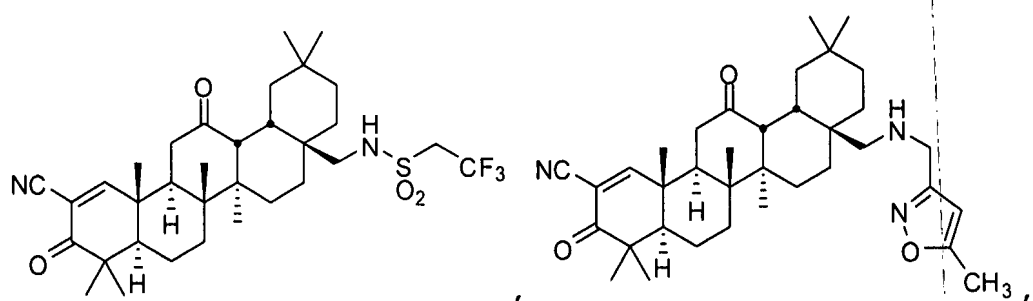
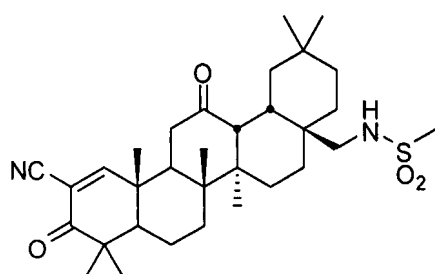
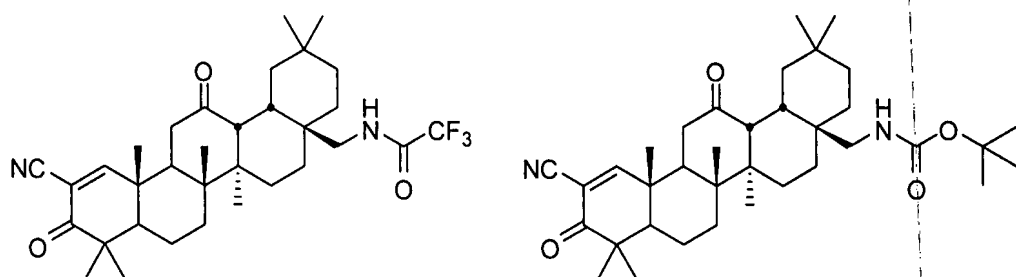
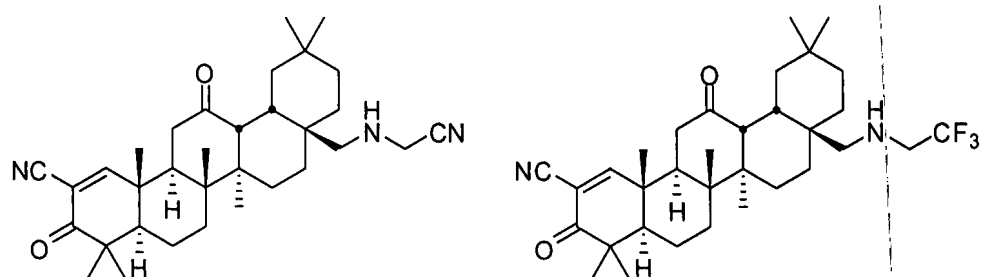
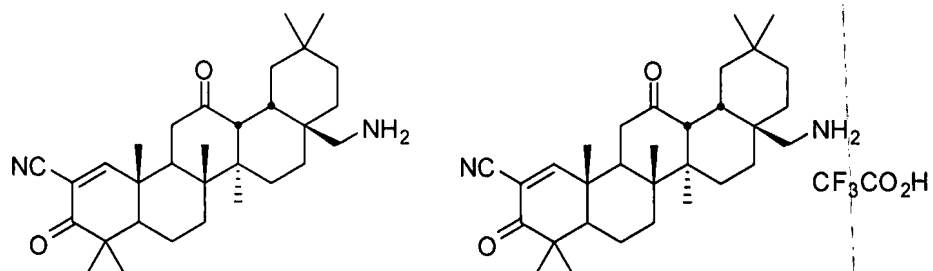
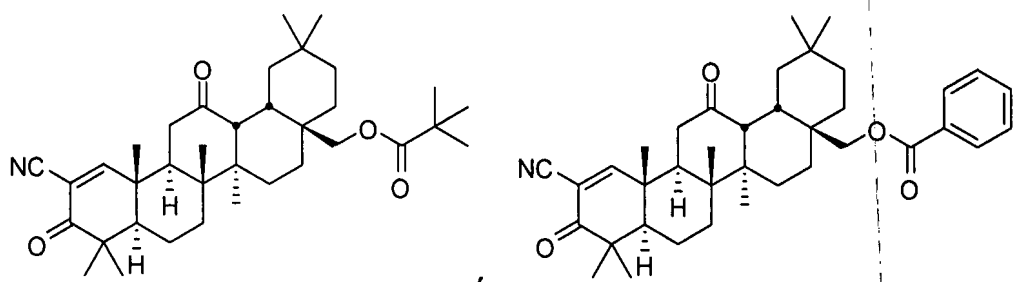


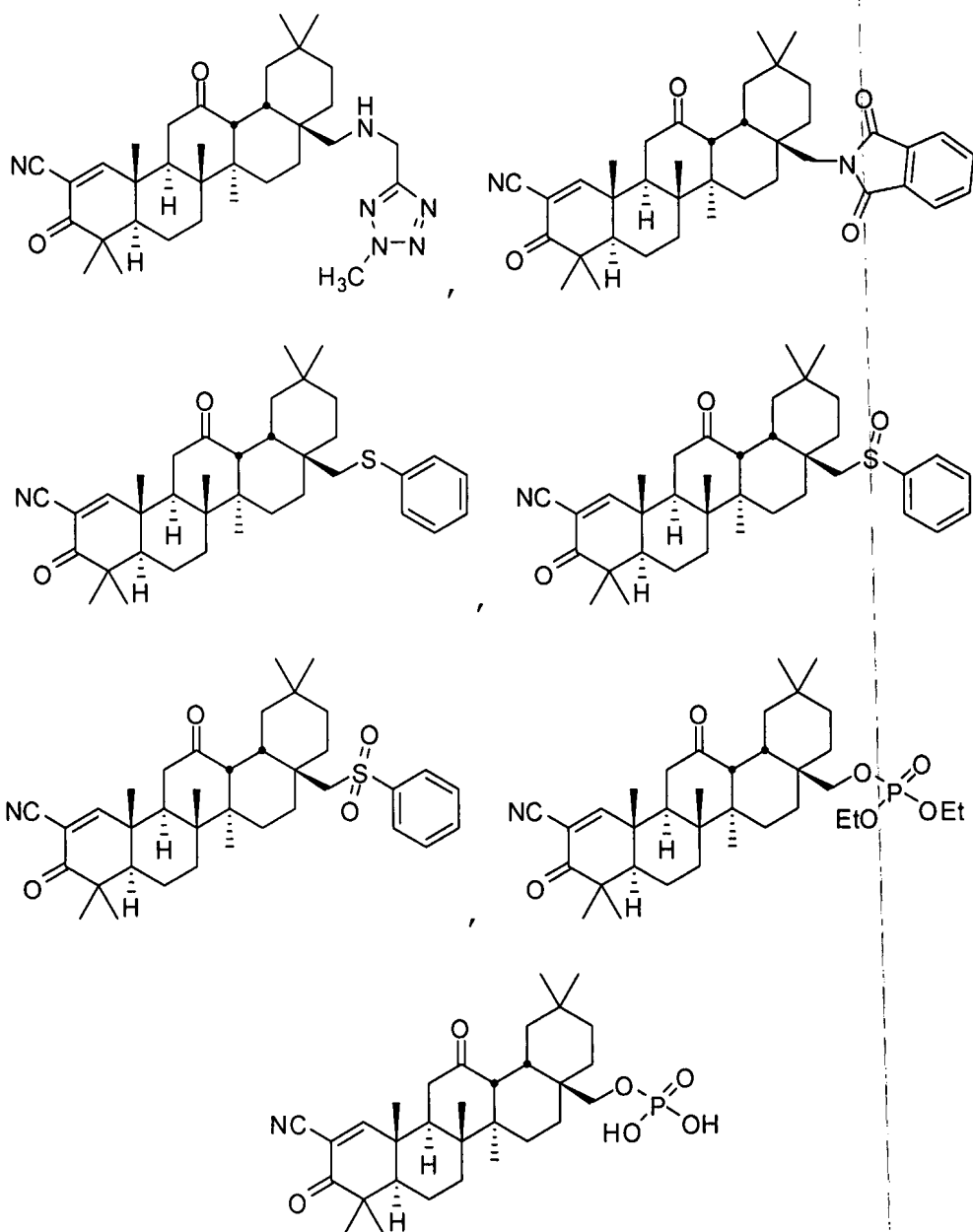
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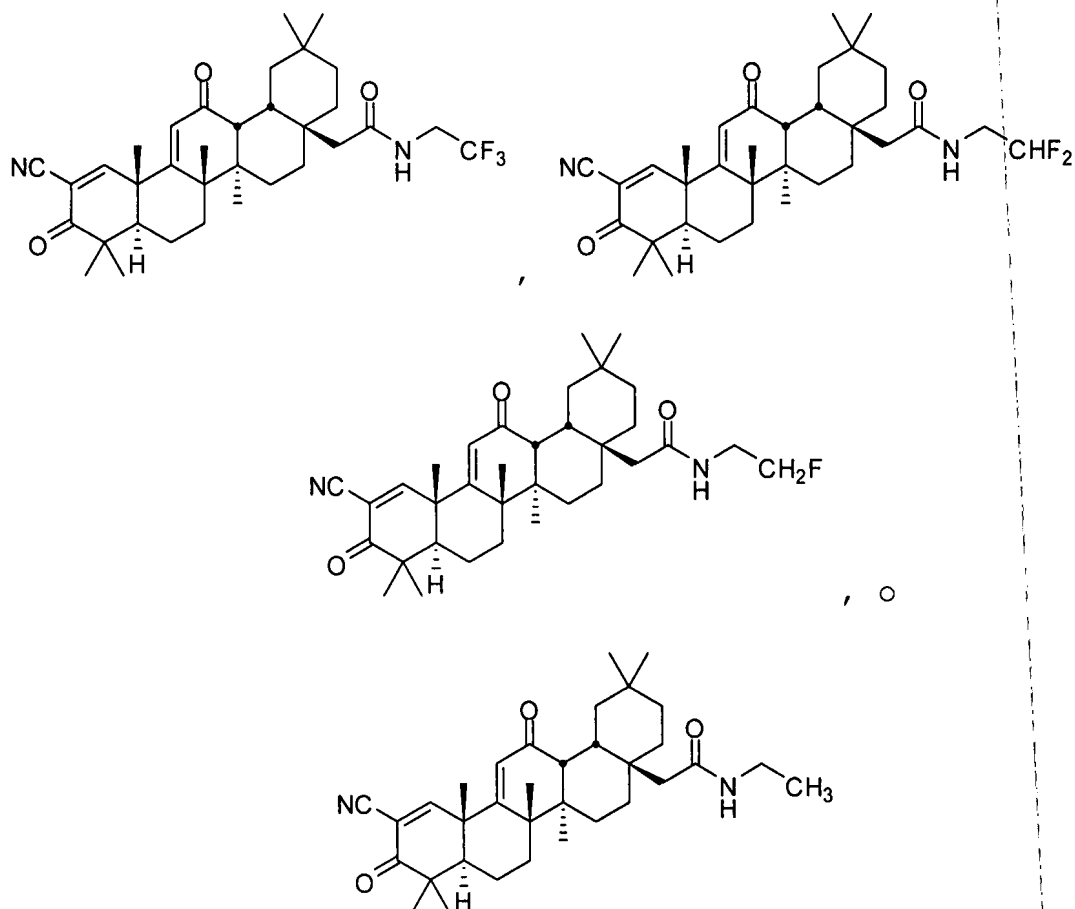
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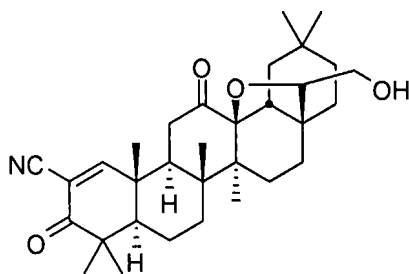


13. El compuesto de la reivindicación 1 además definido como:



5

14. Un compuesto de la fórmula:



- 10 15. Una composición farmacéutica que comprende un compuesto de cualquiera de las reivindicaciones 1-14 y un vehículo aceptable farmacéuticamente.

16. Un kit que comprende:

- 15 un compuesto de cualquiera de las reivindicaciones 1-14; e

instrucciones que comprenden una o más formas de información seleccionadas del grupo integrado por: indicar un estado patológico para el cual se debe administrar el compuesto, información sobre el almacenamiento del compuesto, 5 información de posología e instrucciones sobre la forma de administrar el compuesto.

CHAPTER SIXTEEN

Analog Design

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1 INTRODUCTION

This chapter is limited to nonprotein therapeutic candidates. The subject of **peptide** analogs and peptidomimetic agents merits separate consideration. Contemporary search for new drugs makes extensive use of robotic techniques of combinatorial chemistry and high throughput synthesis, whereby huge numbers of compounds **can** be prepared for high throughput screening. However, this nonselective synthetic method based on a random screening philosophy should not replace the strategy of analog design, but rather it should be considered as a useful prelude to analog design.

In any strategy aimed at designing new drug molecules or analogs of known biologically active compounds, there are no absolute guidelines or rules for procedure; the knowledge, imagination, and intuition of the medicinal chemist are the most important contributors to success. Analog design is as much an art as it is a science. The concept of analog design presupposes that a lead has been discovered; that is, a chemical compound has been identified that possesses some desirable pharmacological property. The search for and identification of leads is a challenge and is a separate topic. It is sufficient for the present discussion to note that lead compounds are frequently identified as endogenous participants (hormones, neurotransmitters, second messengers, or enzyme cofactors) in the body's biochemistry and physiology, or a lead may result from routine, random biological screening of natural products or of synthetic molecules that were created for purposes other than for use as drugs.

