

Clarke, Modet & C^o

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COLOMBIA

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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-143959- 00012-0000

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Tra. 11 PATENTEIYII
Act. 523 RESPUESTA

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Eve: 378 FASENACIONALI
Folios: 41

Re: Expediente No. 10.143.959 —

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. 22083 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 7 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 DEL ÁCIDO OLEANÓLICO CON AMINO Y OTRAS MODIFICACIONES EN C-17**”

- Se canceló la reivindicación 1 y se reemplazó con la antigua reivindicación 2 con el fin de superar la objeción hecha por el Examinador en cuanto a que la reivindicación principal no era concisa debido a que encerraba un gran número de compuestos que pueden no tener soporte en la descripción. La reivindicación más amplia es ahora la antigua reivindicación 2, la cual se ha limitado.

- La cancelación de la reivindicación 1 también elimina las variables R₁', R₂' y R₃. Así esto por supuesto aborda las objeciones del examinador sobre la forma como estas variables no eran claras.
- La cancelación de la reivindicación 1 también elimina la frase "sustituyente convertible *in vivo* en hidrógeno" y de este modo solicitamos se tenga por superada la objeción del examinador relacionada con la aparente falta de claridad con respecto a esta frase.
- La cancelación de la reivindicación 1 también cancela las variables X₁ y X₂, abordando también de esta forma las objeciones del examinador con relación a la misma aparente falta de claridad.
- La frase "o una versión sustituida de cualquiera de estos grupos" se ha eliminado de las reivindicaciones 2 y 3. Ésta se ha reemplazado con los grupos más específicos: -C(O)NH₂, -C(O)NH-alquil_(C≤11), -C(O)NH-alquenal_(C≤11), -C(O)-dialquilamino_(C≤11), -C(O)NH-aril_(C≤11), -C(O)NH-aralquil_(C≤11), -C(O)-heteroaril_(C≤11), -CO₂-alquil_(C≤11), -CO₂-alquenal_(C≤11), y -CO₂-aralquil_(C≤11), así como la frase "o una versión de cualquiera de estos grupos donde uno o más átomos de hidrógeno se reemplazan con un fluoro, hidroxilo o ciano".
- También se eliminaron los grupos heteroaril_(C≤12), heteroaralquil_(C≤12), alcoxi_(C≤12), alquenaloxi_(C≤12), alquiloxi_(C≤12), ariloxi_(C≤12), aralcoxi_(C≤12), heteroariloxi_(C≤12), heteroaralcoxi_(C≤12), tioacil_(C≤12), alquenalilsulfonil_(C≤12), y alquililsulfonil_(C≤12).
- Los grupos restantes están bien definidos y en la sección de definiciones químicas (ver páginas 44-53) y ciertamente no suministran nada más allá de generalización razonable de estos varios compuestos que fueron preparados y ensayados por el solicitante en la descripción.
- Como resultado de estos cambios dos de los compuestos en la reivindicación 7 no se cubren más por la reivindicación 2 y por lo tanto se movieron a la reivindicación 8.

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. En particular, el examinador observa que los compuestos reivindicados, que son derivados de ácidos oleanólicos, tienen la misma estructura básica que los compuestos de D1 y D2, con la principal diferencia que es la naturaleza del sustituyente en lugar de Y. El examinador indica que en D1 este puede ser $-C(O)OMe$, mientras que la antigua reivindicación 1 cubría $-OC(O)R$. A partir de esto el examinador concluye que sería obvio para un experto en la materia hacer referencia a las enseñanzas de D2 con el fin de obtener los compuestos alternos a los compuestos divulgados en D1 y con el fin de llegar a la presente invención.

El solicitante no está de acuerdo con esta conclusión porque no se aprecia el significado del cambio en la posición C-17. Además, el solicitante indica que las reivindicaciones modificadas no cubren más los derivados que tienen un grupo $-OC(O)R$ (aciloxi) en la posición C-17. Por el contrario, estas reivindicaciones cubren los residuos Y unidos en la posición C-17 bien sea un grupo $-NR_1R_2$ o un grupo $-OH$. En contraste, D1 y D2 sólo divulgan compuestos que tienen un átomo de carbono unido directamente a la posición C-17.

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 tienen un átomo de carbono en punto de unión a la posición C-17. Como tal, D1 no divulga ningún compuesto que tiene un heteroátomo unido a la posición C-17. En contraste, las reivindicaciones actuales requieren un $-NR_1R_2$ o un $-OH$ en esta posición.

Por su parte, D2 (*J. Med. Chem.*, 2000, 43, 4233-4246) divulga triterpenoides olean- y urs-1-en-3-uno con varios anillos modificados como agentes potenciales antiinflamatorios y quimiopreventivos de cáncer. Se puede ver a partir de la Tabla 1 de D2 que estos triterpenoides tienen los siguientes grupos funcionales presentes en la posición C-17: $-COOMe$, $-COOH$, $-CH_2OAc$, $-CH_2OH$ y $-CHO$. Como con D1, D2 no divulga compuestos que tienen un átomo de nitrógeno o un oxígeno unido a C-17. En particular, D2 no divulga ninguno de los residuos Y $-NR_1R_2$ y $-OH$.

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. La actividad de estos compuestos mostrada en esta tabla varía por varios órdenes de magnitud, aún cuando uno sólo se enfoca en estos compuestos con diferentes tipos de grupos carbonil en C-17.

Dadas las enormes diferencias en la actividad de los compuestos de la Tabla 7 de D1, es razonable asumir que el efecto de un oxígeno o un nitrógeno unido directamente a C-17 simplemente no se puede predecir. Esto es especialmente cierto en vista de las enseñanzas estándar en el campo, incluyendo *Química Medicinal de Burger y Descubrimiento de Droga*, 6^a ed. (copia del capítulo 16 de esta adjunta; en adelante Burger (2003):

“[U]na simple alteración estructural molecular puede influenciar varios parámetros estructurales y químicos” (página 689, columna de la izquierda, mitad)

También un grupo aciloxi, por ejemplo, $-\text{O}(\text{C}=\text{O})\text{H}$, no parece ser considerado como un bioisostero clásico o no clásico de un grupo ácido carboxílico, por ejemplo, $-(\text{C}=\text{O})\text{OH}$ (ver páginas 690/1, Tablas 16.1 y 16.2). Considere, por ejemplo, que cuando se hacen análogos de arelina (compuesto 16 en la página 693), el cual tiene un grupo éster metilo (como compuesto 115 de D1), que hace un aciloxi no fue considerado.

Dicho esto, aún si $-\text{C}(=\text{O})\text{OR}$ y $-\text{OC}(=\text{O})\text{R}$ *fuera*n considerados para ser bioisosteros, Burger (2003) enseña que

“los bioisosteros puede producir efectos biológicos opuestos” (página 690, columna de la izquierda, mitad: énfasis en original).

También, Burger (2003) concluye esta sección al indicar que

“Aunque la estrategia de reemplazo bioisotérico puede ser una herramienta poderosa y altamente productiva en diseño análogo, Thornbur (2) ha hecho énfasis en que los cambios físicos y químicos fundamentales se pueden esperar para resultar a partir de estas modificaciones moleculares, las cuales pueden profundamente afectar la acción farmacológica de las moléculas resultantes. Los factores que contribuyen incluye el cambio en el tamaño del átomo o grupo introducido, lo cual puede afectar la forma total y el tamaño de la molécula; cambios en los ángulos de unión; cambios en el coeficiente de partición; cambios en pK_a de la molécula; alteración de la reactividad química y la estabilidad química de la molécula, con alteración cualitativa y cuantitativa que la acompaña del metabolismo in vivo de la molécula; y cambio en la capacidad de unión de hidrógeno. Los resultados químicos y biológicos y el significado farmacológico de varios de estos factores son impredecibles y se deben determinar experimentalmente”. (página 694, columna de la derecha; énfasis adicionado).

En vista de esta imprevisibilidad y la posibilidad de efectos opuestos cuando un grupo se reemplaza con su bioisótero, los argumentos del Examinador con respecto a que sería obvio hacer cualquiera de los “compuestos alternos” reivindicaciones está claramente en desacuerdo con las enseñanzas en este campo.

Además, la química para hacer los compuestos reivindicaciones requiere un desarrollo significativo por parte de los inventores de la presente solicitud. En efecto, parecería que donde el examinador se enfoca en las similitudes entre $-C(=O)OMe$ vs. $-OC(=O)R$, el examinador está tratando los átomos en estos grupos como bloques de LEGO® que se puede reacomodar fácilmente sin consideración a limitantes sintéticas o la imprevisibilidad del arte. Los métodos resultantes que superan exitosamente los desafíos sintéticos se describen en detalle en las páginas 107-127 de la descripción. El solicitante respetuosamente manifiesta que estos métodos sintéticos solos justificarían el nivel inventivo para los compuestos reivindicados. El hecho que una cantidad significativa de los compuestos resultantes prometen candidatos clínicos además confirma que ellos no son obvios.

De manera importante, la presente solicitud suministra una cantidad sustancial de datos biológicos muy prometedores en un número representativo de compuestos novedosos y no obvios. Todos estos se pueden fácilmente distinguir de los compuestos descritos en el estado del arte por un heteroátomo unido directamente a la posición C-17, bien sea un grupo $-NR_1R_2$ o un grupo $-OH$. En ausencia de alguna guía o enseñanza de D1 y D2, cuando se consideran separados o en combinación, un experto en la materia no se vería motivado a introducir un residuo Y en la forma de un grupo $-NR_1R_2$ o $-OH$ en C-17. Y sin dicha enseñanza, sugerencia o motivación, un experto en la materia no llegaría a ninguno de los compuestos cubiertos por las presentes 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 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

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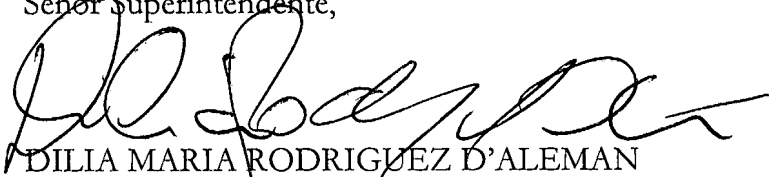
COLOMBIA

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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,

