

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,
Abogado
CARLOS REINALDO OLARTE
office@olartemoure.com

ASUNTO	Radicación	09-2483
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	
	Folios	017

EE-17221

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☒	Cap. I	☒
Vía PCT (fase nacional)	☒	Cap. II	☐

No. Solicitud Internacional PCT/EP2007/006472

Fecha de Presentación Internacional 16 de julio de 2007

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 164-333	14 de enero de 2009
Reivindicaciones:	Folios 334-356	14 de enero de 2009
	Folios 424-447	28 de abril de 2011
Prioridad:	EP 06-014665.1	14 de julio de 2006

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque:
Esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486).
Y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

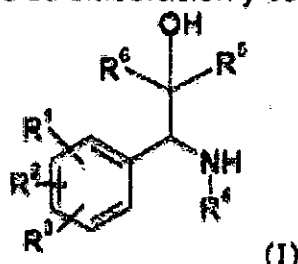
Título de la solicitud: "Bencilaminas, un proceso para su producción y su uso como

Primer Artículo 45- Expediente 09-2483

agentes antiinflamatorios".

El problema planteado en esta solicitud consiste en la necesidad de proporcionar compuestos antiinflamatorios.

Para resolver este problema técnico la solicitud en estudio proporciona un compuesto de la fórmula (I), un proceso para su elaboración y composiciones que lo contienen.



El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07C 215/16, C07D 215/38, A61K 31/136, C07D 401/12; C07C 217/78.

4. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de las reivindicaciones 12-13 no es patentable, de acuerdo con el Art 14.

5. De la Solicitud de Patente

Título

El título incluye la expresión "y su uso como agentes antiinflamatorios", haciendo referencia al uso del compuesto, lo cual, es un ítem no patentable, se sugiere modificar el título por: "Bencilaminas y su proceso de producción".

Reivindicaciones (Art 30 D 486, Art 22 PCT)

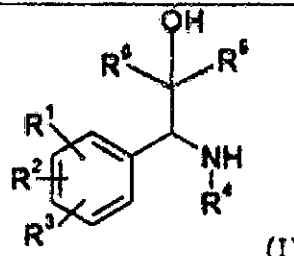
La reivindicación 1 no es concisa cuando utiliza los términos:

- C₁₋₁₀ alquilo, C₁₋₁₀ alcoxi, C₁₋₁₀ alquiltio, C₁₋₁₀ alquilo, C₁₋₁₀ perfluoroalquilo C₁₋₃ alquil, C₁₋₅ alquilo, -(CO)-C₁₋₅ alquilo, C₁₋₅ alquileo, C₁₋₃ alquilo parcial o completamente fluorado, C₂₋₁₀ alquilino, C₁₋₈alquilC₃₋₇cicloalquilo, C₂₋₈alquenoC₃₋₇cicloalquilo: porque da lugar a un amplio número de combinaciones que están por fuera de lo soportado en la descripción.
- Sistema de anillos monocíclico, bicíclico: no se define el número de miembros que tiene el sistema.

- Parcialmente aromático, o no aromático, el cual opcionalmente contiene 1-4 átomos de nitrógeno, 1-2 átomos de oxígeno, y 1-2 átomos de azufre: porque no definen adecuadamente el alcance de la materia que se desea proteger, dando lugar a un amplio número de combinaciones que están por fuera de lo soportado en la descripción.
- C₁₋₈alquilheterociclillo, C₂₋₈alquenilheterociclillo: porque no se define el número y tipo de heteroátomos presentes en el anillo, ni el número de miembros que posee la porción alílica, alqueníllica o aromática.
- Arilo: porque no define el número de miembros que posee el anillo.
- El uso de términos tales como "n", "p", "p+1", "p+2" porque da lugar a un amplio número de combinaciones que están por fuera de lo soportado en la descripción.
- El uso de términos tales como "opcionalmente sustituido", "opcionalmente se puede sustituir con x-y grupos ...": son términos imprecisos que no limitan el alcance de la reivindicación ni la definen de manera adecuada.