Analog design is most fruitful in the study of pharmacologically active molecules that are structurally specific: their biological activity depends on the nature and the details of their chemical structure (including **stereochemistry**). Hence, a seemingly minor modification of the molecule may result in a profound change in the pharmacological response (increase, diminish, completely destroy, or alter the nature of the response). In pursuing analog design

and synthesis, it must be recognized that the newly created analogs are chemical entities different from the lead compound. It is not possible to retain all and exactly the same solubility and solvent partition characteristics, chemical reactivity and stability, acid or base strength, and/or *in vivo* metabolism properties of the lead compound. Thus, although the new analog may demonstrate pharmacological similarities to the lead compound, it is not likely to be identical to it, either chemically or biologically, nor will its similarities and differences always be predictable.

The goal of analog design is twofold: (1) to modify the chemical structure of the lead compound to retain or to reinforce the desirable pharmacologic effect while minimizing unwanted pharmacological (e.g., toxicity, side effects, or undesired routes of and/or unacceptable rates of metabolism) and physical and chemical properties (e.g., poor solubility and solvent partition characteristics or chemical instability), which may result in a superior therapeutic agent; and (2) to use target analogs as pharmacological probes (i.e., tools used for the study of fundamental pharmacological and physiological phenomena) to gain better insight into the pharmacology of the lead molecule and perhaps to reveal new knowledge of basic biology. Studies of analog **structure-activity** relationships may increase the medicinal chemist's ability to predict optimum chemical structural parameters for a given pharmacological action.

Analog design is greatly facilitated if the medicinal chemist can initially define the pharmacophore of the lead compound: that combination of atoms within the molecule that is responsible for eliciting the desired pharmacologic effect. Analog design may be directed toward maintaining this combination of atoms intact in a newly designed molecule or toward a carefully planned, systematic modification of the pharmacophore. If the medicinal chemist is uncertain about the structural features of the pharmacophoric portion of the molecule, a prime initial goal of analog design should be to define the pharmacophore. The medicinal chemist should address the fol-

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lowing questions: What change(s) can be made in the lead molecule that permit(s) retention or reinforcement of pharmacological action? and What change(s) can be made in the molecule that diminish, destroy, or qualitatively change the basic pharmacologic action? The ideal program of analog design should involve *a single* structural change in the lead molecule with each new compound designed and synthesized. An analog in which multiple changes in the structure of the lead molecule have been made simultaneously may occasionally reveal highly desirable pharmacologic effects. However, relatively little useful structure-activity information will be gained from such a molecule. It cannot be readily determined which change (or combination of changes) was responsible for the change in the pharmacological effect. On a practical basis, it is frequently chemically impossible to effect only one discrete change in the lead molecule; one simple molecular structural alteration can influence many structural and chemical parameters. Nonetheless, the medicinal chemist should be cognizant of the disadvantages inherent in "shotgun" (nonsystematic, multiparametric) modification of lead molecules.

In analog design, molecular modification of the lead compound can involve one or more of the following strategies:

- 1 Bioisosteric replacement.
- 2 Design of rigid analogs.
- 3 Homologation of alkyl chain(s) or alteration of chain branching, design of aromatic ring-position isomers, alteration of ring size, and substitution of an aromatic ring for a saturated one, or the converse.
- 4 Alteration of stereochemistry, or design of geometric isomers or stereoisomers.
- 5 Design of fragments of the lead molecule that contain the pharmacophoric group (bond disconnection).
- 6 Alteration of interatomic distances within the pharmacophoric group or in other parts of the molecule.

None of these strategies is inherently preferable to the others; all merit the medicinal chemist's attention and consideration. Appli-

cation of a combination of these strategies to the lead molecule may be advantageous. Considering the possible permutations and combinations of these changes that are possible within a single lead molecule, it is obvious that the number of analogs that can be designed from a lead molecule is potentially extremely large. Some structural changes that might be proposed are chemically impracticable (e.g., the molecule is incapable of existence) or the proposed analog may represent an overwhelmingly formidable synthetic challenge. These negative factors will diminish the population of possible analogs to be considered for synthesis; nevertheless, the medicinal chemist will always be confronted with a multitude of possible target molecules. Rational decisions must be made concerning which compounds should be synthesized, and synthetic priorities must be established for target compounds. All other factors being equal, the medicinal chemist should synthesize the less-challenging compounds first. Beyond this truism, the medicinal chemist's best resources are intuition and imagination. Selection and application of specific molecular modification strategies depend on the chemical structure of the lead compound and, to a certain extent, on the pharmacological action to be studied.

All of the strategies of analog design as well as subsequent decisions concerning target compounds to be synthesized can be facilitated by the use of computational chemistry (computer-assisted molecular modeling) techniques. These may give the medicinal chemist further insights into structural, stereochemical, and electronic implications of the proposed molecular modification.

2 BIOISOSTERIC REPLACEMENT AND NONISOSTERIC BIOANALOGS (NONCLASSICAL BIOISOSTERES)

The concept of bioisosterism derives from Langmuir's (1) observation that certain physical properties of chemically different substances (e.g., carbon monoxide and nitrogen, ketene and diazomethane) are strikingly similar. These similarities were rationalized on the basis that carbon monoxide and nitrogen both have 14 orbital electrons and, similarly,

Table 16.1 Bioisosteric Atoms and Groups

1. Univalent				
-F	-OH	-NH ₂	-CH ₃	-Cl
		S H	-PH ₂	
		-I	<i>t</i> -C ₄ H ₉	
		-Br	<i>i</i> -C ₃ H ₇	
2. Bivalent				
-O-	-S-	-Se-	-CH ₂ -	-NH-
3. Tervalent				
-N=	-CH=			
-P=	-As=			
4. Quadrivalent				
-C-	-Si-			
5. Ring equivalents				
-CH=CH-	-S-(e.g., benzene, thiophene)			
=CH-	=N-(e.g., benzene, pyridine)			
-O-	-S-	-CH ₂ -	-NH-	

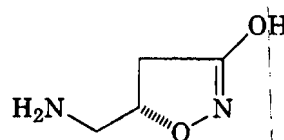
diazomethane and ketene both have 22 orbital electrons. Medicinal chemists have expanded and adapted the original concept to the analysis of biological activity. The following definition has been proposed: "Bioisosteres are groups or molecules which have chemical and physical properties producing broadly similar biological properties" (2). This definition might be modified to include the concept that bioisosteres may produce *opposite* biological effects, and these effects are frequently a reflection of some action on the same biological process or at the same receptor site. Bioisosteric similarity of molecules is commonly assigned on the basis of the number of valence electrons of an atom or a group of atoms rather than on the total number of orbital electrons, as was originally specified by Langmuir. In a remarkable number of instances, compounds result that have similar (or even diametrically opposite) pharmacological effects compared with those of the parent compound. Categories of classic bioisosteres have been described (2) (Table 16.1).

A more recent comprehensive review of bioisosterism appeared in 1996 (3). In a short communication, Burger (4) discussed and provided valuable insights into isosterism and bioanalogy in drug design.

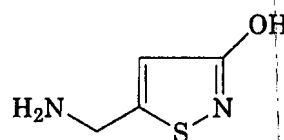
Many compounds have been identified that comply with the "biology" aspect of the bioisostere concept but that do not fit the strict chemical (steric and electronic) definition of

bioisosteres. Floersheim et al. (5) proposed that such compounds be designated as *nonisosteric bioanalogs*, replacing the older term, "nonclassical bioisosteres." However, most of the contemporary literature retains the nonclassical bioisostere terminology. Table 16.2 lists representative nonclassical bioisosteres.

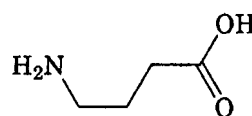
Dihydromuscimol (1) and thiomuscimol (2) are cyclic analogs of γ -aminobutyric acid (GABA) (3), in which the C=N moiety of the



(1)



(2)



(3)

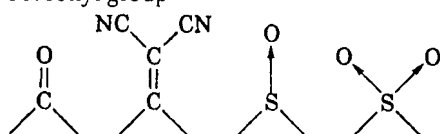
heterocyclic ring is considered to be bioisosteric with the γ -amino group of GABA. The -S- moiety of thiomuscimol is bioisosteric with the ring -O- of dihydromuscimol. Both (1) and (2) are highly potent agonists at GABA_A receptors, as determined in an electrophoresis-based assay (6).

Because of its bioisosteric similarity to the normal physiological substrate L-dopa (4), L-mimosine (5) inhibits catechol oxidation by the enzyme tyrosinase (7). These compounds exemplify a situation in which bioisosteres display *opposite* pharmacologic effects at the same receptor.

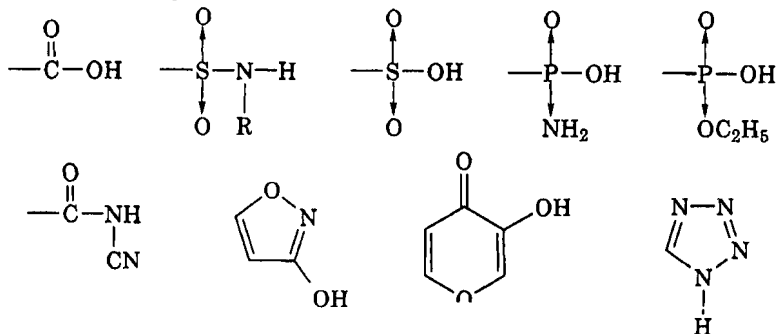
The sulfonium bioisostere (6) of *N,N*-dimethyldopamine (7) retains the dopaminergic agonist effect displayed by (7) (8). The fact that (6) bears a permanent unit positive charge was invoked in support of the hypoth-

Table 162 Nonclassical Bioisosteres

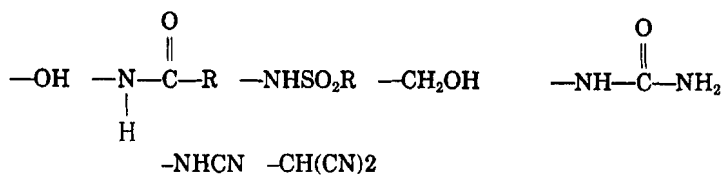
1. Carbonyl group



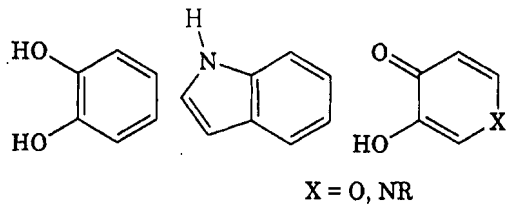
2. Carboxylic acid group



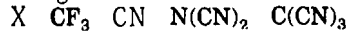
3. Hydroxy group



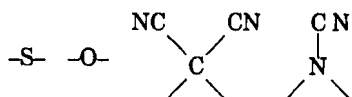
4. Catechol



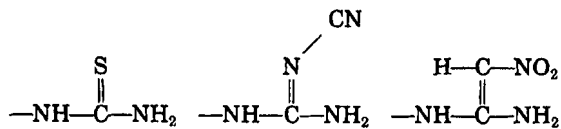
5. Halogen



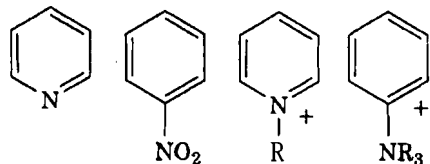
6. Thioether



7. Thiourea



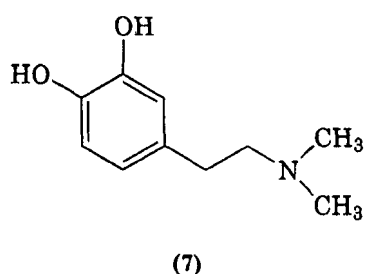
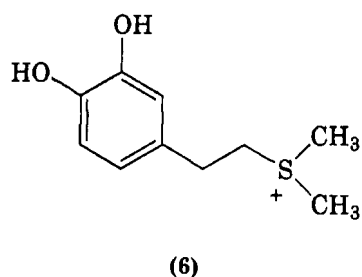
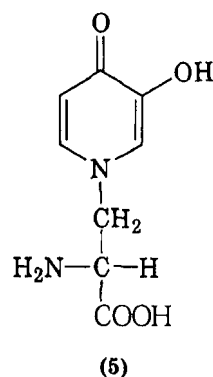
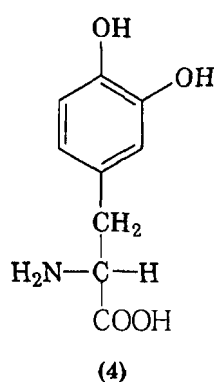
8. Pyridine



9. Hydrogen



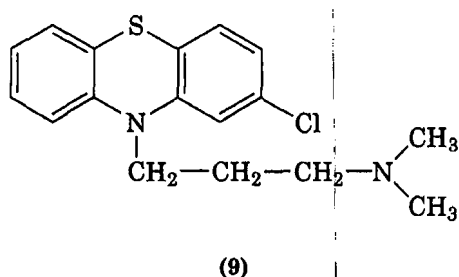
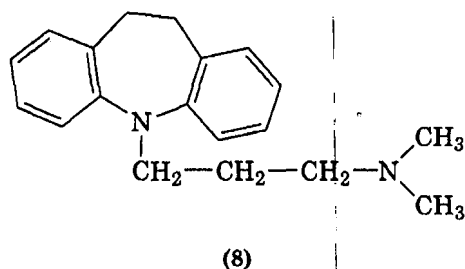
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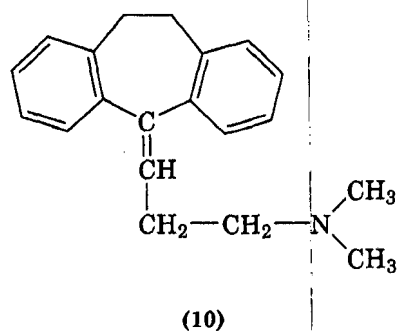
esis that β -phenethylamines such as (7) interact with dopamine receptors in their protonated (cationic) form.