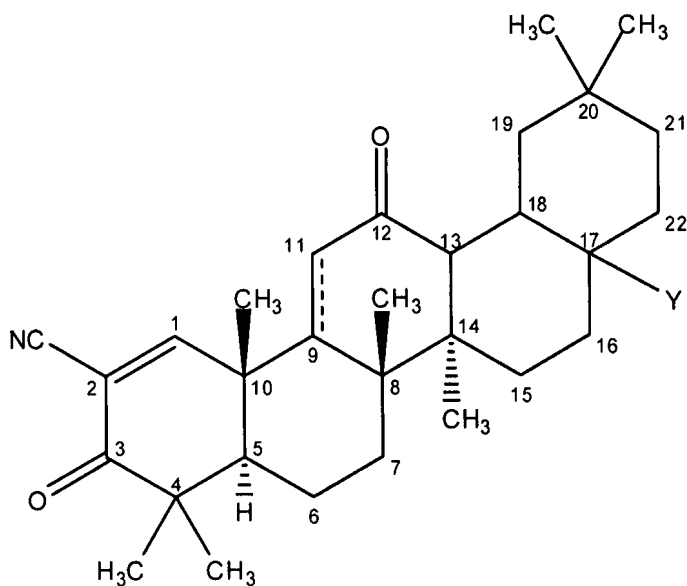


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TP 20824 CSJ
notificaciones@clarkemodet.com.co

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REIVINDICACIONES

1. Un compuesto de fórmula:



en donde:

Y es hidróxi o NR_1R_2 , en donde:

R_1 y R_2 son independientemente:

hidrógeno o hidróxi; o

alquil_(c≤12), alquenil_(c≤12), alquinil_(c≤12),

aril_(c≤12), aralquil_(c≤12), acil_(c≤12),

$-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NH}$ -alquil_(c≤11),

$-\text{C}(\text{O})\text{NH}$ -alquenil_(c≤11),

$-\text{C}(\text{O})$ -dialquilamino_(c≤11),

$-\text{C}(\text{O})\text{NH}$ -aril_(c≤11),

$-\text{C}(\text{O})\text{NH}$ -aralquil_(c≤11),

$-\text{C}(\text{O})$ -heteroaril_(c≤11),

$-\text{CO}_2$ -alquil_(c≤11), $-\text{CO}_2$ -alquenil_(c≤11), y

$-\text{CO}_2$ -aralquil_(c≤11),

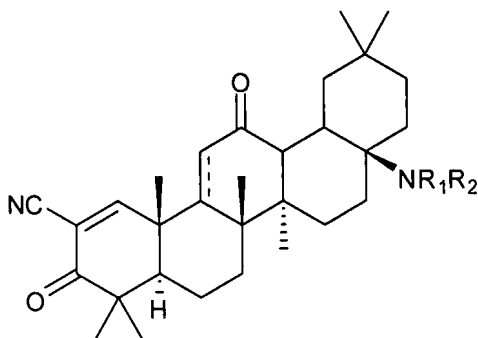
alquilsulfonil_(c≤12),

arilsulfonil_(c≤12),

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



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en donde:

R_1 y R_2 son independientemente:

hidrógeno; o

alquil_(C≤12), alquenil_(C≤12), alquínil_(C≤12),

aril_(C≤12), aralquil_(C≤12), acil_(C≤12),

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-C(O)NH₂, -C(O)NH-alquil_(C≤11),

-C(O)NH-alquenil_(C≤11),

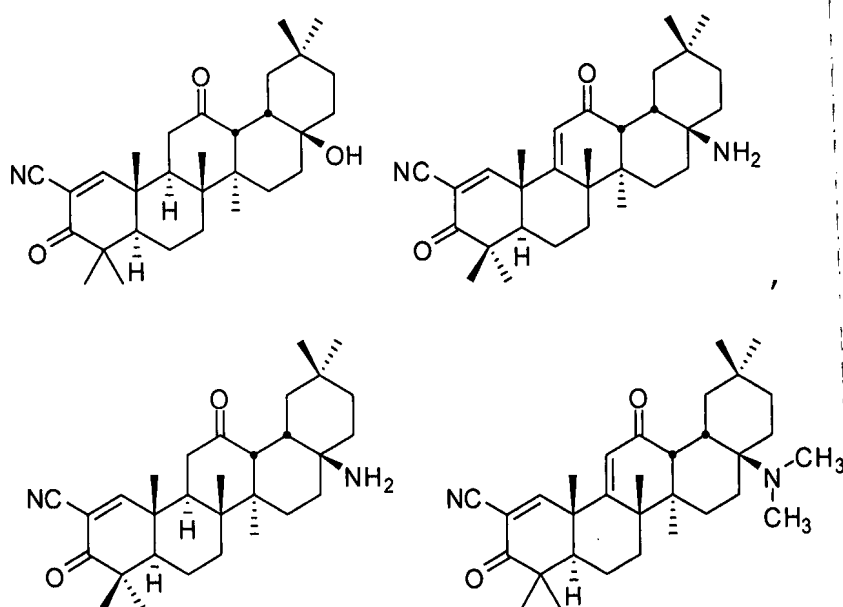
-C(O)-dialquilamino_(C≤11),

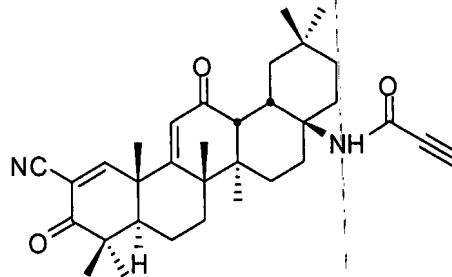
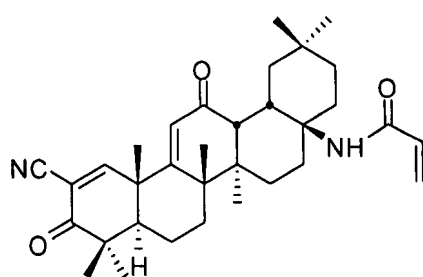
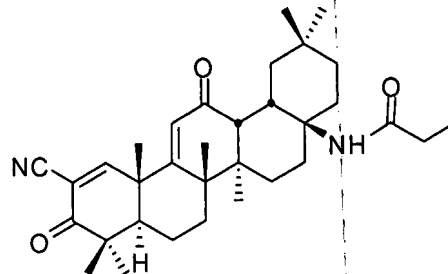
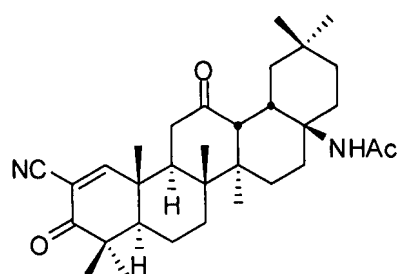
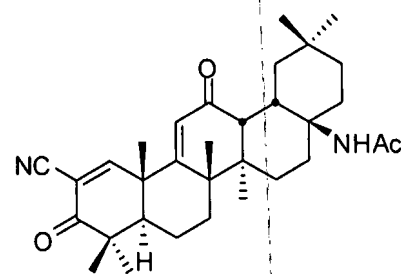
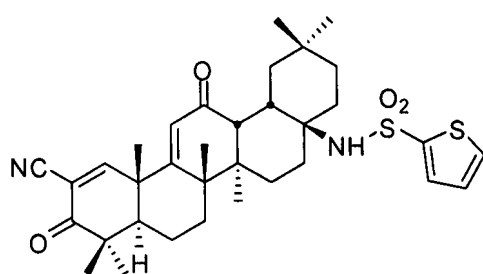
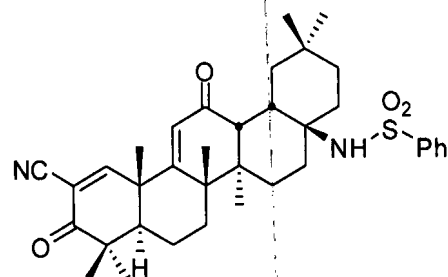
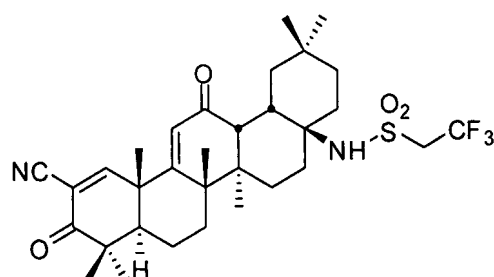
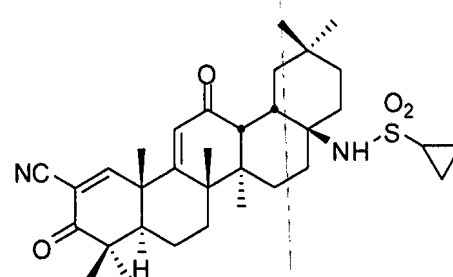
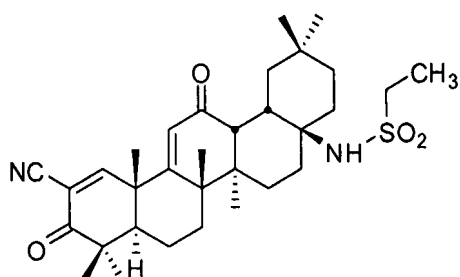
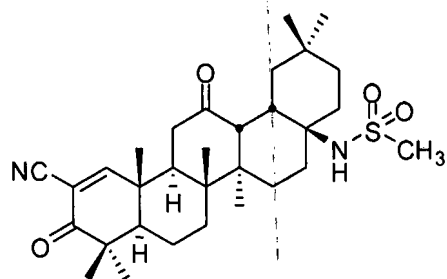
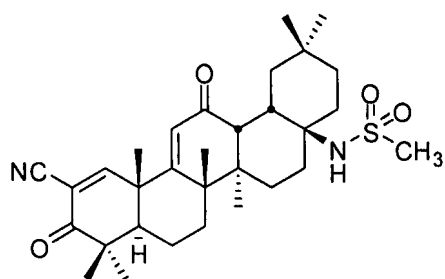
-C(O)NH-aril_(C≤11), -C(O)NH-aralquil_(C≤11),