Todo lo anterior, da lugar a un número indeterminado de compuestos que no se encuentran soportados. Por lo cual, se sugiere al solicitante, definir cada término de manera apropiado y restringir la solicitud a una generalización razonable de los compuestos ejemplificados en la descripción.

Para tal efecto, esta Oficina manifiesta que en la descripción se encuentran soportados los siguientes compuestos a los cuales el solicitante puede tener en cuenta para la respectiva restricción.

 (I)	
R1	H, metoxi, bromometil, hidroxil, clorometil, F, metil
R2	H, F, metoxi, OH, Cl,
R3	H, F, metoxi, OH, Cl
R4	Fenilo, 2 metil-quinolin, naftaleno, quinolin, 2-metil-ftalazin-1-ona, 7-fluoro-2-metil-quinazolin,
R5	Trifluorometil,
R6	Bencil, propil, etil-sufanilmetil, imidazol-2-il-sufanilmetil, etil-sulfonil-metil, imidazol-2-il-sufonilmetil, etil-sufanilmetil, 1,2,4- triazol-3-il-sufanilmetil, 1-metil-imidazol-2-il-sufanilmetil, piridin-2-il-sufanilmetil, isopropilsufanilmetil, butironitrilo, metil-sufanilmetil, dimetilaminometil, etoximetil,

	metoximetil
R1 y R2	Juntos forman 1,3-benzodioxol, 1,3-dihidrobenzofurano, 1,3-dihidro-2,2-dimetilbenzofurano,

Lo anterior, también aplica para las reivindicaciones 2-10, 22-26.

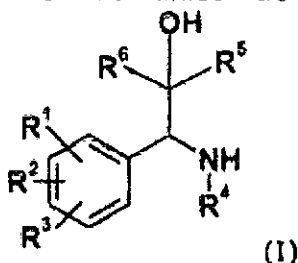
La reivindicación 11 consiste en una forma enantioméricamente pura del compuesto de las reivindicaciones 1-10, lo cual, no constituye una característica esencial, por lo cual, se sugiere retirar la reivindicación del pliego reivindicatorio.

Los procesos de las reivindicaciones 14-17, 20-21 no son claros, pues no definen la materia a proteger adecuadamente, se le recuerda al solicitante que un proceso es correctamente definido cuando: se definen sus etapas, solventes, condiciones, uso de catalizadores, por lo cual se sugiere al solicitante, hacer las aclaraciones necesarias.

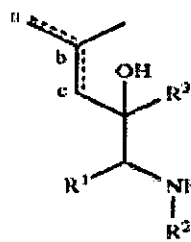
Las reivindicaciones 18 y 19 definen procesos para la preparación de compuestos de fórmula I*, sin embargo incluyen características tales como la definición de radicales, lo cual, no es la manera indicada de definir un proceso, se sugiere definir los radicales en una reivindicación independiente y luego hacer referencia a estos en la reivindicación del proceso, limitándose a describirlo en términos de sus etapas, solventes, condiciones, uso de catalizadores.

6. Unidad de invención (Art 25 D 486)

La presente invención se refiere a compuestos derivados fenoxinilina cuyo concepto inventivo único de la presente solicitud es el compuesto de fórmula (I)



La búsqueda ha revelado que el concepto inventivo único no es inventivo, ya que el



documento D1 define un compuesto de fórmula (párrafo 66 y reivindicación 1) y tienen propiedades antiinflamatorias (párrafo 1). Se diferencian en que los valores del equivalente de R6 de D1 fueron excluidos por un disclaimer.

Como dicho concepto inventivo único no es inventivo, no se cumple el requisito de unidad invención. Debido a que tampoco se encuentran otras características que puedan considerarse como elementos técnicos particulares, no hay unidad de invención.