Bioisosteric replacement strategy has been fruitful in design of psychoactive agents, by

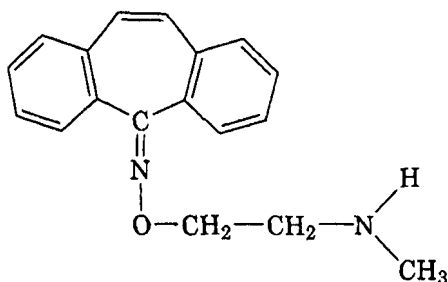
use of the antidepressant dibenzazepine derivative **imipramine** (8) as the lead. The structural similarity between imipramine and the phenothiazine antipsychotics [typified by chlorpromazine (9)] is apparent. Although these two



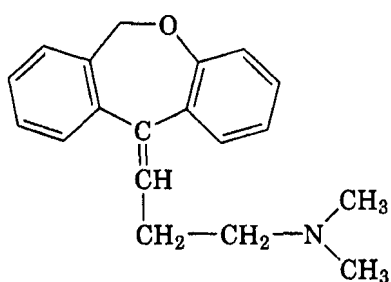
bioisosteric molecules have different pharmacological properties and therapeutic uses and likely have different mechanisms and sites of action in the central nervous system (9), they share the property of being psychotropic agents. They illustrate the observation that bioisosteric manipulation of a molecule may change its mode of action. In the antidepressant dibenzocycloheptene derivative **amitriptyline** (10), the ring nitrogen of imipramine is



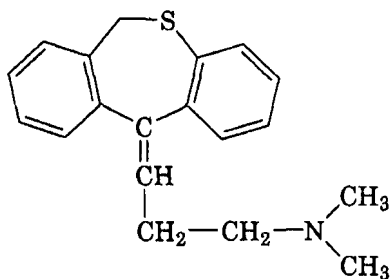
replaced by an exocyclic olefin moiety. Demexiptiline (1), doxepin (12), and dothiepin (13) represent other bioisosteric modifications of imipramine that possess antidepressant ac-



(11)



(12)

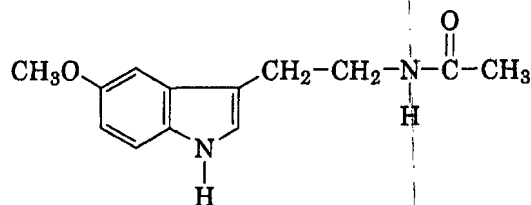


(13)

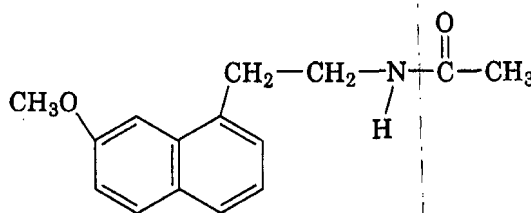
tivity (10). Variations in the precise nature of psychotropic effects manifested by compounds (8-13) may be ascribed to the marked changes in orientation in space of the two benzene ring components of the tricyclic portion of these molecules, imposed on them by the isosteric moieties ($-\text{CH}=\text{CH}-$, $-\text{CH}_2-\text{CH}_2-$, $-\text{S}-$, $-\text{CH}_2\text{O}-$, $\text{CH}_2\text{S}-$). The *Z*-isomer of oxepin is a more potent antidepressant than the *E*-isomer, but the drug is marketed as a mixture of isomers (11). Doxepin is also a potent antagonist at histamine H_1 receptors. The *Z*-isomer is somewhat more potent than the *E*-isomer against histamine in the guinea pig ileum (12). The identity of the geometric isomer of dothiepin (13) used in pharmacological testing is

uncertain. Apparently, attempts were made (13) to isolate the *E*- and *Z*-isomers of all of the compounds prepared in the series studied, but no information was provided about the stereochemistry of the dothiepin material used in the pharmacological studies.

Replacement of the entire indole ring system of melatonin (14) by a naphthalene ring



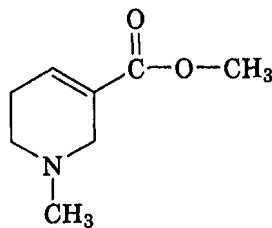
(14)



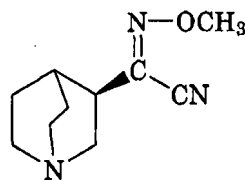
(15)

(15) permitted retention of binding affinity in an ovine pars tuberalis membrane assay (14).

From a study (15) of a series of muscarinic M_1 agonists derived from the structure of arecoline (16) and typified by (17), it was con-



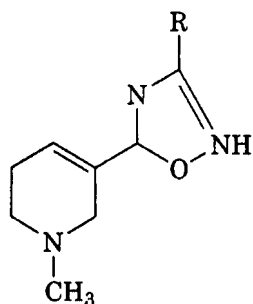
(16)



(17)

cluded that the *Z*-*N*-methoxyimidoyl nitrile group serves as a stable methyl ester bioisostere. The *Z*-isomer has an 18-fold higher affinity than its *E*-isomer for the rat cerebral cortex tissue used in the binding studies.

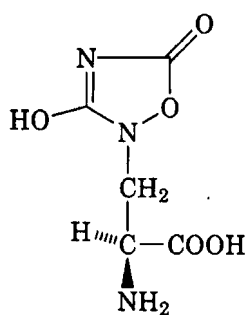
Replacement of the methyl ester moiety of the muscarinic partial agonist arecoline (16) by the putative nonclassical bioisosteric 1,2,4-oxadiazole ring system (18), where R = un-



(18)

branched C₁-C₈ alkyl) permits retention of muscarinic agonism (16).

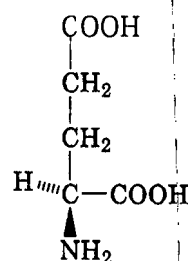
The 1,2,4-oxadiazole ring system of quisqualic acid (19), an agonist at a subpopulation



(19)

of glutamate receptors (17), can be considered to be a nonclassical bioisostere of the corresponding carboxyl group of glutamic acid (20).

Compounds (21-23) illustrate further examples of nonclassical bioisosteres. Compound (21) was reported to display antitrypanosomal activity (18). The analogs (22) and (23) also displayed antitrypanosomal activity (19). Compound (22) demonstrated the most impressive activity (IC₅₀ values of 40 and



(20)

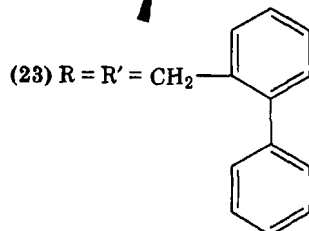
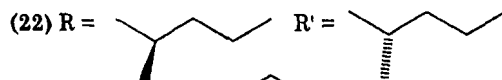
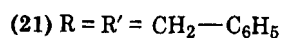
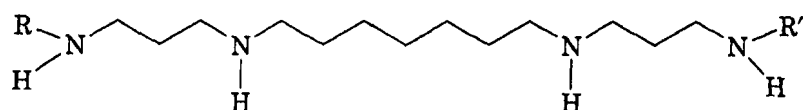
165 nM) with respect to potency and effect on two arsenic-resistant strains of the organism.

Although the strategy of bioisosteric replacement may be a powerful and highly productive tool in analog design, Thornber (2) has emphasized that fundamental chemical and physical chemical changes can be expected to result from these molecular modifications, which may in themselves profoundly affect the pharmacological action of the resulting molecules. Contributing factors include change in the size of the atom or group introduced, which may affect the overall shape and size of the molecule; changes in bond angles; change in partition coefficient; change in the pK_a of the molecule; alteration of chemical reactivity and chemical stability of the molecule, with accompanying qualitative and quantitative alteration of *in vivo* metabolism of the molecule; and change in hydrogen-bonding capacity. The chemical and biological results and pharmacological significance of many of these factors are unpredictable and must be determined experimentally.

3 RIGID OR SEMIRIGID (CONFORMATIONALLY RESTRICTED) ANALOGS

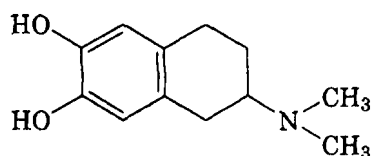
Imposition of some degree of molecular rigidity on a flexible organic molecule (e.g., by incorporation of elements of the flexible molecule into a rigid ring system or by introduction of a carbon-carbon double or triple bond) may result in potent, biologically active agents that show a higher degree of specificity of pharmacologic effect. There are possible advantages to this technique (20): the key functional groups are held in one steric disposition or, in

27



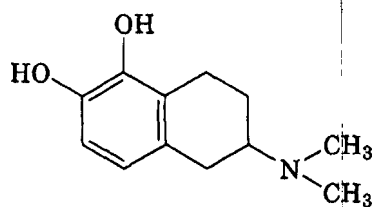
the case of a semirigid structure, the key functional groups are constrained to a limited range of **steric** dispositions and interatomic distances. By the rigid analog strategy, it is possible to approximate "frozen" **conformations** of a flexible lead molecule that, if an enhanced pharmacological effect results, may assist in defining and understanding **structure-activity** parameters, including the three-dimensional geometry of the pharmacophore. These data may be useful in constructing a model of the topography of the receptor. Computational chemistry strategies can be a valuable tool in designing rigid analogs.

The semirigid tetralin congeners (24) and (25) of *N,N*-dimethyldopamine (7) represent



(24)

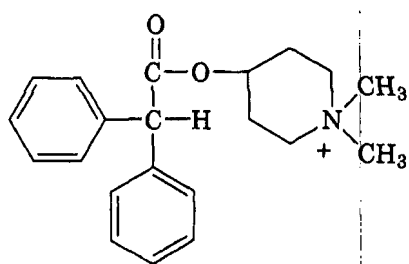
the two rotameric conformational extremes of the spatial relationship of the aromatic ring of **dopamine** to the ethylamine side chain when the ring and the side chain are coplanar. Compounds (24) and (25) display effects at different subpopulations of **dopamine** receptors (21), which have been proposed to reflect dif-



(25)

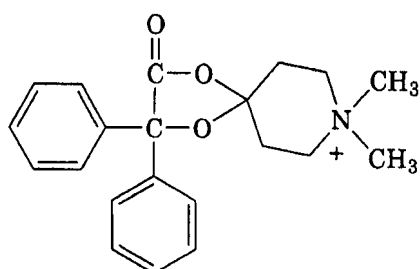
ferent conformations assumed by the flexible **dopamine** molecule at its various *in vivo* sites of action.

Restriction of conformational freedom of the acyl moiety in **4-DAMP** (26), an **antimus-**



(26)

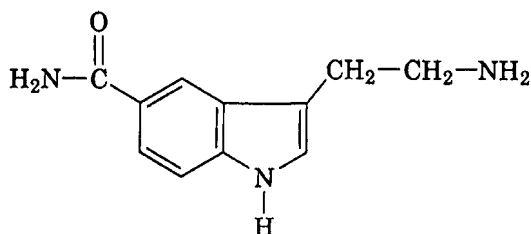
carinic compound displaying higher **affinity** at ileal M_3 acetylcholine receptors than at atrial M_2 receptors) was imposed by the structure of the **spiro-compound** (27) (22).



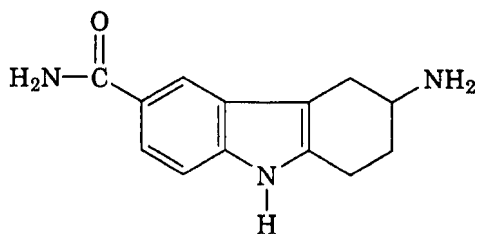
(27)

Spiro-DAMP (27) was slightly more potent at M_2 muscarinic receptors than at M_3 receptors. It was proposed that the geometry of the spiro-molecule might reflect the receptor-bound conformation of 4DAMP (26); this conformation differs from that observed in the crystal structure of 4DAMP.

Conformational restriction was introduced into the side chain of a nonclassical serotonin bioisostere (28), a selective $5HT_{1A}$ and $5HT_{1B}$ receptor agonist) by its incorporation into a fused six-membered ring (29) (23).



(28)

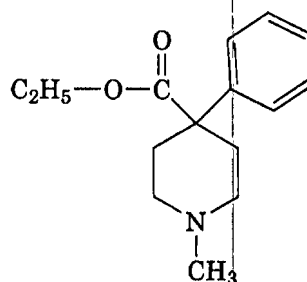


(29)

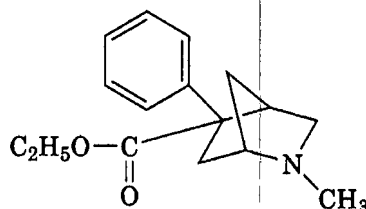
The conformational restrictions imposed on the indole-3-ethylamine moiety permitted retention of affinity for the $5HT_{1A}$ receptor but it diminished affinity for the $5HT_{1B}$ receptor by a factor of 1000. In two functional assays, (29) exhibited potency equal to or marginally greater than that of serotonin. Com-

pound (29) was described as a partial agonist. It was concluded that the conformation of the indole-3-ethylamine portion of the fused system (29) reflects the conformation assumed by the flexible system (28) when it binds to the $5HT_{1A}$ receptor.

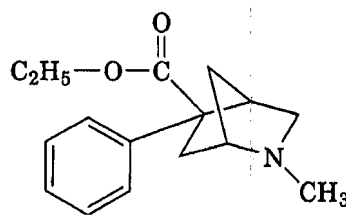
Imposition of rigidity into the piperidine ring of the opioid analgesic meperidine (30) by introduction of a methylene bridge between carbons 2 and 5 resulted in epimers (31) and (32), representing "frozen" conformations of meperidine (24).



(30)



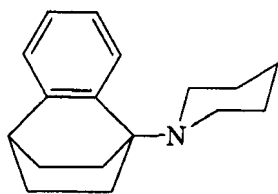
(31)



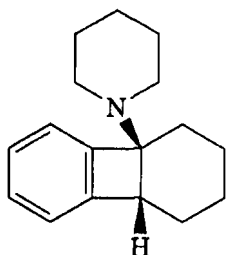
(32)

The exo-phenyl isomer (32) was six times as potent as the endo-phenyl isomer (31), and it was twice as potent as meperidine itself in a benzoquinone-induced writhing assay for analgesic effect.