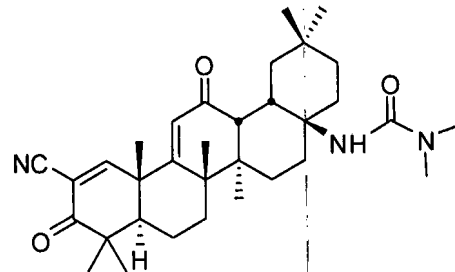
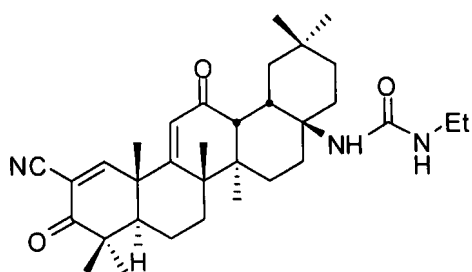
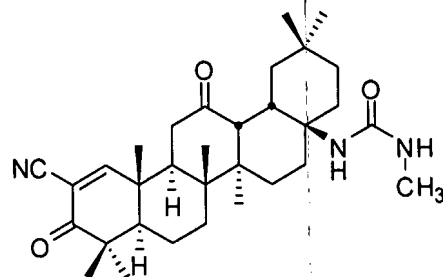
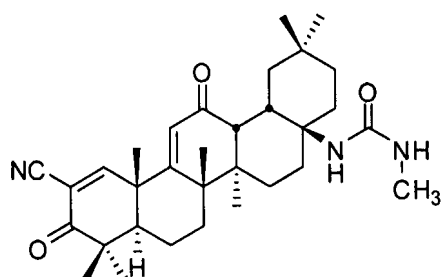
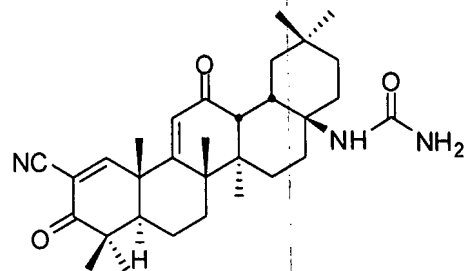
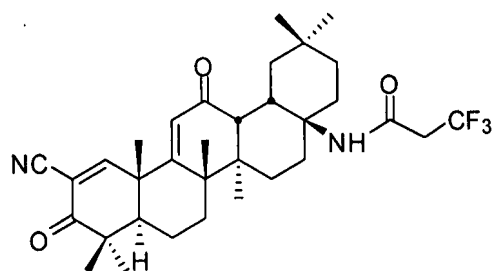
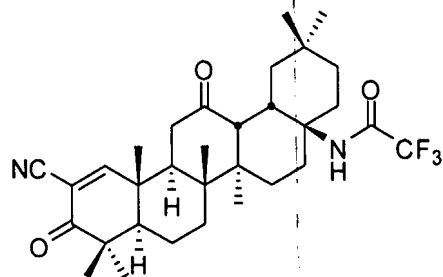
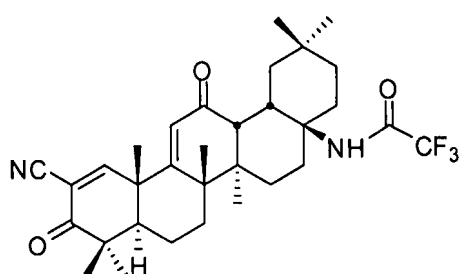
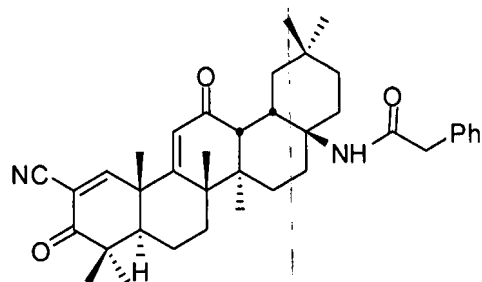
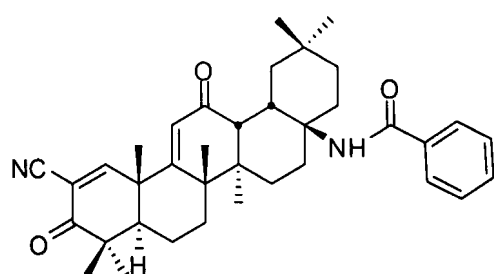
-C(O)-heteroaril_(C≤11), -CO₂-alquil_(C≤11),

-CO₂-alquenil_(C≤11), y -CO₂-aralquil_(C≤11),
 alquilsulfonil, arilsulfonil_(C≤12),
 aralquilsulfonil_(C≤12),
 heteroarilsulfonil_(C≤12), heteroaralquil-
 sulfonil_(C≤12), o una versión de cualquiera
 de estos grupos en donde un hidrógeno
 cualquiera o más se reemplaza con un
 átomo de flúor, con hidroxilo o con ciano;
 o una sal farmacéuticamente aceptable o tautómero de
 éstos .

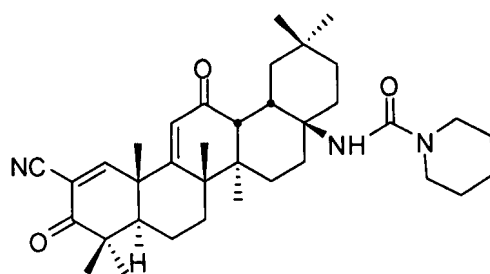
3. El compuesto de la reivindicación 2, en donde el enlace que une el carbono 9 y el carbono 11 es un doble enlace.
4. El compuesto de la reivindicación 2, en donde el enlace que une el carbono 9 y el carbono 11 es un enlace sencillo.
5. El compuesto de la reivindicación 1, además se define como:



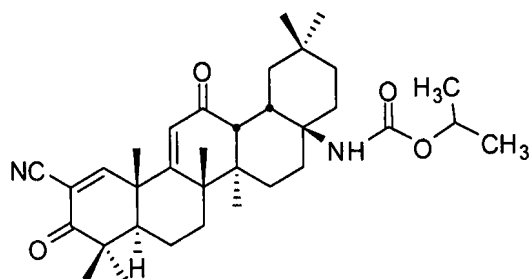
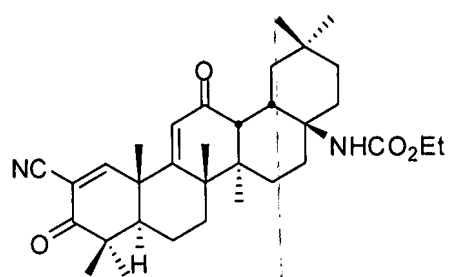
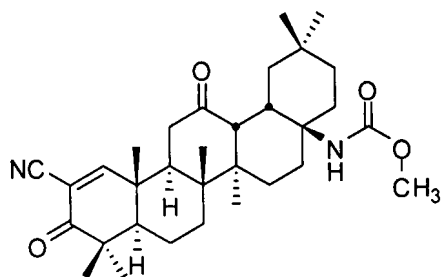
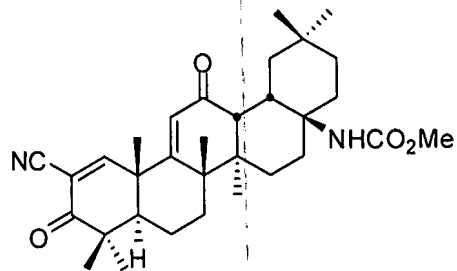
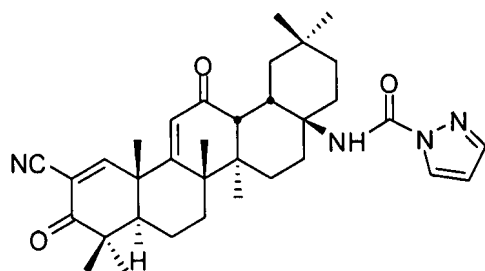
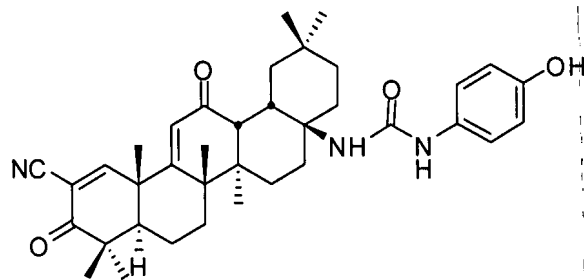
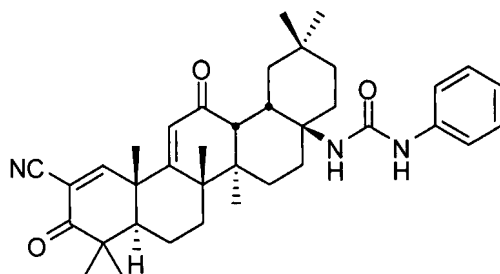
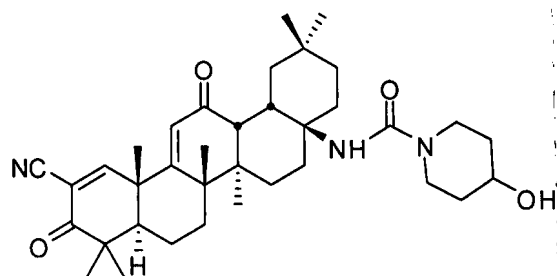


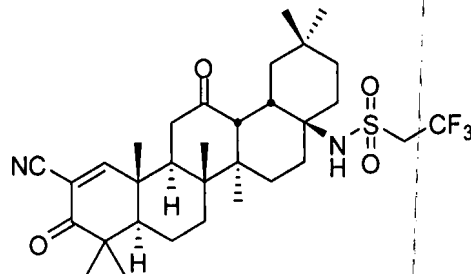
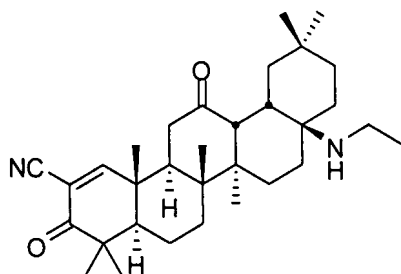
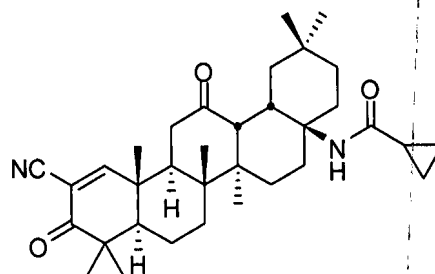
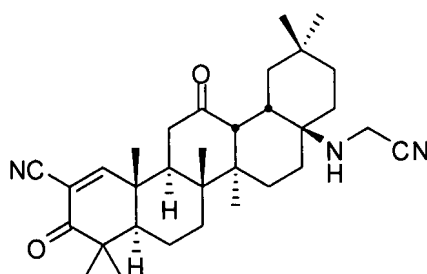
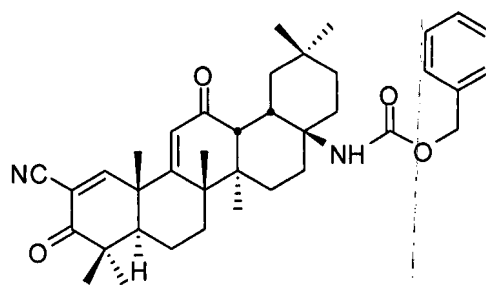
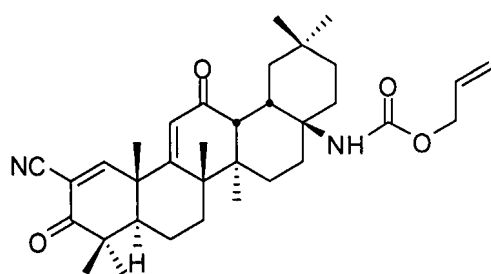