Por lo tanto, existen los siguientes grupos de invenciones:

1. donde R6 es un grupo alquilo.
2. Donde R6 es un grupo aromático.
3. Donde R6 es un grupo heteroalquilo.

Se sugiere presentar las Solicitudes Divisionales que considere necesarias, ó limitar la solicitud inicial a una sola invención, eliminando de ella las otras invenciones.

7. Determinación del Estado de la Técnica

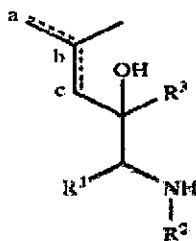
El Estado de la Técnica se determinó con base en la fecha de Presentación de la Solicitud de Prioridad: 14 de julio de 2006

Y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación*
D1	US2005131226	Rearranged pentanols, a process for their production and their use as anti-inflammatory agents	16 de junio de 2005
D2	GB1045180	Quinazoline derivatives	12 de octubre de 1966
D3	Ayhan S. Demir <i>Et al</i> Journal Organic Chemistry	Generation of Acyl Anion Equivalents from Acylphosphonates via Phosphonate-Phosphate Rearrangement: A Highly Practical Method for Cross-Benzoin Reaction. Vol 70, Páginas 10584-10587	28 de agosto de 2005
D4	Principles of medicinal chemistry. Thomas L. Lemke <i>Et al.</i>	Chapter 2 drug desing and relationship of functional groups to pharmacologicactivity, páginas 47-48, sixth Edition	2002

D1

<http://worldwide.espacenet.com/publicationDetails/biblio?CC=US&NR=2005131226&KC=&FT=E&locale=en> EP

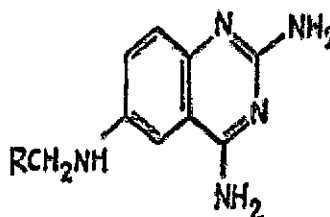


Divulga compuestos de fórmula I
uso como antiinflamatorios

, procesos para su producción y su

D2

http://worldwide.espacenet.com/publicationDetails/biblio?CC=GB&NR=1045180&KC=&FT=E&locale=en_EP



Divulga 2,4-diaminoquinazolines de formula (III) los cuales poseen actividad antiviral, diuretica, antibacterial, anti-parasitaria, antihelmíntica, anti-malárica.

D3 (folios 469-472)

Generation of Acyl Anion Equivalents from Acylphosphonates via Phosphonate-Phosphate Rearrangement: A Highly Practical Method for Cross-Benzoin Reaction. 70, Páginas 10584-10587

D4 (folios 473-474)

Principles of medicinal chemistry. Thomas L. Lemke Et al. Chapter 2 drug design and relationship of functional groups to pharmacologic activity, páginas 47-48, sixth Edition,

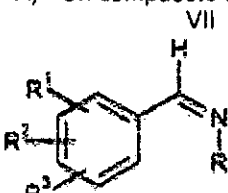
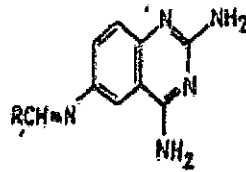
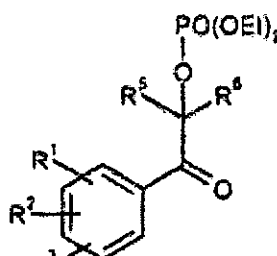
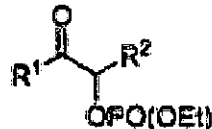
Divulga que técnicas como el isosterismo y el alargamiento y acortamiento de las cadenas alquílicas son técnicas comúnmente empleadas para modificar compuestos activos y proveer compuestos alternativos con actividad terapéutica.

8. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

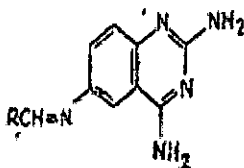
La reivindicación 22 consiste en un compuesto de fórmula VII y de fórmula XII

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Características esenciales	D2	D3
A) Un compuesto de fórmula VII  (VII)	Un compuesto de fórmula (II)  (página 2) Donde R es un grupo fenilo mono di o tri sustituido con alquilo inferior (pagina uno columna izquierda líneas 19 a 25)	No es mencionado
B) Un compuesto de fórmula XII 	No es mencionado	Un compuesto de fórmula  Donde R1 es fenilo y R2 es fenil sustituido (página 10585)

A) Novedad frente a D2

Las características **esenciales** del compuesto VII de la reivindicación 22 habían sido divulgadas previamente en D2, el cual divulga Un compuesto de fórmula (II)

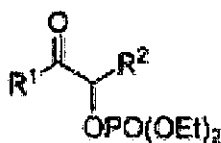


(página 2), donde R es un grupo fenilo mono di o tri sustituido con alquilo inferior (pagina uno columna izquierda líneas 19 a 25)

En consecuencia, el compuesto VII de la reivindicación 22 no es nuevo, según lo divulgado en el documento D2.

b) Novedad frente a D3

Las características **esenciales** del compuesto XII de la reivindicación 22 habían sido divulgadas previamente en D3, el cual divulga un compuesto de fórmula



Donde R1 es fenilo y R2 es fenil sustituido (folio 470, página 10585)

En consecuencia, el compuesto XII de la reivindicación 22 no es nuevo, según lo divulgado en el documento D3.

Nivel Inventivo (Art 16 D486)

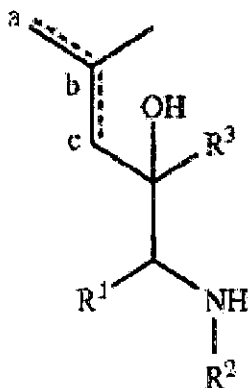
La reivindicación 1 consiste un compuesto de fórmula (I)

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Características esenciales	D1	D4
Un compuesto de fórmula (I)	Un compuesto de fórmula (I) Donde R1 es un grupo fenilo sustituido (párrafo 9)	Divulga que las alteraciones en las cadenas de alquilo, tales como aumentar, disminuir la longitud de cadena o la ramificación, pueden tener efectos sobre la actividad farmacológica. Estos pequeños cambios son aspectos importantes en el diseño de análogos.
R⁴ significa un sistema de anillos monocíclico, o bicíclico, aromático, parcialmente aromático, o no aromático, el cual opcionalmente contiene 1-4 átomos de nitrógeno, 1-2 átomos de oxígeno y/o 1-2 átomos de azufre y opcionalmente se sustituye en una o más posiciones con un radical que se selecciona entre el grupo carbonilo, halógeno, hidroxilo, o (C₁₋₅)-alquilo, el cual opcionalmente se puede sustituir con 1-3 grupos hidroxilo, 1-3 grupos (C₁₋₅)alcoxi y/o 1-3 Grupos COOR⁶, (C₁₋₅) alcoxi, (C₁₋₅)-alquiltio, (C₁₋₅)-perfluoroalquilo, ciano, nitro.	R² equivalente del R⁴ es un sistema de anillos monocíclico, bicíclico o, aromático, parcialmente aromático o, o no aromático, opcionalmente que contiene 1-3 átomos de nitrógeno, 1-2 átomos de oxígeno y/o 1-2 átomos de azufre y opcionalmente está sustituido en uno o más lugares de un radical que se selecciona del grupo carbonilo, halógeno, hidroxilo, o (C₁₋₅)-alquilo, que puede estar opcionalmente sustituido por 1-3 grupos hidroxilo, 1-3 grupos (C₁₋₅)-alcoxi y/o 1-3 grupos COOR⁶, (C₁₋₅) alcoxi, (C₁₋₅)-alquiltio, (C₁₋₅)-perfluoroalquilo, ciano, nitro.(párrafos 10 y 11)	