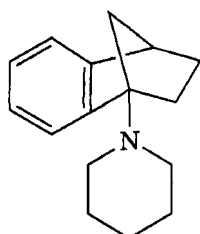
Rigid analogs (33), (34), and (35) of phenylcyclidine (36) possess a rigid carbocyclic struc-



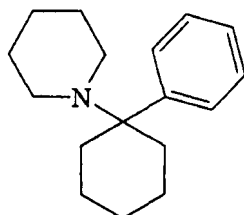
(33)



(34)



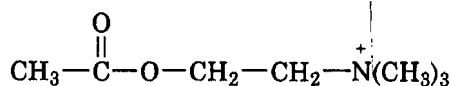
(35)



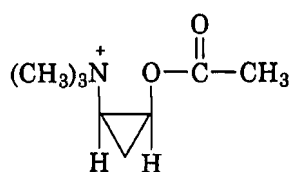
(36)

ture and an attached piperidine ring that is free to rotate. All three rigid analogs showed low to no **affinity** for the PCP receptor, but they had good affinity in a α -receptor-binding assay (25). These binding data were proposed to be useful in defining a model for the σ -receptor pharmacophore. This study also provided additional evidence that the α -receptor is independent of the PCP-binding site (cf. Ref. 26 and references therein).

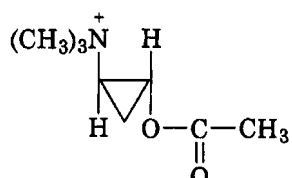
Incorporation of the choline portion of acetylcholine (37) into a cyclopropane ring system resulted in *cis*- and *trans*-1,2-disubstituted molecules, (38) and (39), in which the



(37)



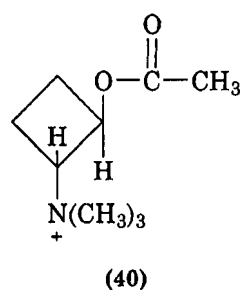
(38)



(39)

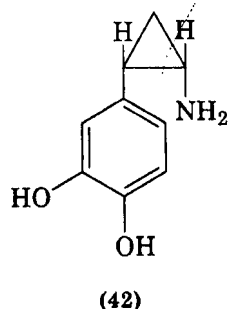
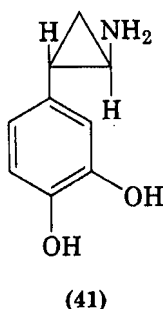
acetylcholine molecule is locked into folded ("cisoid") and extended ("transoid") conformations.

The (1*S*), (2*S*)-(+)-*trans*-isomer (39) was somewhat more potent than acetylcholine itself in tissue and whole-animal assays for muscarinic agonism (27) and it was an excellent substrate for acetylcholinesterase. The (1*R*), (2*R*) enantiomer of (39) was exponentially less potent than its (1*S*), (2*S*) enantiomer in the assays cited, but it was a good substrate for acetylcholinesterase. The (2)-*cis*-isomer (38) was almost inert at nicotinic and muscarinic receptors and it was a poor substrate for acetylcholinesterase. These data were taken as evidence that the flexible acetylcholine molecule interacts with muscarinic receptors in an extended geometry of the chain of atoms (28). When this semirigid analog strategy was applied to a cyclobutane ring system (compound 40), there was a marked loss of pharmacologic effect (29). This result is enigmatic; differences in interatomic distances and bond angles in the pharmacophoric moiety as well

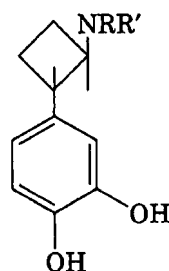


as differences in extraneous molecular bulk seem insufficient to account for the dramatic difference in pharmacological potencies between the three- and the four-membered ring systems.

The cyclopropane ring was employed to impart a degree of rigidity to the side chain of dopamine (structures 41 and 42) (30).

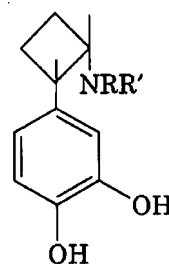


Neither isomer displayed effects at dopamine receptors, but both were α -adrenoceptor agonists, with the ($\pm$)-*trans*-isomer (41) being approximately five times more potent than the ($\pm$)-*cis*-isomer (42). It was suggested (31) that these findings may contribute to determining the preferred conformation of β -phenethylamines at the α -adrenoceptor. The racemic *trans*-cyclobutane congeners (43a) and (43b) are more potent than their racemic *cis*-isomers (44a) and (44b) in binding studies on rat



(43a) R = R' = CH₃

(43b) R = R' = H

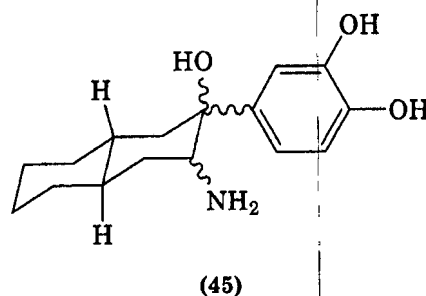


(44a) R = R' = CH₃

(44b) R = R' = H

corpus striatum tissue, but the binding affinities for (43a) and (43b) are much less than that of dopamine (32). Racemic *trans*-(43a) was more potent than the *trans*-primary amine (43b), but it was still much less potent than dopamine. The racemic *cis*-isomer of (44b) demonstrated very low affinity for the receptor.

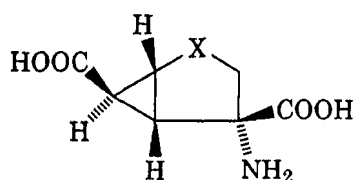
A β -phenethylamine moiety was incorporated into the *trans*-decalin ring system (45)



and the racemic modifications of all four possible isomers were prepared as "frozen" analogs of possibly significant conformations of the flexible norepinephrine molecule (33). All four compounds displayed approximately equal (extremely low) potency. This result il-

illustrates that the achievement of conformational integrity by incorporation of a flexible pharmacophore into a bulky, complex molecule may be at the expense of biological activity.

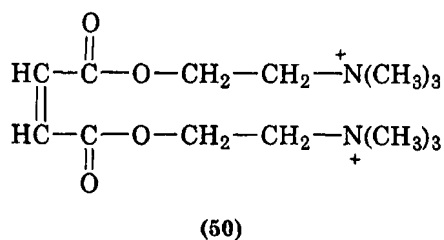
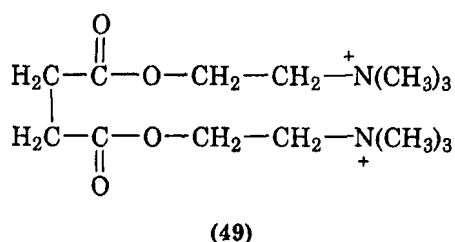
Rigidity was introduced into the glutamic acid moiety in a series of bioisosteric congeners (46–48) (34). These systems showed po-



- (46) X = CH₂
 (47) X = O
 (48) X = S

tent agonist activity at subpopulations of metabotropic glutamate receptors. The geometry of these congeners led to the conclusion that glutamic acid itself interacts with the metabotropic glutamate receptors in a fully extended conformation.

The rotational orientation of the ester moieties of the myoneural blocking agent succinylcholine (49) was restricted by introduction of a double bond into the succinic acid portion (50), (51) (35). The E-fumarate ester



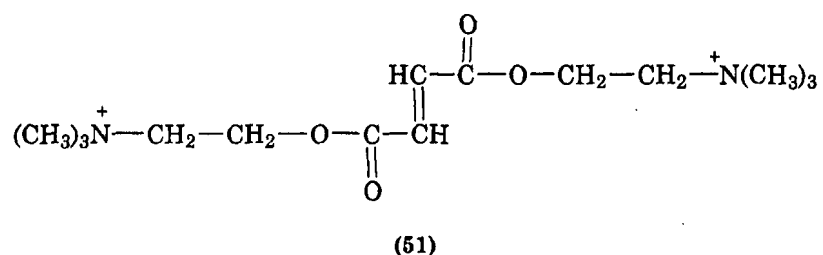
(51) was approximately one-half as potent as the flexible succinate ester (49), whereas the Z-maleate ester (50) was 1/40 as potent as the

succinate. These results led to the conclusion that the molecular shape of the E-ester (51) more closely approximates that assumed by succinylcholine when it interacts with myoneural nicotinic receptors.

Restricted rotation was also introduced into the succinic acid moiety of succinylcholine by preparation of the choline esters of *cis*- and *trans*-cyclopropane-1,2-dicarboxylic acids (52) and (53) (36, 37). Myoneural blocking activity was assessed in dogs (37) and cats (36) and, as indicated above for the E- and Z-olefinic esters (51) and (50), the extended *trans*-isomer (53) demonstrated much greater potency and a longer duration of action than those of the *cis*-isomer (52). The cyclobutane congeners (54) and (55) presented unexpected results that are difficult to rationalize; the *cis*-isomer (54) was much less potent than the *trans*-isomer (55) in a cat assay for myoneural blockade, but it presented a decidedly longer duration of action than that of the *trans*-isomer (36).

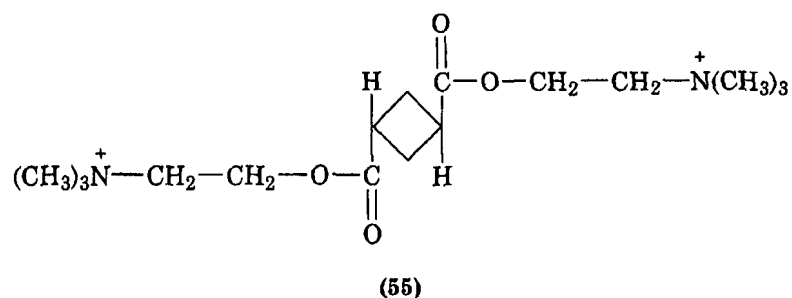
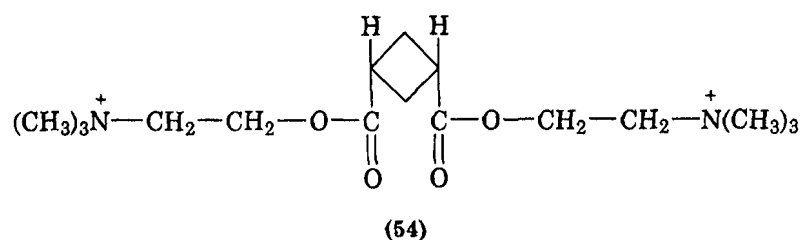
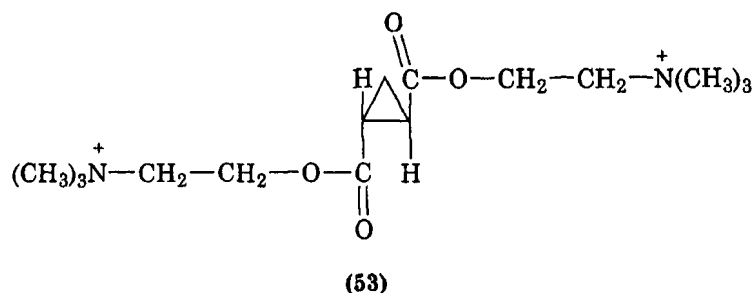
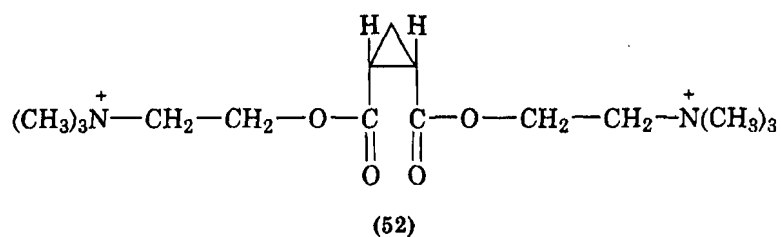
4 HOMOLOGATION OF ALKYL CHAIN OR ALTERATION OF CHAIN BRANCHING; CHANGES IN RING SIZE; RING-POSITION ISOMERS; AND SUBSTITUTION OF AN AROMATIC RING FOR A SATURATED ONE, OR THE CONVERSE

Change in size or branching of an alkyl chain on a bioactive molecule may have profound (and sometimes unpredictable) effects on physical and pharmacological properties. Alteration of the size and/or shape of an alkyl substituent can affect the conformational preference of a flexible molecule and may alter the spatial relationships of the components of the pharmacophore, which may be reflected in the ability of the molecule to achieve complementarity with its receptor or with the catalytic surface of a metabolizing enzyme. The alkyl group itself may represent a binding site with the receptor (through hydrophobic interactions), and alteration of the chain may alter its binding capacity. Position isomers of substituents (even alkyl groups) on an aromatic ring may possess different pharmacological properties. In addition to their ability to affect electron distribution over an aromatic ring sys-

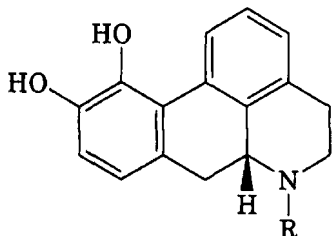


tem, position isomers may differ in their complementarity to receptors, and the position of a substituent on a ring may influence the spatial occupancy of the ring system with respect to the

remainder of a **conformationally** variable molecule. What has sometimes been **trivialized** as "methyl group roulette" may indeed be an important parameter in the design of analogs.

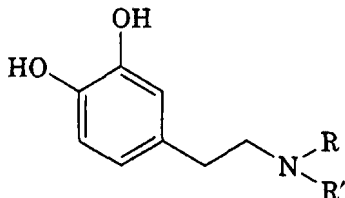


Homologation of the N-alkyl chain in norapomorphine (56) from methyl (57) to *n*-propyl (59) produced incremental increases in emetic response in dogs and in stereotypy responses in rodents (38, 39).