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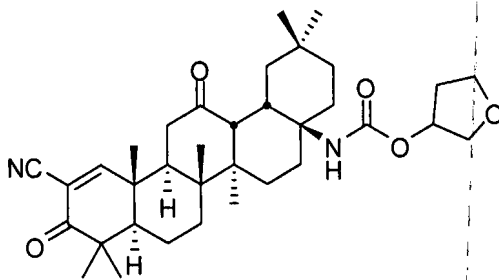
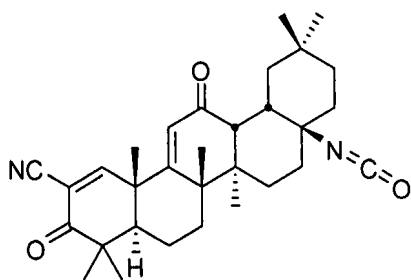


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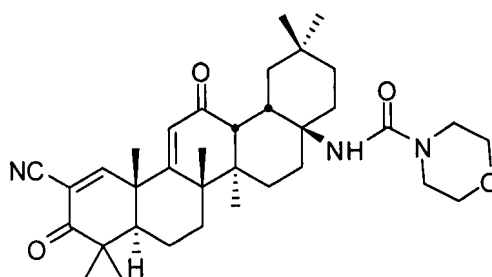


6. Un compuesto de la fórmula:



5

, 0



7. Una composición farmacéutica que contiene un compuesto de cualquiera de las reivindicaciones 1-6 y un vehículo aceptable farmacéuticamente.

10

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-	

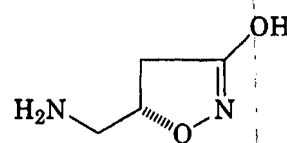
diazomethane and ketene both have 22 orbital electrons. Medicinal chemists have expanded and adapted the original concept to the analysis of biological activity. The following definition has been proposed: "Bioisosteres are groups or molecules which have chemical and physical properties producing broadly 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.

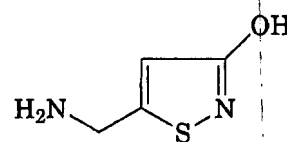
Many compounds have been identified that comply with the "biology" aspect of the bioisostere concept but that do not fit the strict chemical (steric and electronic) definition of

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.

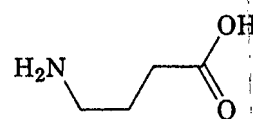
Dihydromuscimol (1) and thiomuscimol (2) are cyclic analogs of γ -aminobutyric acid (GABA) (3), in which the C=N moiety of the



(1)



(2)



(3)

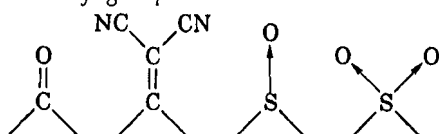
heterocyclic ring is considered to be bioisosteric with the γ -amino group of GABA. The -S- moiety of thiomuscimol is bioisosteric with the ring -O- of dihydromuscimol. Both (1) and (2) are highly potent agonists at GABA_A receptors, as determined in an electrophoresis-based assay (6).

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.

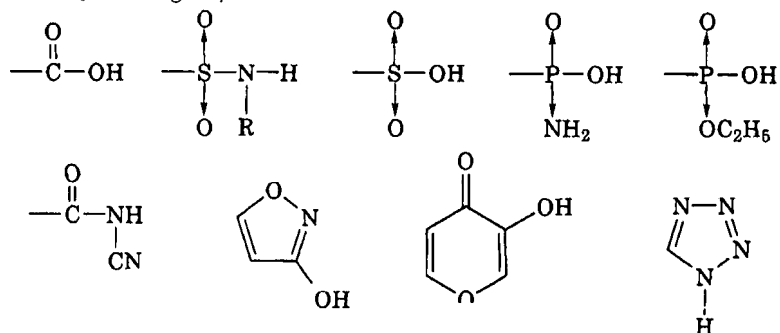
The sulfonium bioisostere (6) of *N,N*-dimethyldopamine (7) retains the dopaminergic agonist effect displayed by (7) (8). The fact that (6) bears a permanent unit positive charge was invoked in support of the hypoth-

Table 162 Nonclassical Bioisosteres

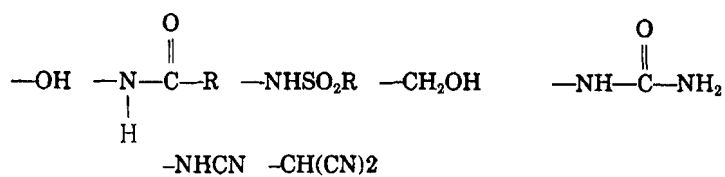
1. Carbonyl group



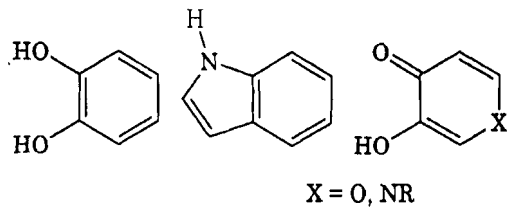
2. Carboxylic acid group



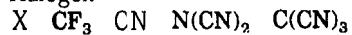
3. Hydroxy group



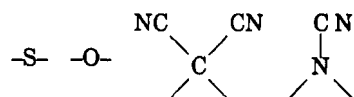
4. Catechol



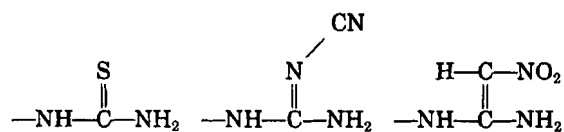
5. Halogen



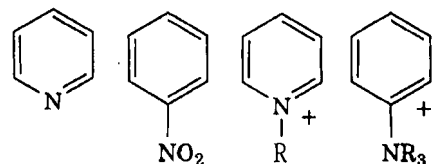
6. Thioether



7. Thiourea



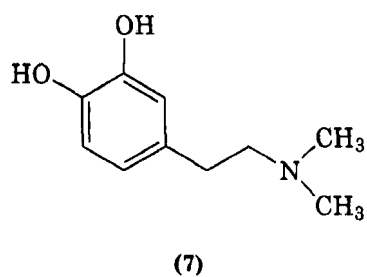
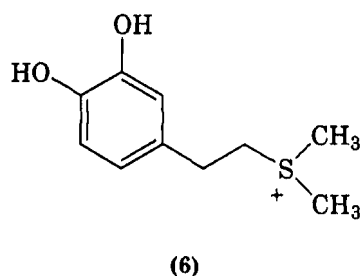
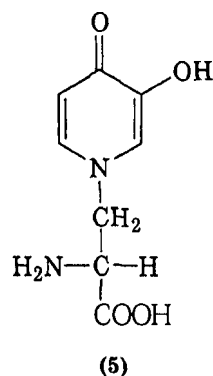
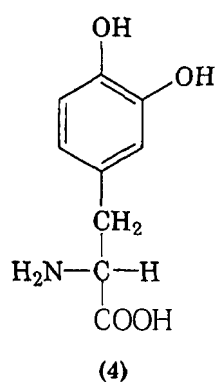
8. Pyridine



9. Hydrogen



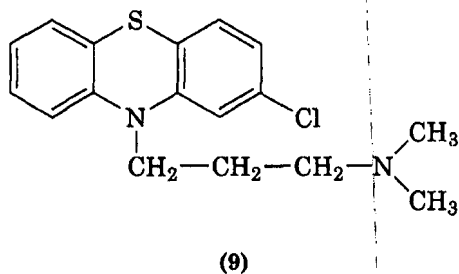
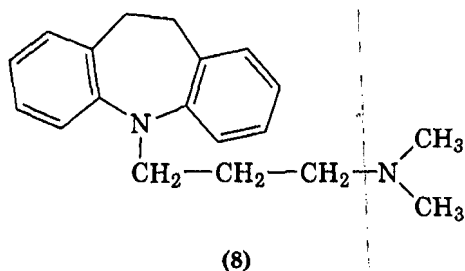
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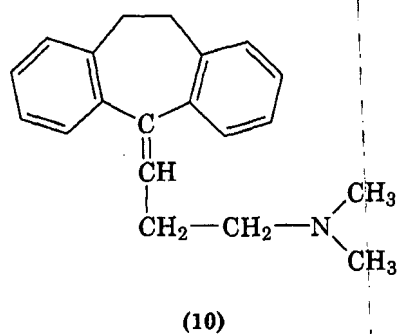
esis that β -phenethylamines such as (7) interact with dopamine receptors in their protonated (cationic) form.

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

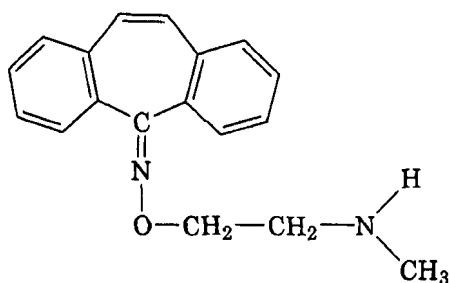
use of the antidepressant dibenzazepine derivative imipramine (8) as the lead. The structural similarity between imipramine and the phenothiazine antipsychotics [typified by chlorpromazine (9)] is apparent. Although these two



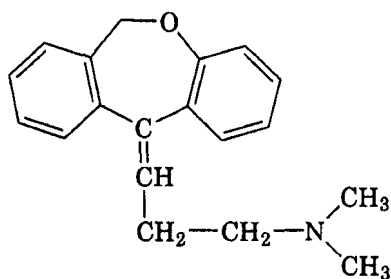
bioisosteric molecules have different pharmacological properties and therapeutic uses and likely have different mechanisms and sites of action in the central nervous system (9), they share the property of being psychotropic agents. They illustrate the observation that bioisosteric manipulation of a molecule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



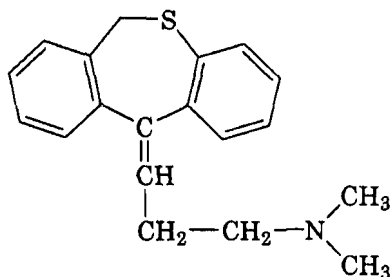
replaced by an exocyclic olefin moiety. Demexiptiline (1), doxepin (12), and dothiepin (13) represent other bioisosteric modifications of imipramine that possess antidepressant ac-



(11)



(12)