R ⁵ significa un grupo C ₁₋₃ -alquilo parcial o completamente fluorado,	R ⁶ significa un grupo C ₁₋₃ -alquilo parcial o completamente fluorado (párrafo 19)	
R ⁶ es C ₁₋₁₀ alquilo, -R ⁹ (que puede ser arilo), con la excepción de -CH ₂ CH(CH ₃) ₂ , -CH=C(CH ₃) ₂ , -CH ₂ -C(CH ₃)=CH ₂	El equivalente de R ⁶ es un 2-metil-propil, 2-metil-prop-2-en-1-il, 2-metil-prop-1-en-1-il, (párrafo 20)	

El documento D1 se considera el estado de la técnica cercano a la invención definida en la reivindicación 1 porque divulga un compuesto de fórmula (I)



que posee actividad antiinflamatoria, Donde R¹ es un grupo fenilo sustituido (párrafo 9)

R² equivalente del R⁴ es un sistema de anillos monocíclico, bicíclico o, aromático, parcialmente aromático o, o no aromático, opcionalmente que contiene 1-3 átomos de nitrógeno, 1-2 átomos de oxígeno y/o 1-2 átomos de azufre y opcionalmente está sustituido en uno o más lugares de un radical que se selecciona del grupo carbonilo, halógeno, hidroxilo, o (C1-5)-alquilo, que puede estar opcionalmente sustituido por 1-3 grupos hidroxilo, 1-3 grupos (C1-5)-alcoxi y/o 1-3 grupos COOR⁶, (C1-5) alcoxi, (C1-5)-alquiltio, (C1-5)-perfluoroalquilo, ciano, nitro. (párrafos 10 y 11), R⁵ significa un grupo C1-3-alquilo parcial o completamente fluorado (párrafo 19).

La diferencia entre la invención, definida en la reivindicación 1 y compuesto de fórmula (I) de D1 consiste en que los valores de R⁶ de la actual invención excluyen los valores de R⁶. CH₂CH(CH₃)₂, -CH=C(CH₃)₂, -CH₂-C(CH₃)=CH₂.

Sin embargo, en la solicitud no se proporcionan datos que evidencien que los compuestos reclamados exhiban efectos o propiedades inesperadas en relación con los compuestos de D1. Además, el solicitante reclama compuestos que tienen un grupo alquilo simple como sustituyente de R⁶ y por lo tanto, solo una ligera diferencia respecto de los compuestos de D1 (propilo en lugar de isobutilo en los compuestos excluidos por el disclaimer). A estos compuestos no puede atribuírseles altura inventiva ya que no puede considerarse que el cambio de isobutilo a propilo tenga una gran influencia en la actividad dándoles un efecto mejorado frente a los compuestos de D1 y por tanto no se demuestra un efecto técnico inesperado.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: "cómo proporcionar compuestos alternativos a los conocidos en D1".

Sin embargo, el documento D4 ya divulga que las alteraciones menores en las cadenas de alquilo, tales como aumentar, disminuir la longitud de cadena o la ramificación de la misma, pueden tener efectos sobre la actividad farmacológica. Estos pequeños cambios son aspectos importantes en el diseño de análogos (Folios 473-474, páginas 47 -48)

En consecuencia, la persona del oficio normalmente versada en la materia se vería fuertemente motivada a incluir las enseñanzas sobre las variaciones en la longitud de la cadena alquímica divulgada anteriormente en D4 en los sustituyentes de R6 de los compuestos de D1 para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual se considera obvia.

Conclusión:

La reivindicación 1 cumple el requisito de novedad (Art. 16), pero no cumple con el requisito de nivel inventivo (Art. 18).

Puesto que las reivindicaciones dependientes 2 a 11 no mencionan características inventivas adicionales tampoco se pueden considerar inventivas.