- (56) R = H
 (57) R = CH₃
 (58) R = C₂H₅
 (59) R = *n*-C₃H₇
 (60) R = *n*-C₄H₉

The next member of the series, the *n*-butyl homolog (60), demonstrated a tremendous loss in potency and activity compared to that of the lower homologs (39). Studies of *N,N*-dialkyl dopamines (61–64) revealed that some



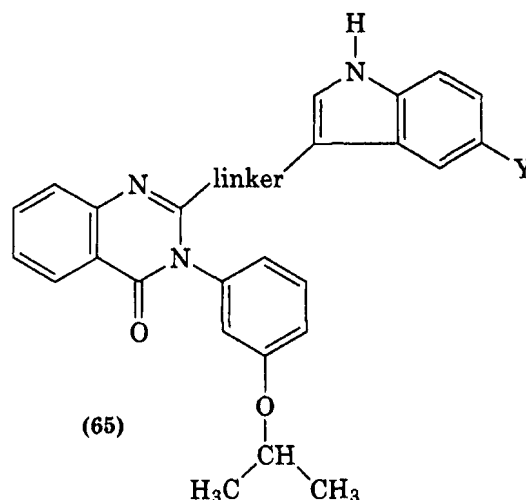
- (61) R = R' = CH₃
 (62) R = R' = *n*-C₃H₇
 (63) R = *n*-C₃H₇; R' = *n*-C₄H₉
 (64) R = R' = *n*-C₄H₉

combinations of alkyl groups may impart a high degree of dopamine agonist effects (40).

NJV-dimethyldopamine (61) is extremely potent in assays for dopaminergic agonism (pigeon pecking, emesis in dogs, and inhibition of cat cardioaccelerator nerve), as is *N,N*-di-*n*-propyldopamine (62) (41). *N,n*-Propyl-*N,n*-butyldopamine (63) is potent in behavioral assays in nigra-lesioned rats (42). However, NJV-di-*n*-butyldopamine (64) is virtually inert in these assays (41, 42). *N,N*-di-*n*-Pentyldopamine was reported (43) to be inert in a caudectomized mouse behavioral assay and in a rotatory behavioral assay in nigra-lesioned

rats. It seems likely that the enhanced dopaminergic agonist effects conferred by *N*-ethyl and *N,n*-propyl groups on aporphine and β -phenethylamine-derived molecules are not related merely to enhanced lipophilic character or to partitioning phenomena, but rather to the likelihood that the two- and three-carbon chains have a positive affinity for subsites on certain dopamine receptors. It may be speculated that these receptor subsites do not accommodate longer alkyl chains (e.g., *n*-butyl or *n*-pentyl). However, different assays for dopaminergic stimulant effects and different animal species were used in refs. 41, 42, and 43, and care must be exercised in drawing firm structure-activity relationship conclusions based on these data.

The alkyl linker between the two heterocyclic ring systems in structure (65) was modified



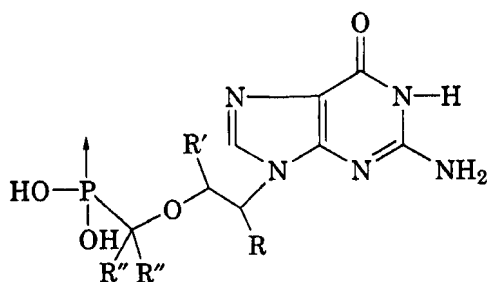
- (66) linker = Y = H
 (67) linker = Y = H
 (68) linker = Y = H
 (69) linker = Y = H

fied in studies of the ability of analogs to bind to the cholecystokinin-B receptor (44). When this linking group was $-\text{CH}_2-\text{CH}_2-$, the compound (structure 66) was extremely potent in radioligand displacement assays on mouse brain membranes. Introduction of carbon-car-

bon unsaturation (*E*-olefin) into the linker (structure 67) resulted in a 16-fold decrease in binding ability; this suggests that conformational restriction and limitation of molecular flexibility have deleterious effects on biological activity. However, no data were reported on the *Z*-isomer of this olefinic molecule, so that caution should be exercised in drawing conclusions. Introduction of a bromine substituent (65, Y = Br) into (66) produced a threefold increase in potency, whereas the same structural modification of the olefin (67) resulted in a threefold decrease in potency.

Branching the linker chain with a methyl group adjacent to the quinazolinone ring (68) resulted in a 350-fold decrease in affinity. However, chain branching with a methyl group in the alternate position on the ethylene chain produced compound (69), whose receptor affinity was of the same order of magnitude as the extremely potent lead compound (66). The exponential difference in receptor-binding ability exhibited by the two isomeric branched-chain linker compounds (68) and (69) was ascribed to unfavorable steric interactions between the receptor and the linker methyl group of (68) (44). This conclusion may be compromised by the fact that both (68) and (69) were evaluated as their racemates.

A study (45) of 2-(phosphonmethoxy)ethylguanidines (70-73) as antiviral (herpes and



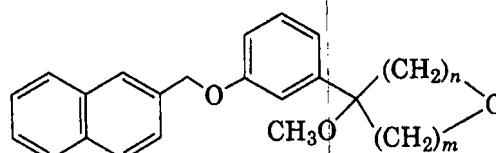
- (70) R = R' = H
 (71) R = H; R' = CH₃
 (72) R = CH₃; R' = H
 (73) R = R' = H; R = gem-dimethyl

HIV) agents revealed that branching of the ethylene chain by introduction of a methyl group at the 1'-position (as in racemic 72) diminished antiviral activity 25-fold and dimin-

ished toxicity 16-fold compared to that of the nonmethylated system (70).

In contrast, (*R*)-(71), the 2'-methyl congener, exhibited only a fivefold decrease in antiviral potency compared to that of compound (70), but it also exhibited a 30-fold lessening of toxicity, to produce a substantial increase in therapeutic index over that of (70). The (*S*)-(71) enantiomer was somewhat less potent than its (*R*)-enantiomer. The gem-dimethyl congener (73) was also somewhat less potent than the (*R*)-2'-monomethyl compound (71) and it was markedly more toxic. The (*S*)-2'-methyl stereoisomer of (71) exhibited a decidedly lower therapeutic index than that of its (*R*)-enantiomer.

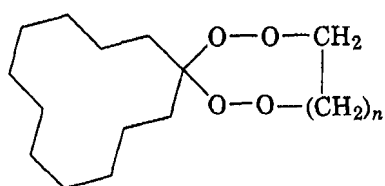
Closely related to alteration of chain length and/or chain branching is alteration of ring size. Compound (74) showed nano-



- (74) $n = 1$; $m = 2$
 (75) $n = m = 1$
 (76) $n = 1$; $m = 3$
 (77) $n = 1$; $m = 4$
 (78) $n = 2$; $m = 2$
 (79) $n = 2$; $m = 3$

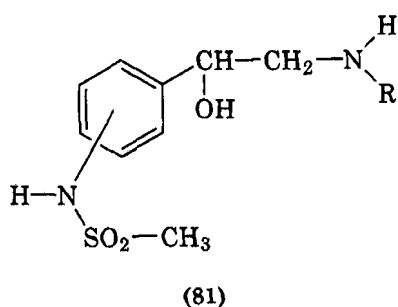
molar-level activity as an inhibitor of 5-lipoxygenase (46). The size of the oxygen-containing ring as well as the position of the oxygen member with respect to the methoxy and aryl substituents was varied. The (seven-membered) oxepane ring derivative (79) and the (six-membered) tetrahydropyran ring derivative (78) showed two- to 10-fold enhanced potency over that of the tetrahydrofuran lead compound (74). The other analogs shown demonstrated much weaker enzyme inhibitory activity.

In a series of spiro-tetraoxacycloalkanes (80), with varying heterocyclic ring sizes, it was found that the compound where $n = 1$ demonstrated marked antimalarial activity against *P. bergeri* and *P. falciparum*, and showed low toxicity (47). The analog in which

(80) $n = 1, 2, 3, 4, 5, 6$

$n = 4$ showed strong activity against *P. falci-parum* but it was unimpressive in the *P. bergeri* assay.

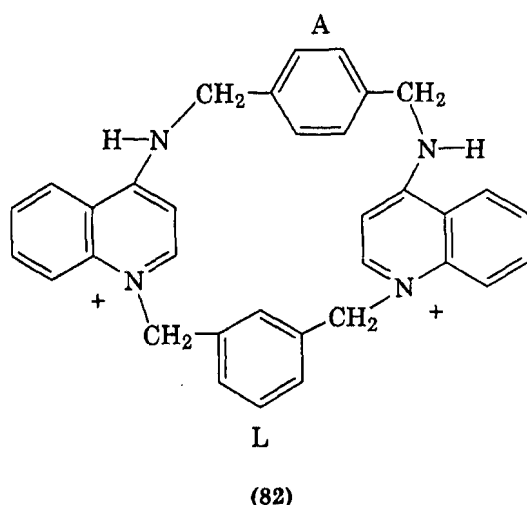
In a series of arylsulfonamidophenethanolamines (81) (48), derivatives bearing the sul-



(81)

fonamido group meta to the ethanolamine side chain displayed properties of a β -adrenoceptor partial agonist, whereas 19 compounds bearing the sulfonamidogroup in the *para* position were β -antagonists.

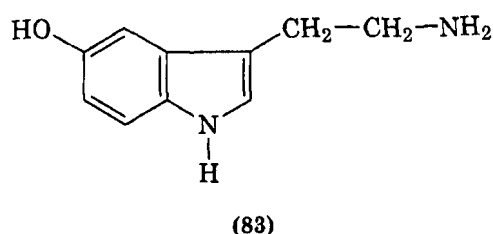
Changing the positions of attachment of the two benzene rings linking the quinolinium moieties of the calcium-activated potassium channel blocker (82) reduced activity 10- to



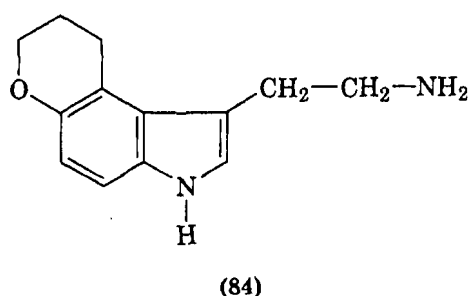
(82)

60-fold in a rat superior cervical ganglion assay (49). Other structural variations studied included benzene ring A meta-substituted and benzene ring L meta-substituted; benzene ring A meta-substituted and benzene ring L para-substituted; and benzene ring A *para*-substituted and benzene ring L *para*-substituted. All of these variations were much less potent than those of (82).

The phenolic group of serotonin (83) was incorporated into a pyran ring (84) (50), thus



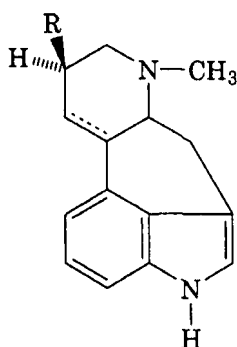
(83)



(84)

also introducing an alkyl substituent at position 4 of the indole ring system.

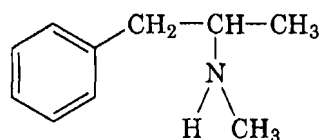
This tricyclic analog (84) lacked serotonin-like affinity for 5-HT₁ receptors, but it demonstrated high and selective affinity for 5-HT₂ receptors. Like serotonin, it stimulated phosphatidyl inositol turnover in rat brain slices. The low affinity for 5-HT₁ receptors was rationalized, in part, on the basis of steric interference between the dihydropyran ring and the aminoethyl side chain, which inhibits the tryptamine system from assuming the folded ergotlike conformation, as illustrated in (85), which probably approximates the conformation of serotonin at 5-HT₁ receptors. The methyl ether of serotonin exhibits approximately the same affinity for 5-HT₁ sites as does serotonin (51). The methyl ether also has marked affinity for 5-HT₁ and 5-HT₂ receptors, but it has diminished affinity (compared with serotonin) at 5-HT₂ receptors. It was



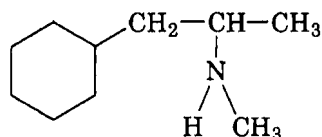
(85)

suggested (50) that the high affinity for the 5-HT₁ receptor exhibited by such compounds as (84) demonstrates that the C-5 hydroxyl group of serotonin can function as a hydrogen-bond acceptor at the receptor.

Replacement of the benzene ring of the potent indirect acting central noradrenergic stimulant methamphetamine (86) by a cyclohexane ring (compound 87) results in some



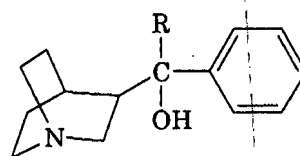
(86)



(87)

loss of pressor effect, but the drug, like amphetamine, has been used as a nasal decongestant, and it has CNS-mediated anorexigenic effect (52, 53). It is said to have somewhat less central stimulant action than the corresponding aromatic ring derivatives (54a-d).

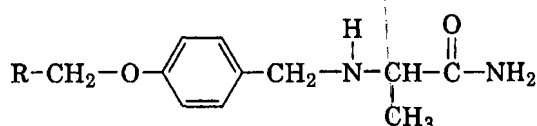
The benzene (88) and cyclohexane (89) congeners have almost identical effects in blocking bronchoconstriction produced by histamine, serotonin, or acetylcholine in the guinea pig *in vivo* (55). They also showed identical LD₅₀ values in mice. The stereochemistry of these compounds was not addressed.



(88) R = C₆H₅

(89) R = *c*-C₆H₁₁

In a study of anticonvulsant agents, the (*S*)-benzene ring analog (90) was somewhat more potent in a mouse assay than was the (*S*)-cyclohexane analog (91) (56). There was



(90) R = C₆H₅

(91) R = *c*-C₆H₁₁

only a slight difference in potency between (*R*)- and (*S*)-(90). The (*R*)-enantiomer of (91) was not reported.

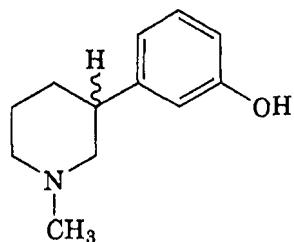
5 ALTERATION OF STEREOCHEMISTRY AND DESIGN OF STEREOISOMERS AND GEOMETRIC ISOMERS

The earlier, almost universally accepted belief that if one enantiomer of a chiral molecule demonstrates pharmacological activity, the other enantiomer will be pharmacologically inert, is not valid. It must be anticipated that all stereoisomers of an organic molecule will exhibit pharmacological effects, frequently widely different and unpredictable. Many examples of qualitative and quantitative differences in metabolism of enantiomers are documented (57).

(±)-3-(3-Hydroxyphenyl)-*N*-*n*-propylpiperidine (3-PPP, 92) was originally described (58) as having highly selective activity at dopaminergic autoreceptors.