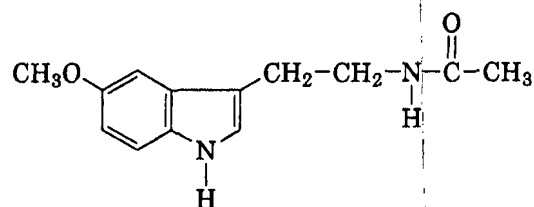


(13)

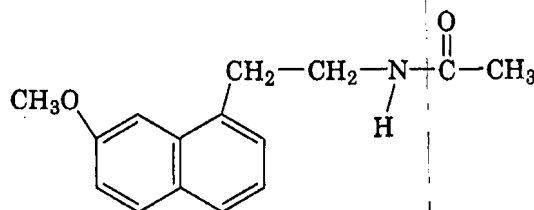
tivity (10). Variations in the precise nature of psychotropic effects manifested by compounds (8-13) may be ascribed to the marked changes in orientation in space of the two benzene ring components of the tricyclic portion of these molecules, imposed on them by the isosteric moieties ($-\text{CH}=\text{CH}-$, $-\text{CH}_2-\text{CH}_2-$, $-\text{S}-$, $-\text{CH}_2\text{O}-$, $\text{CH}_2\text{S}-$). 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



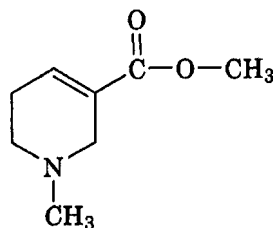
(14)



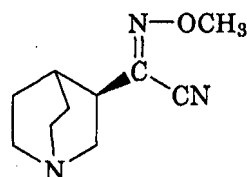
(15)

(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)

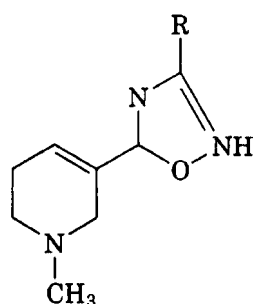


(17)

22

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.

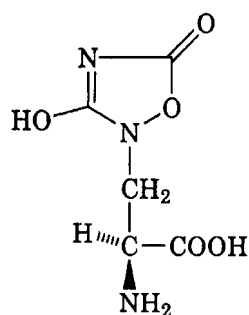
Replacement of the methyl ester moiety of the muscarinic partial agonist arecoline (16) by the putative nonclassical bioisosteric 1,2,4-oxadiazole ring system (18), where R = un-



(18)

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

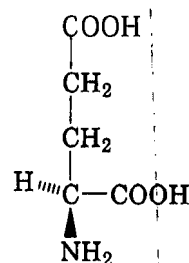
The 1,2,4-oxadiazole ring system of quisqualic acid (19), an agonist at a subpopulation



(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



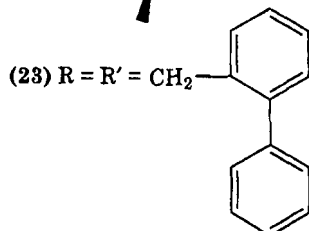
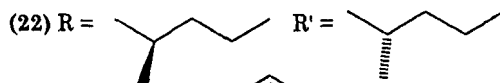
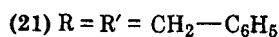
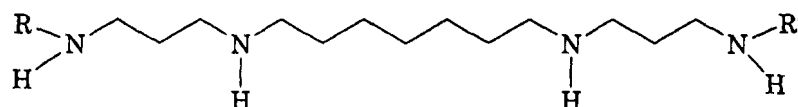
(20)

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.

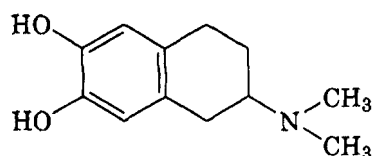
3 RIGID OR SEMIRIGID (CONFORMATIONALLY RESTRICTED) ANALOGS

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



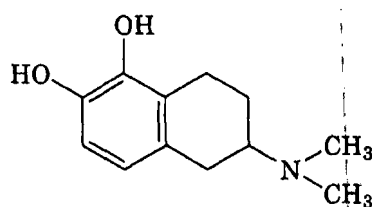
the case of a semirigid structure, the key functional groups are constrained to a limited range of **steric** dispositions and interatomic distances. By the rigid analog strategy, it is possible to approximate "frozen" **conformations** of a flexible lead molecule that, if an enhanced pharmacological 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)

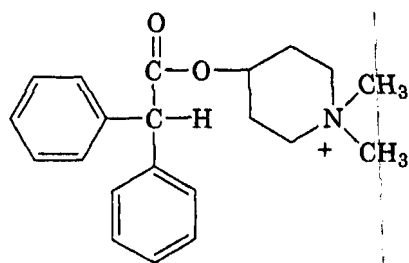
the two rotameric conformational extremes of the spatial relationship of the aromatic ring of **dopamine** to the ethylamine side chain when the ring and the side chain are coplanar. Compounds (24) and (25) display effects at different subpopulations of **dopamine** receptors (21), which have been proposed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



(25)

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

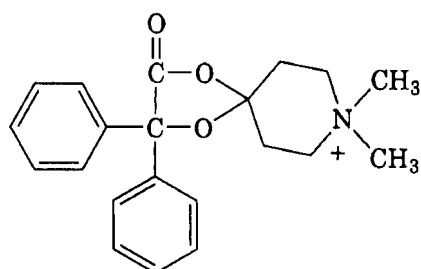
Restriction of conformational freedom of the acyl moiety in **4-DAMP** (26), an **antimus-**



(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).

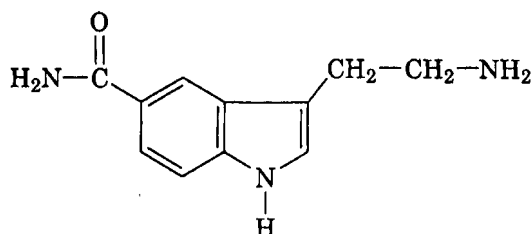
22



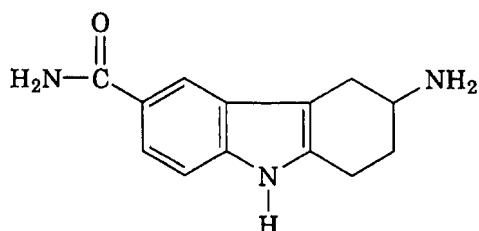
(27)

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)

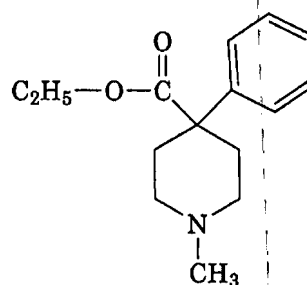


(29)

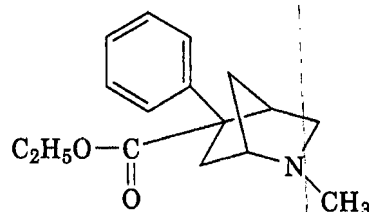
The conformational restrictions imposed on the indole-3-ethylamine moiety permitted retention of affinity for the $5HT_{1A}$ receptor but it diminished affinity for the $5HT_{1B}$ receptor by a factor of 1000. In two functional assays, (29) exhibited potency equal to or marginally greater than that of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

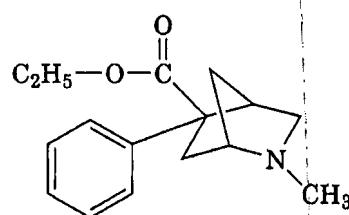
Imposition of rigidity into the piperidine ring of the opioid analgesic meperidine (30) by introduction of a methylene bridge between carbons 2 and 5 resulted in epimers (31) and (32), representing "frozen" conformations of meperidine (24).



(30)



(31)

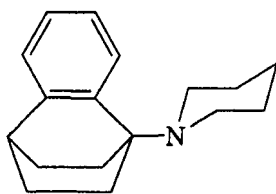


(32)

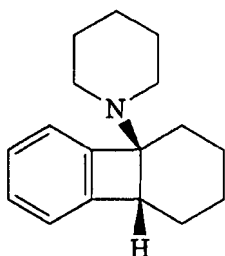
The exo-phenyl isomer (32) was six times as potent as the *endo*-phenyl isomer (31), and it was twice as potent as meperidine itself in a benzoquinone-induced writhing assay for analgesic effect.

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

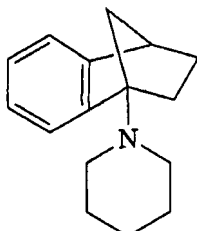
27



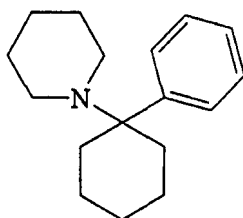
(33)



(34)



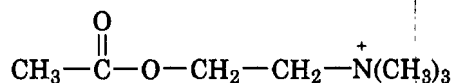
(35)



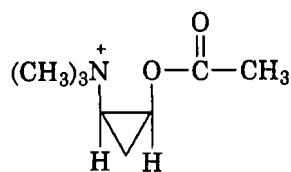
(36)

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).

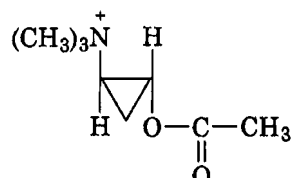
Incorporation of the choline portion of acetylcholine (37) into a cyclopropane ring system resulted in *cis*- and *trans*-1,2-disubstituted molecules, (38) and (39), in which the



(37)



(38)

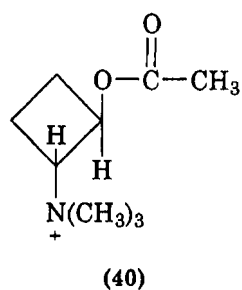


(39)

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

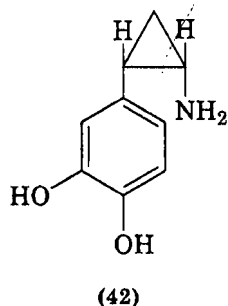
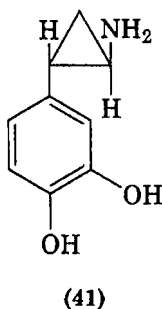
The (1*S*), (2*S*)-(+)-*trans*-isomer (39) was somewhat more potent than acetylcholine itself in tissue and whole-animal assays for muscarinic agonism (27) and it was an excellent substrate for acetylcholinesterase. The (1*R*), (2*R*) enantiomer of (39) was exponentially less potent than its (1*S*), (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

ver

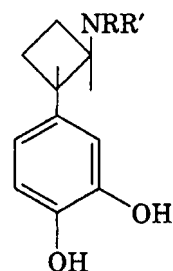


as differences in extraneous molecular bulk seem insufficient to account for the dramatic difference in pharmacological potencies between the three- and the four-membered ring systems.

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

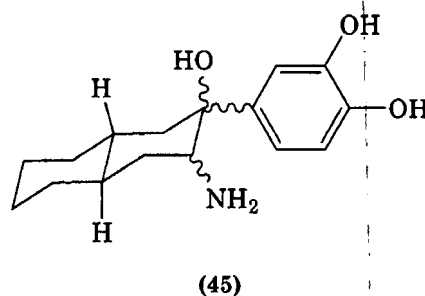


(44a) R = R' = CH₃

(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.

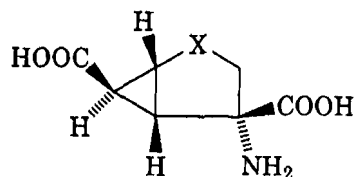
A β -phenethylamine moiety was incorporated into the *trans*-decalin ring system (45)



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.

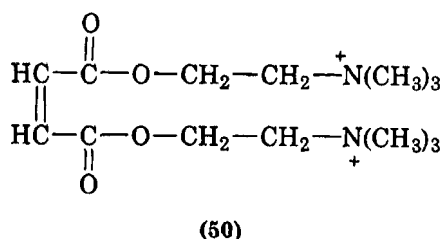
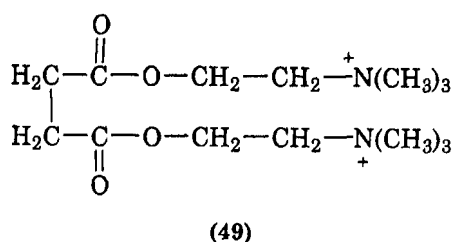
Rigidity was introduced into the glutamic acid moiety in a series of bioisosteric congeners (46–48) (34). These systems showed po-



- (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



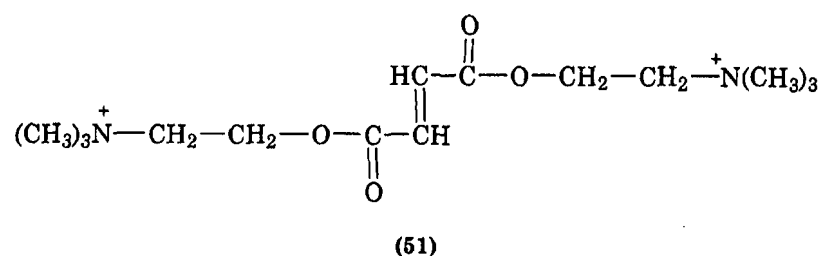
(51) was approximately one-half as potent as the flexible succinate ester (49), whereas the Z-maleate ester (50) was 1/40 as potent as the

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).

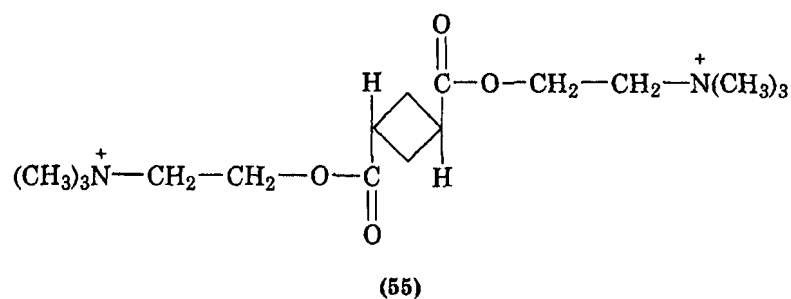
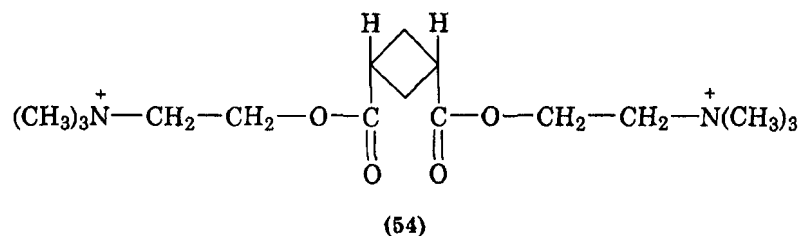
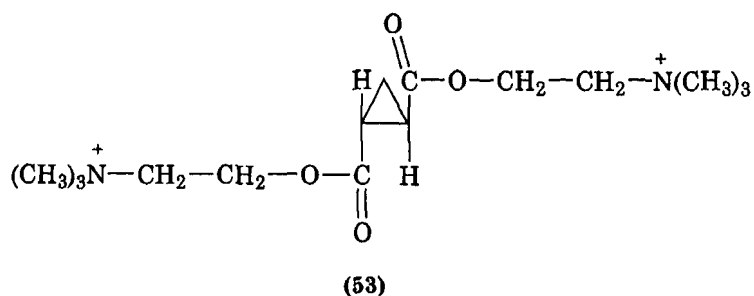
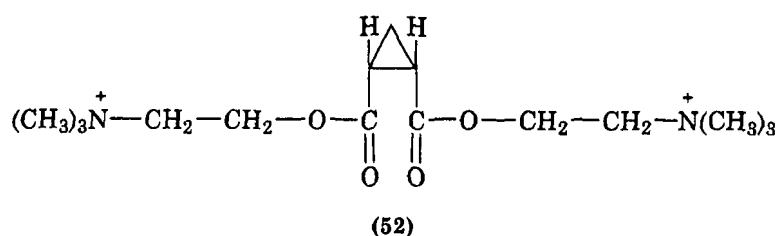
4 HOMOLOGATION OF ALKYL CHAIN OR ALTERATION OF CHAIN BRANCHING; CHANGES IN RING SIZE; RING-POSITION ISOMERS; AND SUBSTITUTION OF AN AROMATIC RING FOR A SATURATED ONE, OR THE CONVERSE

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-



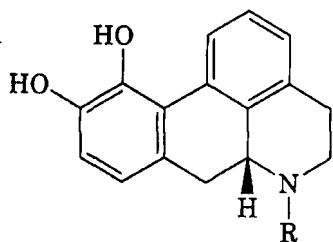
tem, position isomers may differ in their complementarity to receptors, and the position of a substituent on a ring may influence the spatial occupancy of the ring system with respect to the

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.



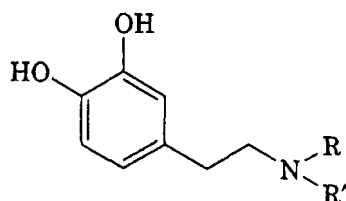
27

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



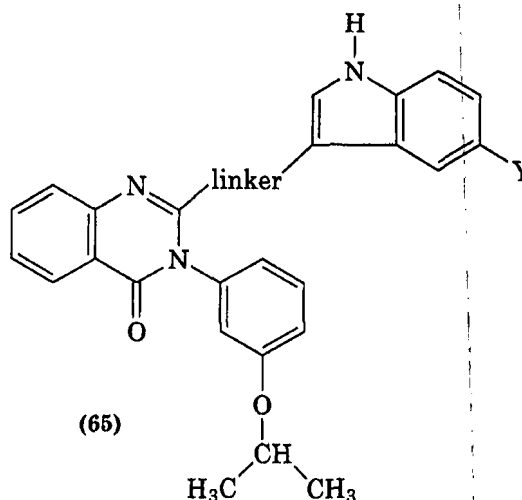
- (61) R = R' = CH₃
 (62) R = R' = *n*-C₃H₇
 (63) R = *n*-C₃H₇; R' = *n*-C₄H₉
 (64) R = R' = *n*-C₄H₉

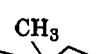
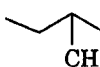
combinations of alkyl groups may impart a high degree of dopamine agonist effects (40).

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 modi-



- (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 -CH₂-CH₂-, 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.

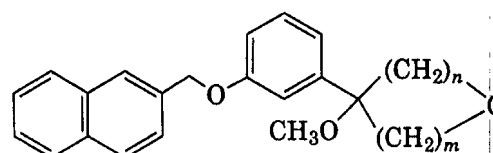
Branching the linker chain with a methyl group adjacent to the quinazolinone ring (68) resulted in a 350-fold decrease in affinity. However, chain branching with a methyl group in the alternate position on the ethylene chain produced compound (69), whose receptor affinity was of the same order of magnitude 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-(phosphonomethoxy)ethylguanidines (70-73) as antiviral (herpes and

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) $n = 1$; $m = 2$

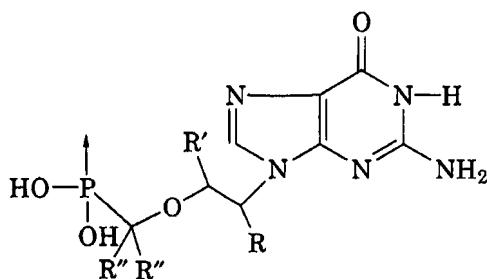
(75) $n = m = 1$

(76) $n = 1$; $m = 3$

(77) $n = 1$; $m = 4$

(78) $n = 2$; $m = 2$

(79) $n = 2$; $m = 3$



(70) $R = R' = H$

(71) $R = H$; $R' = CH_3$

(72) $R = CH_3$; $R' = H$

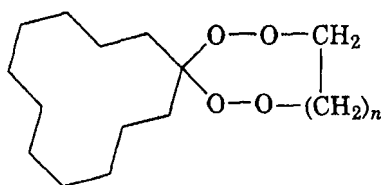
(73) $R = R' = H$; $R = \text{gem-dimethyl}$

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-

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.

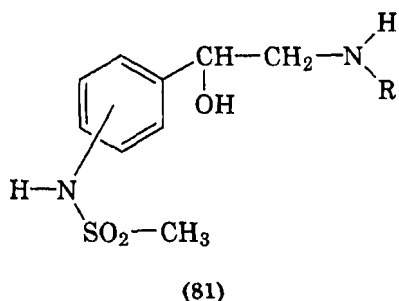
In a series of spiro-tetraoxacycloalkanes (80), with varying heterocyclic ring sizes, it was found that the compound where $n = 1$ demonstrated marked antimalarial activity against *P. bergeri* and *P. falciparum*, and showed low toxicity (47). The analog in which

29

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

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

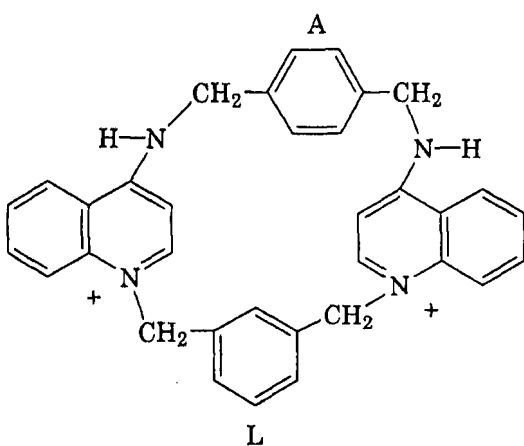
In a series of arylsulfonamidophenethanolamines (81) (48), derivatives bearing the sul-



(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.