At high doses (*R*)-(92) selectively stimulated presynaptic dopaminergic receptor sites, whereas at lower doses it selectively stimulated postsynaptic receptor sites (59). In contrast, the (*S*)-enantiomer stimulated presynaptic dopamine receptors and at the same dose level, it blocked postsynaptic dopamine recep-

37

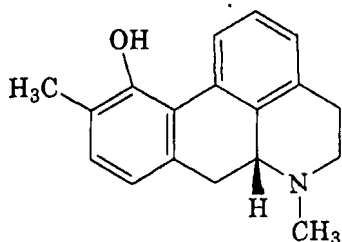


(92)

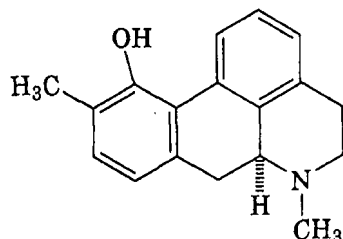
tors. Thus, this enantiomer exhibits a bifunctional mode of dopaminergic attenuation: that of presynaptic agonism and postsynaptic antagonism. The observed pharmacological effects of the racemic modification are the sum total of the complex activities of the two enantiomers, and the pharmacology of racemic 3PPP is not an accurate reflection of the pharmacological properties of the individual enantiomers. The contemporary literature strongly reflects the philosophy that pharmacological testing only of a racemic mixture is inadequate and may be misleading.

(*R*)-(-)-11-Hydroxy-10-methylaporphine (93) is a highly selective serotonergic 5HT₁ agonist (60).

Remarkably, the (*S*)-enantiomer (94) is a potent antagonist at this same subpopulation of serotonin receptors (guinea pig ileum prep-



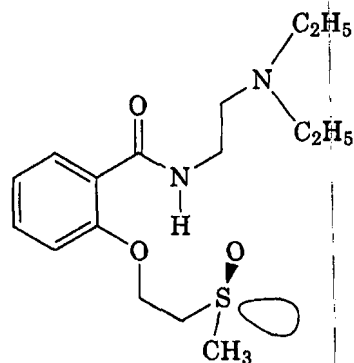
(93)



(94)

aration) (61). Both enantiomers bind strongly to 5HT₁ receptors from rat forebrain membrane. The phenomenon of enantiomers that possess opposite effects (agonist-antagonist) at the same receptor, once considered to be extremely rare, has recently been noted more often, probably because of the increasing recognition by medicinal chemists and pharmacologists that each member of an enantiomeric pair may possess its own unique and unpredictable pharmacology.

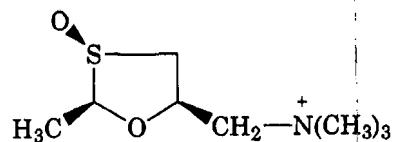
In addition to stereochemistry about a carbon center, other potentially chiral atoms offer possibilities for pharmacological significance. Agastroprokinetic compound (95) with



(95)

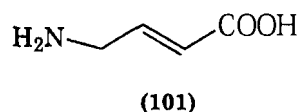
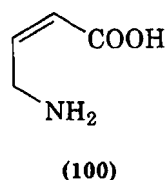
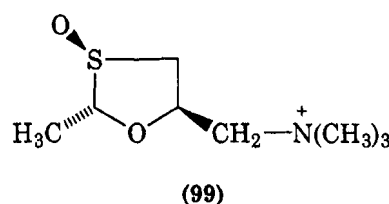
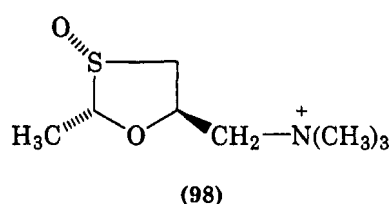
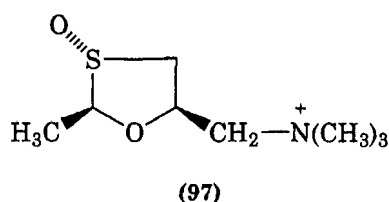
serotonergic activity bears a chiral sulfoxide moiety (62). The enantiomers are equipotent, but the (*S*)-enantiomer demonstrates a greater intrinsic activity than that of the (*R*)-enantiomer.

Casy (63) cited pharmacological differences between stereoisomers of chiral sulfoxide moieties in cholinergic oxathiolane congeners (96-99) of muscarine.



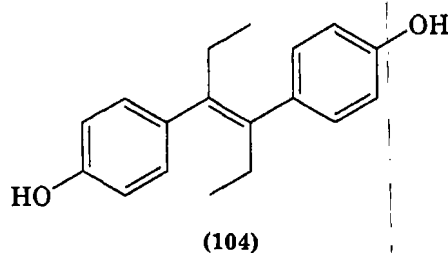
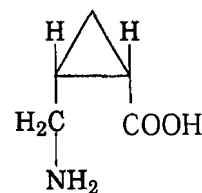
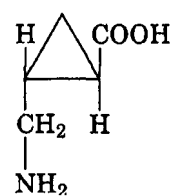
(96)

cis- and trans-4Aminocrotonic acids (100) and (101) were prepared (64) as congeners of γ -aminobutyric acid (GABA) (6).

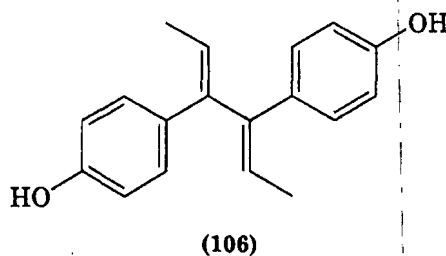
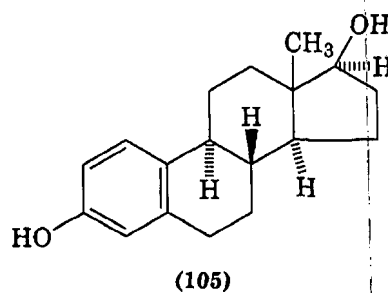


The folded 2-isomer (100) was inactive in assays for GABA agonism, whereas the extended E-isomer (101) was active. These data demonstrate biological differences of geometric isomers, which in turn involve a parameter discussed previously: imposition of a degree of structural rigidity on the molecule. A strategy analogous to this *E/Z* olefinic GABA congener design addressed *cis*- and *trans*-1,2-disubstituted cyclopropane derivatives (102) and (103), whose relative effects at GABA receptors paralleled those of the olefinic derivatives (65).

The E-isomer of the diethylstilbestrol structure (104) has 10 times the estrogenic potency of the *Z*-isomer; this effect has been rationalized from the conclusion that the E-

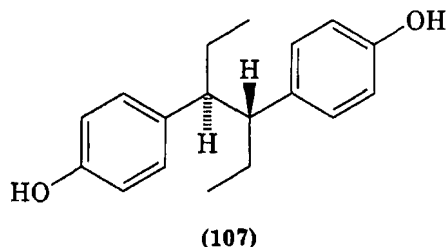


geometric isomer is an open-chain analog of the natural estrogen estradiol (105) (66). In dienestrol (106), the geometric isomerism possible with olefinic moieties has been further



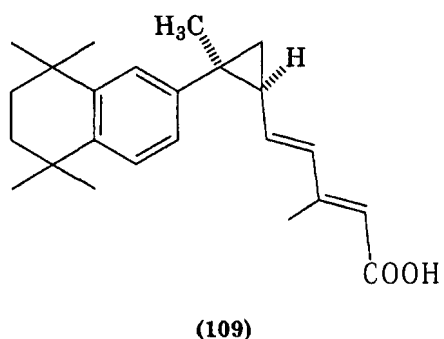
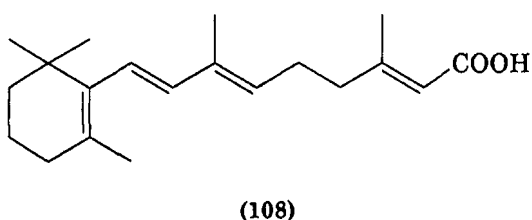
exploited to achieve a similar kind of open-chain analogy to the steroid ring system as in diethylstilbestrol, and a high level of estrogenic activity results.

Hexestrol (107), the saturated congener of



diethylstilbestrol (104), is the meso-form of the molecule. It has the greatest estrogenic potency of the three possible stereoisomers; however, it is less potent than diethylstilbestrol (67).

A partial restriction of side-chain flexibility in retinoic acid (108) was achieved by incorporating portions of the side chain into a benzene ring and a cyclopropane ring (109) (68).

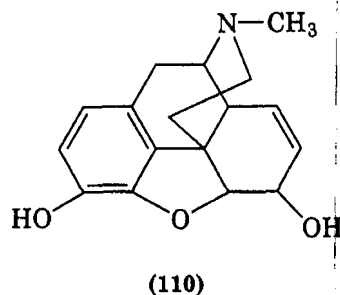


Introduction of the cyclopropane ring changes the corresponding trans-olefinic moiety of (108) to a cisoid disposition in (109), thus changing the overall steric disposition of the side chain. Moreover, the cyclopropane ring introduces chirality into the molecule. The (*S,S*)-enantiomer shown is a potent reti-

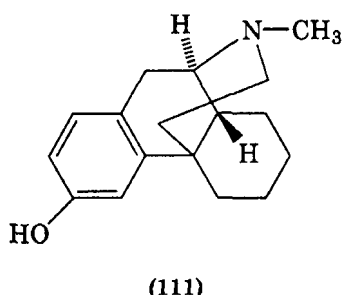
noid X-receptor ligand and it is inactive at the retinoic acid receptor, whereas the (*R,R*)-enantiomer is an extremely weak agonist at the retinoid X-receptor, although it has some effect at the retinoic acid receptor. Thus, the molecular modifications shown in (109) result in selectivity of action at these two receptors.

6 FRAGMENTS OF THE LEAD MOLECULE

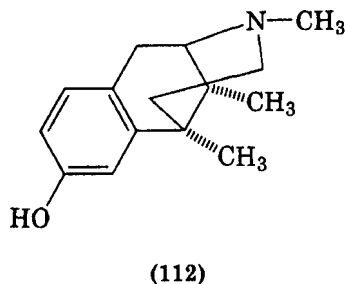
Design of fragments of a lead molecule is based on the premise that some lead molecules, especially polycyclic natural products, may be much more structurally complex than is necessary for optimal pharmacologic effect. It is hypothesized that a pharmacophoric moiety may be buried within the complex structure of the lead compound and, if this pharmacophore can be clearly defined, it may be possible to "dissect" it out chemically. The result may be biologically active, simpler molecules that may themselves be used as leads in further analog design. A bond disconnection strategy may be employed in which bonds in the polycyclic structure are broken or removed to destroy one or more of the rings. The result may be a valuable drug that is more accessible (through chemical synthesis) than the original lead molecule. A possible disadvantage to this strategy of analog design is that the greater flexibility that is introduced into a rigid molecule may compromise or destroy the conformational integrity that may have existed in the pharmacophoric portion, at the expense of activity and/or potency. There may be a similar destruction of chiral centers, which may be undesirable. Morphine (110) typifies a lead molecule for which fragment analog design has been used.



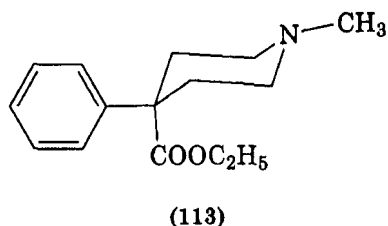
The analgesic preceptor pharmacophore of morphine has been defined (69) as comprising the basic nitrogen atom, the aromatic ring located three carbon atoms from the nitrogen, and a quaternary carbon adjacent to the aromatic ring, which provides a region of molecular bulk. A bond disconnection strategy involved disruption of the hydrofuran ring to give rise to morphinan derivatives [e.g., levorphanol (111)], whose pharmacologic effects



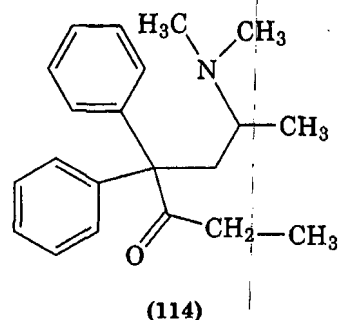
closely parallel those of morphine (70). Further simplification of the morphine ring system led to benzomorphan derivatives, typified by metazocine (112), in which morphinelike



analgesic activity is retained. Finally, 4-phenylpiperidine derivatives typified by meperidine (113) and the nonheterocyclic system



methadone (114) present the putative analgesic pharmacophore with a seemingly minimal number of extraneous atoms. These simple compounds retain opioid analgesic activity. It



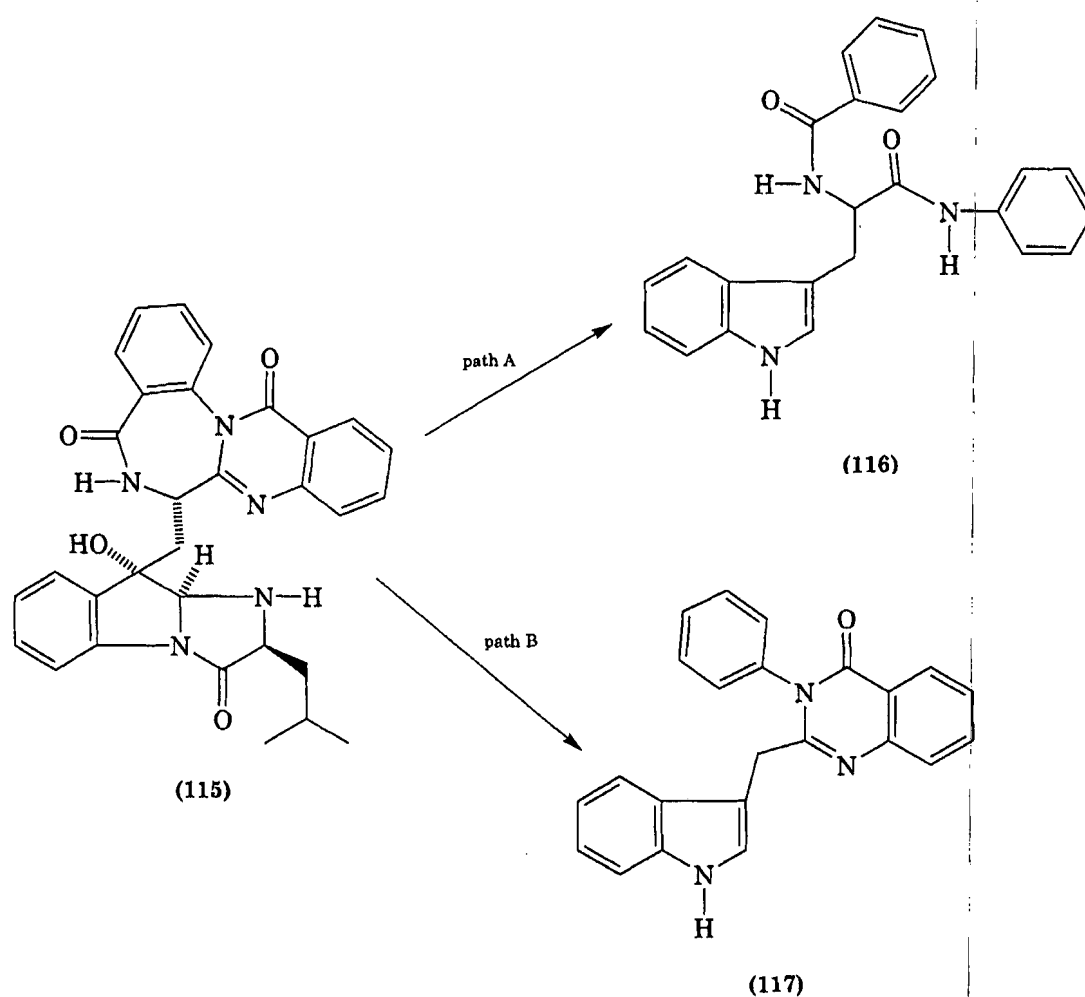
must be noted, however, that the discovery of analgesic activity in 4-phenylpiperidine derivatives was not a result of a systematic structure-activity study of the morphine molecule, but was serendipitous (71).