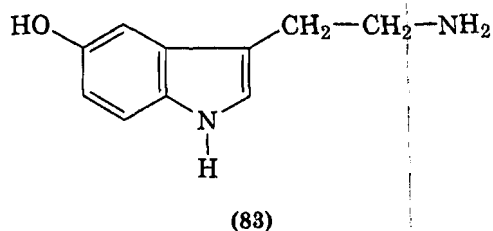
Changing the positions of attachment of the two benzene rings linking the quinolinium moieties of the calcium-activated potassium channel blocker (82) reduced activity 10- to



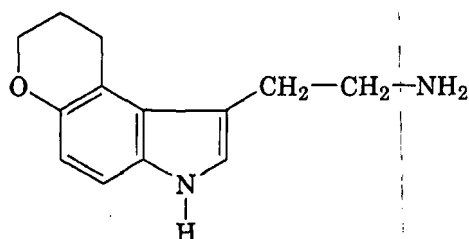
(82)

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



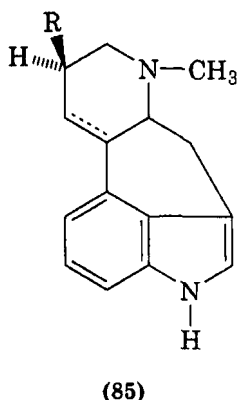
(83)



(84)

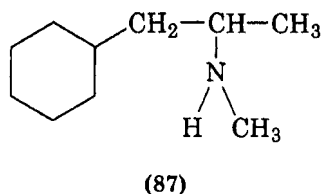
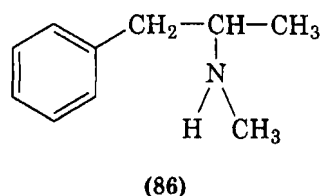
also introducing an alkyl substituent at position 4 of the indole ring system.

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



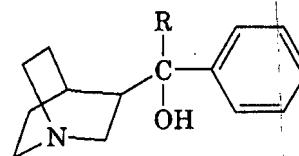
suggested (50) that the high affinity for the 5-HT₁ receptor exhibited by such compounds as (84) demonstrates that the C-5 hydroxyl group of serotonin can function as a hydrogen-bond acceptor at the receptor.

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



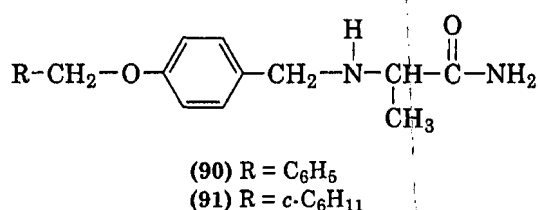
loss of pressor effect, but the drug, like amphetamine, has been used as a nasal decongestant, and it has CNS-mediated anorexigenic effect (52, 53). It is said to have somewhat less central stimulant action than the corresponding aromatic ring derivatives (54a-d).

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



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

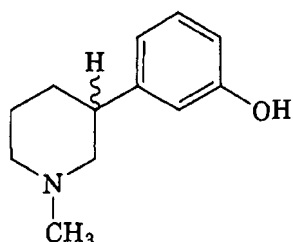
5 ALTERATION OF STEREOCHEMISTRY AND DESIGN OF STEREOISOMERS AND GEOMETRIC ISOMERS

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-

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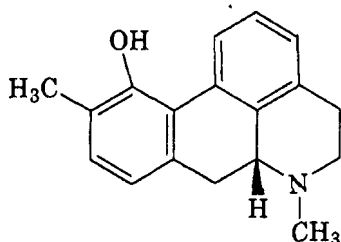


(92)

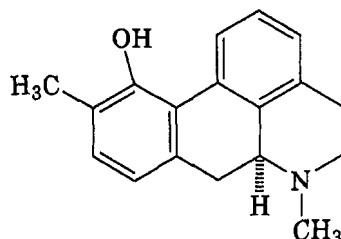
tors. Thus, this enantiomer exhibits a bifunctional mode of dopaminergic attenuation: that of presynaptic agonism and postsynaptic antagonism. The observed pharmacological effects of the racemic modification are the sum total of the complex activities of the two enantiomers, and the pharmacology of racemic 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 5HT₂ agonist (60).

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



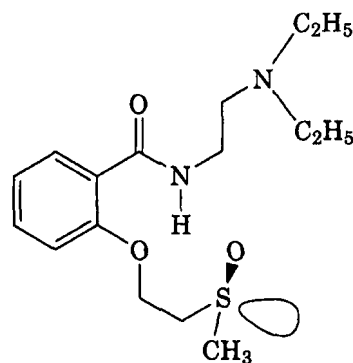
(93)



(94)

aration) (61). Both enantiomers bind strongly to 5HT₂ 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.

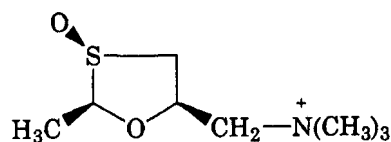
In addition to stereochemistry about a carbon center, other potentially chiral atoms offer possibilities for pharmacological significance. Agastropokinetic compound (95) with



(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.

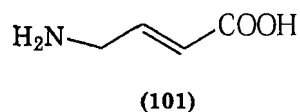
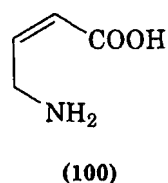
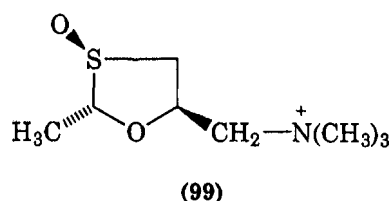
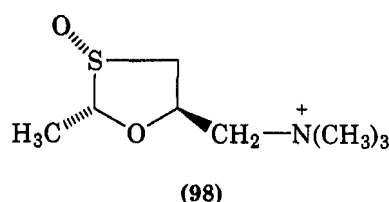
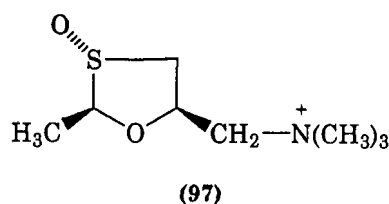
Casy (63) cited pharmacological differences between stereoisomers of chiral sulfoxide moieties in cholinergic oxathiolane congeners (96-99) of muscarine.



(96)

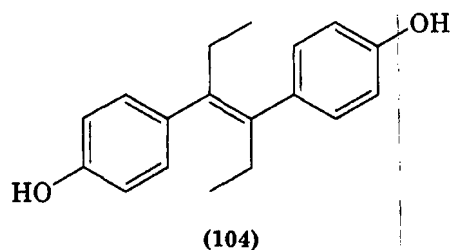
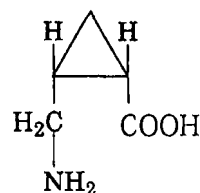
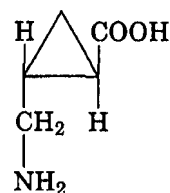
cis- and trans-4Aminocrotonic acids (100) and (101) were prepared (64) as congeners of γ -aminobutyric acid (GABA) (6).

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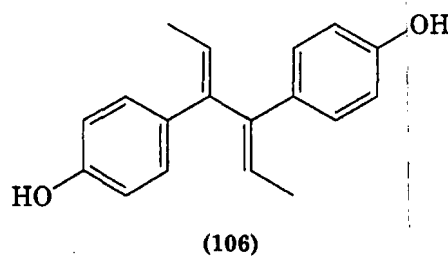
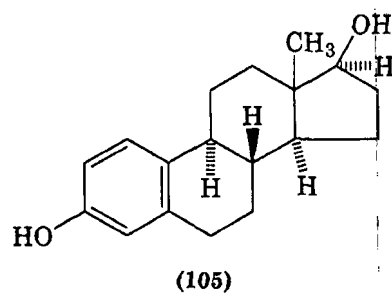


The folded 2-isomer (100) was inactive in assays for GABA agonism, whereas the extended E-isomer (101) was active. These data demonstrate biological differences of geometric isomers, which in turn involve a parameter discussed previously: imposition of a degree of structural rigidity on the molecule. 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-

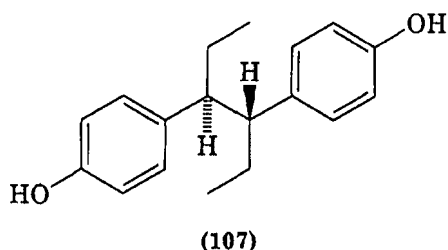


geometric isomer is an open-chain analog of the natural estrogen estradiol (105) (66). In dienestrol (106), the geometric isomerism possible with olefinic moieties has been further



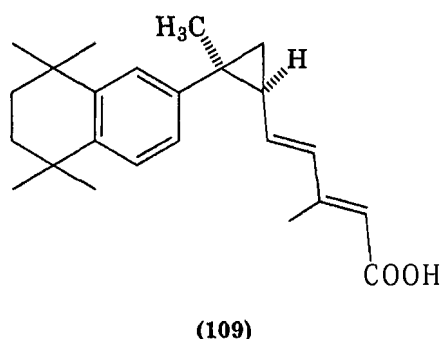
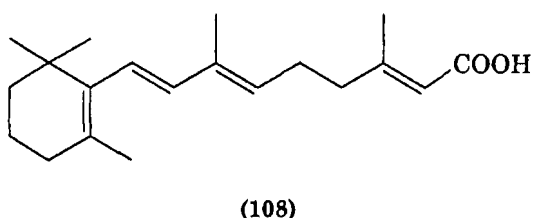
exploited to achieve a similar kind of open-chain analogy to the steroid ring system as in diethylstilbestrol, and a high level of estrogenic activity results.

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).

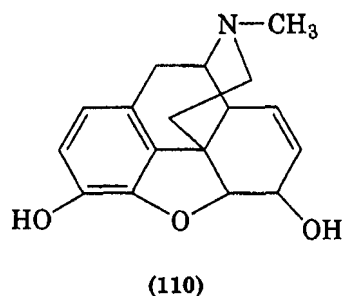


Introduction of the cyclopropane ring changes the corresponding trans-olefinic moiety of (108) to a cisoid disposition in (109), thus changing the overall steric disposition of the side chain. Moreover, the cyclopropane ring introduces chirality into the molecule. The (*S,S*)-enantiomer shown is a potent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

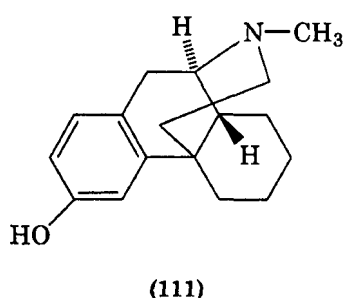
6 FRAGMENTS OF THE LEAD MOLECULE

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.