Asperlicin (115), a potent cholecystokinin-A antagonist, was subjected to two different bond disconnection strategies, as indicated (72).

Path A leads to tryptophan derivatives (116), some of which are potent cholecystokinin antagonists (73). Some quinazolinone derivatives (117) of disconnection pathway B showed extremely high potency and excellent selectivity as cholecystokinin-B receptor subtype ligands (44). A combination of X-ray crystallography and computational chemistry was used in the decision-making process in the bond disconnection (44) and in the design of the specific target molecules.

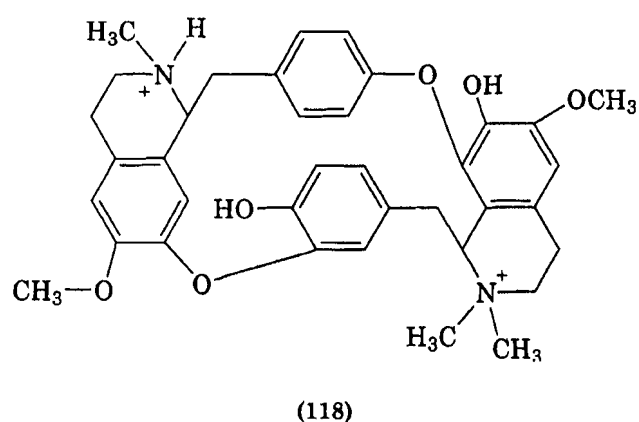
The myoneural-blocking pharmacophore in d-tubocurarine (118) was speculated to include the two cationic heads (the quaternary ammonium group and the protonated tertiary amine); the cationic heads are separated by 10 atoms (nine carbons and one oxygen).

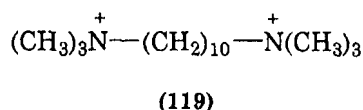
Based on these parameters, a simple molecule, decamethonium (119), in which two trimethylammonium heads are separated by 10 methylene groups to approximate the internitrogen distance in d-tubocurarine, was designed independently by two groups of investigators (74, 75). This synthetic fragment/analog of d-tubocurarine exhibits a high degree of potency and activity in production of flaccid paralysis of skeletal muscles, superficially like that of the lead compound. However, the myoneural blockade from d-tubocurarine is of the nondepolarizing type, whereas decamethonium produces a depolarizing skel-



etal muscle blockade. This fundamental mechanistic difference is probably attributed, at least in part, to the flexibility of the decamethonium molecule compared with that of d-tubocurarine. There is a considerable differ-

ence in the spectrum and severity of side effects and in the technique of employment of these two drugs in clinical practice. In all types of analog design, changes in chemical structure may result in unanticipated changes in

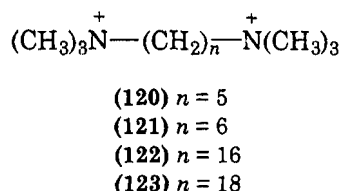




mechanism of action, even though the chemical nature of the pharmacophore may not be altered.

7 VARIATION IN INTERATOMIC DISTANCES

Alteration of distances between portions of the pharmacophore of a molecule (or even between other portions of the molecule) may produce profound qualitative and/or quantitative changes in pharmacological actions. In α,ω -bis-trimethylammonium polymethylene compounds (120-123), maximal activity for

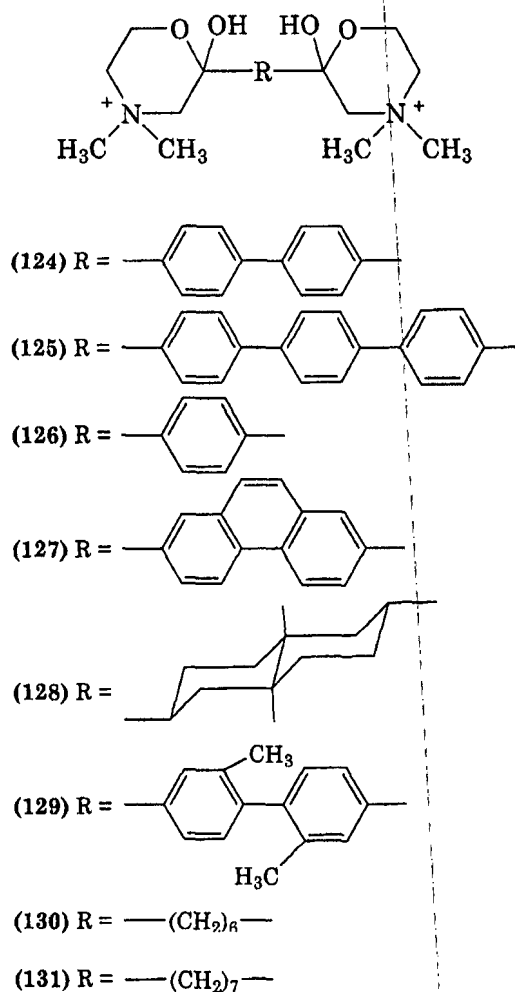


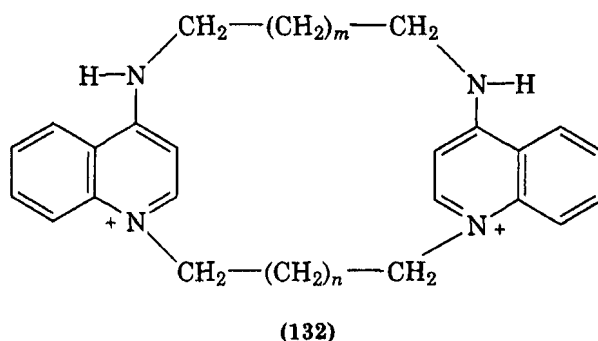
blockade of autonomic ganglia (nicotinic N_2 receptors) resides in those derivatives where $n = 5$ or 6 (compounds 120 and 121) (76, 77).

Ganglionic effects drop drastically when $n = 4$ or 7. These observations have been rationalized as being a reflection of attainment of optimal interquaternary distance in the penta- and hexamethylene congeners, for optimal interaction with ganglionic receptor subsites. Remarkably, as the number of methylene groups in (120) is greatly increased, a high level of ganglionic-blocking potency returns. The hexadecyl and octadecyl congeners (122) and (123) are approximately four times as potent at autonomic ganglia as the penta- and hexamethylene compounds. As was mentioned previously, polymethylene bis-quaternary systems, in which the cationic heads are separated by 10 methylene groups, have potent effects at myoneural junctions (nicotinic N_1 receptors) and have little ability to affect nerve activity at autonomic ganglia. Thus, extension of a bis-quaternary polyalkylene molecule from five or six methylenes to 10 pro-

duces a pharmacological change from ganglionic blockade to myoneural blockade, and further extension to 16-18 methylenes results in loss of myoneural effects and a return of ganglionic blocking action.

Hemicholinium (124) competitively inhibits the high affinity, sodium-dependent uptake of choline into the nerve terminal (the rate-determining step in acetylcholine synthesis in the nerve terminal), thus depleting stores of acetylcholine and producing slow onset, long-duration myoneural blockade (78, 79). In a series of congeners of hemicholinium, the central biphenyl portion of the molecule was changed to terphenyl (125) and to *p*-phenylene (126). Both changes resulted in profound loss of the myoneural blockade characteristic of hemicholinium (68). This result was ascribed to alteration of the proposed opti-



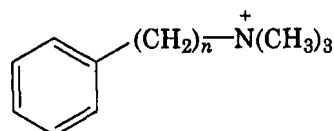


imum interquaternary nitrogen distance of 14.4 Å in hemicholinium (124), to 18.4 Å in the terphenyl analog, and to 10.2 Å in the *p*-phenylene analog.

The central biphenyl spacer in hemicholinium was changed to a 2,7-disubstituted phenanthrene (127), *trans,trans*-4,4'-bicyclohexyl (128), and 2,2'-dimethylbiphenyl (129). In all three of these systems the 14.4-Å interquaternary distance found in hemicholinium was maintained; all of these congeners were qualitatively and quantitatively similar to hemicholinium in inhibition of neuromuscular transmission. Conformational analysis of the **polyalkylene** congeners (130) and (131) demonstrated that, when the flexible polyalkylene chain is maximally extended and is in a staggered conformation, the interquaternary distance in the hexamethylene congener (130) is approximately 14 Å, and in the **heptamethylene** congener (131) it is approximately 15 Å. Both compounds exhibited hemicholinium-like inhibition of neuromuscular transmission, although they were less potent than hemicholinium (80). This diminution of potency might be ascribed to the compromising of another structural parameter in the hemicholinium molecule: the rigidity of the central biphenyl spacer unit that maintains the inter-nitrogen distance.

Replacement of the benzene ring linkers of (82) (see above) by alkyl linkers (structure 132) permitted retention of blocking activity on calcium-activated potassium channels (81). The most potent member of the series studied was that in which $m = n = 3$. In this compound the two respective internitrogen distances closely approximate those in the benzene ring-linked compound (82).

In a series of phenylalkylenetrimethylammonium derivatives (133–136), nicotinic agonism is maximal when $n = 3$ (compound 136).



(133) $n = 0$

(134) $n = 1$

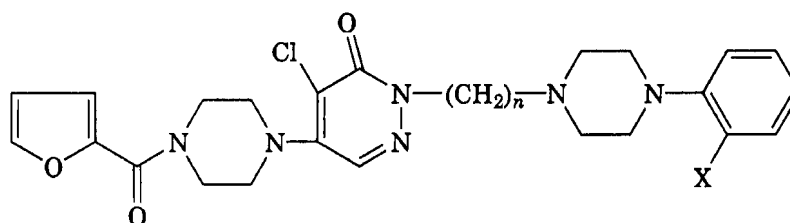
(135) $n = 2$

(136) $n = 3$

It was concluded (82) that a moiety (here, a benzene ring) with high electron density three or four single bond lengths (~ 6 Å) from the **cationic** center is a requirement for nicotinic agonism in the series. These conclusions may be compromised by the fact that the **alkylene** series was not extended beyond the **three-carbon** spacer chain. Therefore, it is not known whether the four-carbon **homolog** would display greater or lesser potency than that of the three-carbon molecule. Peculiarly, the first two members of the series have only very weak nicotine-like activity in the presence of atropine.

A series of compounds, illustrated by (137), was evaluated for *in vitro* affinity for α_1 and α_2 -adrenoceptors by radioligand-binding assays (83). All compounds showed good affinities for the α_1 adrenoceptor, with K_i values in the low nanomolar range. The polymethylene chain spacer between **furoylpiperazinylpyradizine** and aryl **piperazine** moieties was shown to influence the affinity and selectivity of these compounds. A gradual increase in **affinity** for the α_1 adrenoceptor was observed, by length-

44



(137)

ening the polymethylene chain, up to a maximum of seven carbon atoms.

The α_2/α_1 ratio of adrenoceptor-binding affinities for the series of compounds did not parallel the α , adrenoceptor-binding affinities for the series, although all of the seven (C_1 - C_7) congeners of (137) had somewhat more affinity for the α , receptor.

REFERENCES

1. I. Langmuir, *J. Am. Chem. Soc.*, **41**, 868 (1919).
2. C. W. Thornber, *Chem. Soc. Rev.*, **8**, 563 (1979).
3. G. A. Patani and E. G. La Voie, *Chem. Rev.*, **96**, 3147 (1996).
4. A. Burger, *Med. Chem. Res.*, **4**, 89 (1994).
5. P. Floersheim, E. Pombo-Villar, and G. Shapiro, *Chimia*, **46**, 323 (1992).
6. P. Krosgaard-Larsen, H. Hjeds, E. Falk, F. S. Jørgenson, and L. Nielsen, *Adv. Drug Res.*, **17**, 38 (1988).
7. H. Hashiguchi and H. Takahashi, *Mol. Pharmacol.*, **13**, 362 (1977).
8. K. Anderson, A. Kuruvilla, N. Uretsky, and D. Miller, *J. Med. Chem.*, **24**, 683 (1981).
9. R. J. Baldessarini in A. G. Gilman, L. S. Goodman, T. W. Rall, and F. Murad, Eds., *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 7th ed., Macmillan, New York, 1985, pp. 393-397, 414.
10. S. I. Ankier in G. P. Ellis and G. B. West, Eds., *Progress in Medicinal Chemistry*, Vol. 23, Elsevier, Amsterdam, 1986, p. 121.
11. E. I. Isaacson in J. N. Delgado and W. A. Remers, Eds., *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 10th ed., Lippincott-Raven, Philadelphia, 1998, p. 473.
12. L. Otsuki, J. Ishiko, M. Sakai, K. Shiniahara, and T. Momiyama, *Pharmacometrics (Tokyo)*, **6**, 973 (1972).
13. M. Protiva, M. Rajsner, V. Seidlova, E. Adlerova, and Z. Vejdelek, *Experientia*, **18**, 326 (1962).
14. S. Yous, J. Andrieux, H. E. Howell, P. J. Morgan, P. Reynard, B. Pfeiffer, D. Lessieur, and B. Guardiola-Lemaitre, *J. Med. Chem.*, **35**, 1484 (1992).
15. S. M. Bromidge, F. Brown, F. Cassidy, M. S. G. Clark, S. Dabbs, M. S. Hadley, J. Hawkins, J. M. Loudon, C. B. Naylor, B. S. Orlek, and G. J. Riley, *J. Med. Chem.*, **40**, 4265 (1997).
16. P. Sauerberg, J. W. Kindtler, L. Nielsen, M. J. Sheardown, and T. Honoré, *J. Med. Chem.*, **34**, 687 (1991).
17. M. Hollmann, A. O'Shea-Greenfield, S. W. Rogers, and S. Heinemann, *Nature*, **342**, 643 (1989).
18. F. H. Bellevue, M. L. Boahbedason, R. H. Wu, R. A. Casero Jr., D. Rattendi, C. J. Bacchi, and P. M. Wooster, *Bioorg. Med. Chem. Lett.*, **6**, 2765 (1996).
19. P. M. Wooster, *Annu. Rep. Med. Chem.*, **36**, 99 (2001).
20. E. Mutschler and G. Lambrecht in E. Ariens, W. Soudjin, and P. B. M. W. M. Timmermans, Eds., *Stereochemistry and Biological Activity of Drugs*, Blackwell, Oxford, UK, 1983, p. 65.
21. J. G. Cannon in E. Jucker, Ed., *Progress in Drug Research*, Vol. 29, Birkhauser Verlag, Basel, Switzerland, 1985, pp. 324-334.
22. C. Melchiorre, A. Chiarini, M. Gianella, D. Giardina, W. Quaglia, and V. Tumiatti in V. Claassen, Ed., *Trends in Drug Research*, Vol. 13, Elsevier, Amsterdam, 1990, pp. 37-48.
23. F. D. King, A. M. Brown, L. M. Gaster, A. J. Kaumann, A. D. Medhurst, S. G. Parker, A. A. Parsons, T. L. Patch, and P. Raval, *J. Med. Chem.*, **36**, 1918 (1993).
24. P. S. Portoghese, A. A. Mikhail, and H. J. Kupferberg, *J. Med. Chem.*, **11**, 219 (1968).
25. R. M. Moriarty, L. A. Enache, L. Zhao, R. Giliardi, M. V. Mattson, and O. Prakash, *J. Med. Chem.*, **41**, 468 (1998).

us

26. C. M. Bertha, B. J. Vilner, M. V. Mattson, W. D. Bowen, K. Becketts, H. Xu, R. B. Rothman, J. L. Flippen-Anderson, and K. C. Rice, *J. Med. Chem.*, **38**, 4776 (1995).
27. C. Y. Chiou, J. P. Long, J. G. Cannon, and P. D. Armstrong, *J. Pharmacol. Exp. Ther.*, **166**, 243 (1969).
28. J. G. Cannon and P. D. Armstrong, *J. Med. Chem.*, **13**, 1037 (1970).
29. J. G. Cannon, T. Lee, V. Sankaran, and J. P. Long, *J. Med. Chem.*, **18**, 1027 (1975).
30. P. W. Ehrhardt, R. J. Gorczynski, and W. G. Anderson, *J. Med. Chem.*, **22**, 907 (1975).
31. R. R. Ruffolo in G. Kunos, Ed., *Adrenoceptors and Catecholamine Action, Part B*, Wiley-Interscience, New York, 1983, pp. 10-11.
32. H. J. Komiskey, J. F. Bossart, D. D. Miller, and P. N. Patel, *Proc. Natl. Acad. Sci. USA*, **75**, 2641 (1978).
33. E. E. Smissman and W. H. Gastrock, *J. Med. Chem.*, **11**, 860 (1968).
34. J. A. Monn, M. J. Valli, S. M. Massy, M. M. Hansen, T. J. Kress, J. P. Wępsiec, A. R. Harkness, J. L. Grutsch Jr., R. A. Wright, B. G. Johnson, S. L. Andrés, A. Kingston, R. Tomlinson, R. Lewis, K. R. Griffey, J. P. Tizzano, and D. D. Schoepp, *J. Med. Chem.*, **42**, 1027 (1999).
35. J. F. McCarthy, J. G. Cannon, and J. P. Buckley, *J. Pharm. Sci.*, **52**, 1168 (1963).
36. J. F. McCarthy, J. G. Cannon, J. P. Buckley, and W. J. Kinnard, *J. Med. Chem.*, **7**, 72 (1964).
37. A. Burger and G. R. Bedford, *J. Med. Chem.*, **6**, 402 (1963).
38. M. V. Koch, J. G. Cannon, and A. M. Burkman, *J. Med. Chem.*, **11**, 977 (1968).
39. E. R. Atkinson, F. J. Bullock, F. E. Granchelli, S. Archer, F. J. Rosenberg, D. G. Teiger, and F. C. Nachod, *J. Med. Chem.*, **18**, 1000 (1975).
40. J. G. Cannon in ref. 21, pp. 309-310.
41. J. G. Cannon, F.-L. Hsu, J. P. Long, J. R. Flynn, B. Costall, and R. J. Naylor, *J. Med. Chem.*, **21**, 248 (1978).
42. J. L. Ginos and F. C. Brown, *J. Med. Chem.*, **21**, 155 (1978).
43. J. L. Ginos, G. C. Cotzias, and D. Doroski, *J. Med. Chem.*, **21**, 160 (1978).
44. M. J. Yu, J. R. McCowan, N. R. Mason, J. B. Deeter, and L. G. Mendelsohn, *J. Med. Chem.*, **35**, 2534 (1992).
45. K.-L. Yu, J. J. Bronson, H. Yang, A. Patick, M. Alam, V. Brankovan, R. Datema, M. J. M. Hitchcock, and J. C. Martin, *J. Med. Chem.*, **35**, 2958 (1992).
46. G. C. Crawley, R. I. Dowell, P. N. Edwards, S. J. Foster, R. M. McMillan, E. R. H. Walker, and D. Waterson, *J. Med. Chem.*, **35**, 2600 (1992).
47. H.-S. Kim, Y. Nagai, K. Ono, K. Begum, Y. Wataya, Y. Hamada, K. Tsuchiya, A. Masuyama, M. Nojima, and K. J. McCullough, *J. Med. Chem.*, **44**, 2357 (2001).
48. R. H. Uloth, J. R. Kirk, W. A. Gould, and A. A. Larsen, *J. Med. Chem.*, **9**, 88 (1966).
49. J. Campos-Rosa, D. Galanakis, A. Piergentili, K. Bhandari, C. R. Ganellin, P. M. Dunn, and D. H. Jenkinson, *J. Med. Chem.*, **43**, 420 (2000).
50. J. E. Macor, C. B. Fox, C. Johnson, B. K. Koe, L. A. Label, and S. H. Zorn, *J. Med. Chem.*, **35**, 3625 (1992).
51. R. A. Glennon in J. G. Cannon, Ed., *Advances in CNS Drug-Receptor Interactions*, JAI Press, Greenwich, CT, 1991, pp. 147-148.
52. B. B. Hoffman in J. G. Hardman and L. E. Limbird, Eds., *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th ed., McGraw-Hill, New York, 2001, p. 218.
53. R. L. Johnson in J. N. Delgado and W. A. Remers, Eds., *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 10th ed., Lippincott-Raven, Philadelphia, 1998, p. 493.
54. (a) A. M. Lands, J. R. Lewis, and V. L. Nash, *J. Pharmacol. Exp. Ther.*, **83**, 253 (1945); (b) A. M. Lands, V. L. Nash, and B. L. Dertlinger, *J. Pharmacol. Exp. Ther.*, **89**, 382 (1947); (c) D. F. Marsh and D. A. Herring, *J. Pharmacol. Exp. Ther.*, **97**, 68 (1949); (d) E. J. Fellows, E. Macko, and R. A. McLean, *J. Pharmacol. Exp. Ther.*, **100**, 267 (1950).
55. M. D. Mashkovsky, L. N. Yakhoutov, M. E. Kaminka, and E. E. Mikhlin in E. Jucker, Ed., *Progress in Drug Research*, Vol. 27, Birkhauser Verlag, Basel, Switzerland, 1983, pp. 35-38.
56. P. Pevarello, A. Bonsignori, P. Dostert, F. Heidemperger, V. Pinciroli, M. Colombo, R. A. McArthur, P. Salvati, C. Post, R. G. Fariello, and M. Varasi, *J. Med. Chem.*, **41**, 579 (1998).
57. A. F. Casy, *The Steric Factor in Medicinal Chemistry. Dissymmetric Probes of Pharmacological Receptors*, Plenum, New York/London, 1993, pp. 52-61.
58. S. Hjorth, A. Carlsson, H. Wikstrom, P. Lindberg, D. Sanchez, U. Hacksell, L.-E. Arvidsson, O. Svensson, and J. L. G. Nilsson, *Life Sci.*, **28**, 1225 (1981).
59. H. Wikstrom, D. Sanchez, P. Lindberg, U. Hacksell, L.-E. Arvidsson, A. M. Johansson, S.-O. Thorberg, J. L. G. Nilsson, K. Svensson, S.

u6

- Hjorth, D. Clark, and A. Carlsson, *J. Med. Chem.*, **27**, 1030 (1984).
60. J. G. Cannon, P. Mohan, J. Bojarski, J. P. Long, R. K. Bhatnagar, P. A. Leonard, J. R. Flynn, and T. K. Chatterjee, *J. Med. Chem.*, **31**, 313 (1988).
61. J. G. Cannon, S. T. Moe, and J. P. Long, *Chirality*, **3**, 19 (1991).
62. B. T. Butler, G. Silvey, D. M. Houston, D. R. Borcharding, V. L. Vaughn, A. T. McPhail, D. M. Radzik, H. Wynberg, W. Ten Hoeve, E. Van Echten, N. K. Ahmed, and M. D. Linnik, *Chirality*, **4**, 155 (1992).
63. See ref. 57, pp. 244-247, see also M. Pigini, L. Brasili, M. Gianella, and F. Gualtieri, *Eur. J. Med. Chem.*, **16**, 415 (1981).
64. G. A. Johnston, D. R. Curtis, P. M. Beart, C. J. A. Game, R. M. McColloch, and B. Twitchin, *J. Neurochem.*, **24**, 157 (1975).
65. R. D. Allan, D. R. Curtis, P. M. Headley, G. A. Johnson, D. Lodge, and B. Twitchen, *J. Neurochem.*, **34**, 652 (1980).
66. D. S. Fullerton in R. F. Doerge, Ed., *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 8th ed., Lippincott, Philadelphia, 1982, p. 670.
67. R. W. Brueggemeier, D. D. Miller, and D. T. Wiatak in W. O. Foye, T. L. Lemke, and D. A. Williams, Eds., *Principles of Medicinal Chemistry*, 4th ed., Williams & Wilkins, Media, PA, 1995, p. 474.
68. V. Vuligonda, S. M. Thacher, and R. A. S. Chandraratna, *J. Med. Chem.*, **44**, 2298 (2001).
69. T. Nogrady, *Medicinal Chemistry*, 2nd ed., Oxford University Press, New York, 1988, p. 457.
70. J. H. Jaffe and W. R. Martin in ref. 9, p. 513.
71. J. V. Aldrich in M. E. Wolff, Ed., *Burger's Medicinal Chemistry and Drug Discovery*, 5th ed., Vol. 3, Wiley-Interscience, New York, 1996, p. 357.
72. M. J. Yu, K. J. Thrasher, J. R. McCowan, N. R. Mason, and L. G. Mendelsohn, *J. Med. Chem.*, **34**, 1505 (1991).
73. F. W. Hahne, R. T. Jensen, G. F. Lemp, and J. D. Gardner, *Proc. Natl. Acad. Sci. USA*, **78**, 6304 (1981).
74. R. B. Barlow and H. R. Ing, *Nature*, **161**, 718 (1948).
75. W. D. M. Paton and E. J. Zaimis, *Nature*, **161**, 718 (1948).
76. D. J. Triggle, *Neurotransmitter-Receptor Interactions*, Academic Press, New York, 1971, p. 360.
77. V. Trcka in D. A. Kharkevich, Ed., *Handbook of Experimental Pharmacology*, Vol. 53, Springer-Verlag, New York, 1980, p. 138.
78. J. G. Cannon, T. M.-L. Lee, A. M. Nyanda, B. Bhattacharyya, and J. P. Long, *Drug Des. Devel.*, **1**, 209 (1987).
79. J. G. Cannon, *Med Res. Rev.*, **14**, 505 (1994).
80. J. G. Cannon, T. M.-L. Lee, Y.-a. Chang, A. M. Nyanda, B. Bhattacharyya, J. R. Flynn, T. Chatterjee, R. K. Bhatnagar, and J. P. Long, *Pharm. Res.*, **5**, 359 (1988).
81. J.-Q. Chen, D. Galanakis, C. R. Ganellin, P. M. Dunn, and D. H. Jenkinson, *J. Med. Chem.*, **43**, 3478 (2000).
82. W. C. Holland in E. J. Ariens, Ed., *Proceedings of the Third International Pharmacological Meeting*, Vol. 7, Pergamon, Oxford, UK, 1966, pp. 295-303 K.C. Wong and J. P. Long, *J. Pharmacol. Exp. Ther.*, **137**, 70 (1962).
83. R. Barbaro, L. Betti, F. Corelli, G. Giannacinni, L. Maccari, F. Manetti, G. Straoaggetti, and S. Corsano, *J. Med. Chem.*, **44**, 2118 (2001).

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