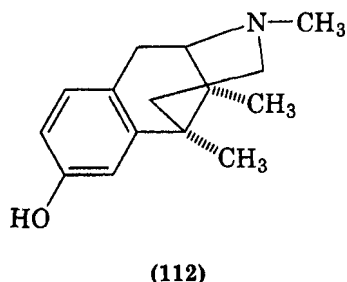


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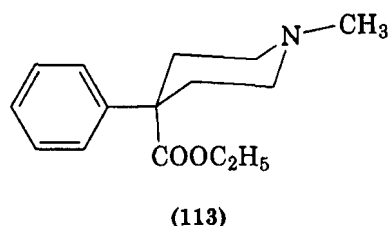
The analgesic preceptor pharmacophore of morphine has been defined (69) as comprising the basic nitrogen atom, the aromatic ring located three carbon atoms from the nitrogen, and a quaternary carbon adjacent to the aromatic ring, which provides a region of molecular bulk. A bond disconnection strategy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



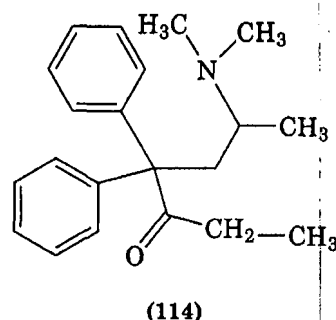
closely parallel those of morphine (70). Further simplification of the morphine ring system led to benzomorphan derivatives, typified by metazocine (112), in which morphinelike



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



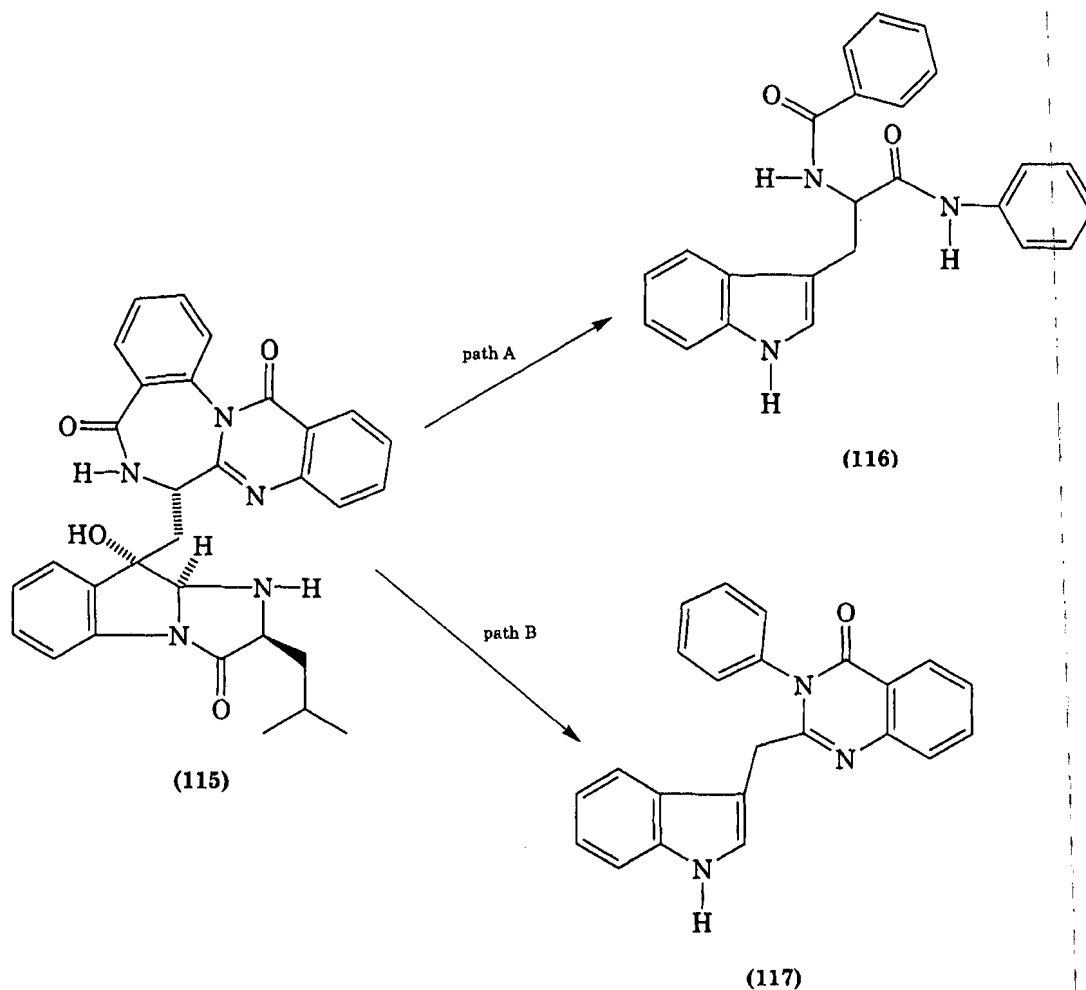
must be noted, however, that the discovery of analgesic activity in 4-phenylpiperidine derivatives was not a result of a systematic structure-activity study of the morphine molecule, but was serendipitous (71).

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.

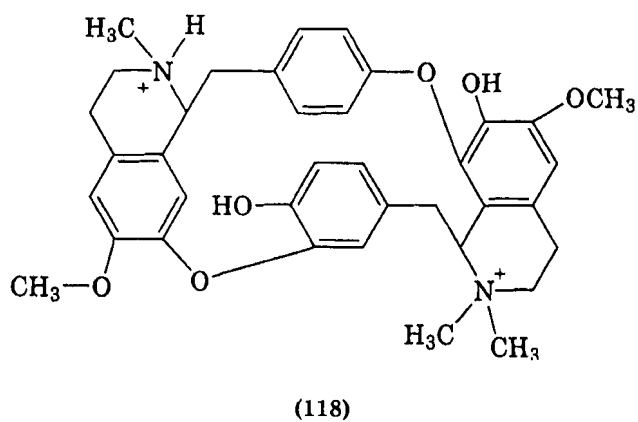
The myoneural-blocking pharmacophore in d-tubocurarine (118) was speculated to include the two cationic heads (the quaternary ammonium group and the protonated tertiary amine); the cationic heads are separated by 10 atoms (nine carbons and one oxygen).

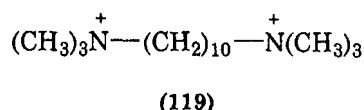
Based on these parameters, a simple molecule, decamethonium (119), in which two trimethylammonium heads are separated by 10 methylene groups to approximate the internitrogen distance in d-tubocurarine, was designed independently by two groups of investigators (74, 75). This synthetic fragment/analog 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

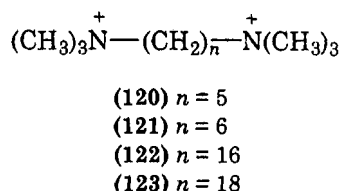




mechanism of action, even though the chemical nature of the pharmacophore may not be altered.

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

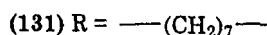
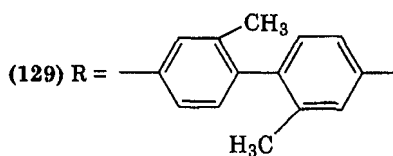
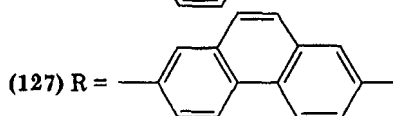
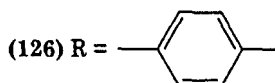
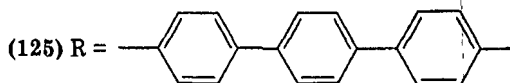
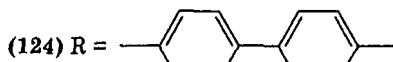
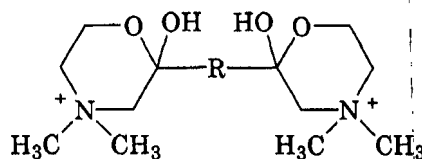


blockade of autonomic ganglia (nicotinic N_2 receptors) resides in those derivatives where $n = 5$ or 6 (compounds 120 and 121) (76, 77).

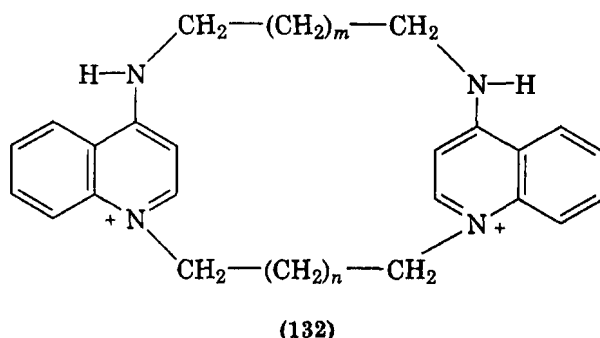
Ganglionic effects drop drastically when $n = 4$ or 7. These observations have been rationalized as being a reflection of attainment of optimal interquaternary distance in the penta- and hexamethylene congeners, for optimal interaction with ganglionic receptor subsites. Remarkably, as the number of methylene 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-



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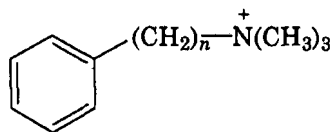


imum interquaternary nitrogen distance of 14.4 Å in hemicholinium (124), to 18.4 Å in the terphenyl analog, and to 10.2 Å in the *p*-phenylene analog.

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) $n = 1$

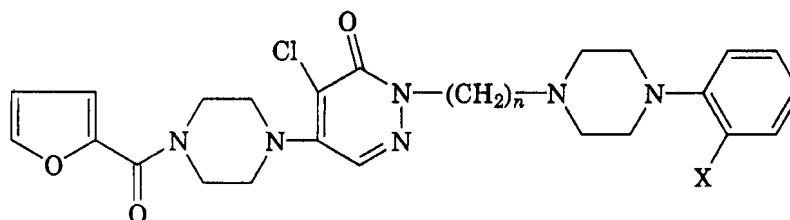
(135) $n = 2$

(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 furoylpiperazinylpyridazinone 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-

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(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.

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