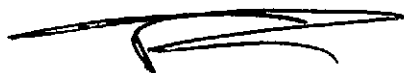
9. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US2005131226	1-11	Nivel inventivo
D2	GB1045180	22, 24	Novedad
D3	Journal Organic Chemistry Generation of Acyl Anion Equivalents from Acylphosphonates via Phosphonate-Phosphate Rearrangement: A Highly Practical Method for Cross-Benzoin Reaction	22, 24	Novedad
D4	Principles of medicinal chemistry Chapter 2 drug design and relationship of functional groups to pharmacologic activity,	1-11	Nivel inventivo

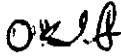
En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
02 OCT. 2012

Elaborado por: Harvey Alonso Jaramillo 
Revisado Por: Jacqueline Alfonso

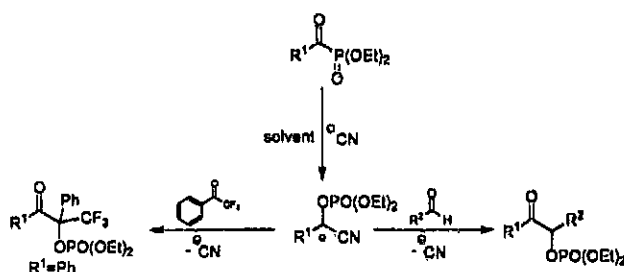
Generation of Acyl Anion Equivalents from Acylphosphonates via Phosphonate–Phosphate Rearrangement: A Highly Practical Method for Cross-Benzoin Reaction

Ayhan S. Demir,* Ömer Reis, A. Çiğdem İğdir, İlker Esiringü, and Serkan Eymur

Department of Chemistry, Middle East Technical University, 06531 Ankara, Turkey

asdemir@metu.edu.tr

Received August 28, 2005



Acylphosphonates are potent acyl anion precursors that generate acyl anion equivalents under the promotion of cyanide anion via phosphonate–phosphate rearrangement. These anions readily react with aldehydes to provide cross-benzoin products. In this way it is possible to synthesize a variety of aromatic–aromatic, aromatic–aliphatic, and aliphatic–aromatic benzoin. Moreover the reaction of benzoylphosphonate with potent electrophile 2,2,2-trifluoroacetophenone provided the corresponding aldehyde–ketone coupling product in high yield.

Polarity reversal (umpolung) of carbonyl group (acyl anion equivalents) provides a powerful alternative to traditional carbon–carbon bond construction methods and adds new dimensions of flexibility to the design of synthetic targets.¹ These useful entities have been traditionally obtained by functional group manipulation and stoichiometric strong base deprotonation of the corresponding carbonyl compounds. Recently impressive progress has been made in the catalytic generation of acyl anion equivalents, especially in the benzoin² and Stetter³ reactions. As far as the cross-benzoin and intramolecular Stetter reactions are concerned, the use of acylsilanes^{4,5}

as acyl anion precursors based on the nucleophile-promoted Brook rearrangement⁶ is the most practical and selective method available. However, acylsilanes for use as precursors suffer from tedious preparative operations that often require a stoichiometric strong base or metal nucleophiles, and most of the time they are synthesized from the corresponding acyl anions.⁷ Thus, there is always a need for practical and easily accessible acyl anion precursors that can engage in catalytic carbon–carbon bond-forming reactions.

Phosphorus, like silicon, has the ability to migrate from carbon to oxygen and oxygen to carbon. In fact deprotonation of α -hydroxyphosphonates and base-catalyzed addition of dialkyl phosphites to acylphosphonates induce such phosphonate–phosphate rearrangements, which have a close analogy to the 1,2-Brook rearrangement of acylsilanes.⁸ We envisioned that the typical nucleophilic catalysis of benzoin and Stetter reactions might promote acylphosphonates to generate an appropriate concentration of the corresponding acyl anion equivalents that are sufficiently nucleophilic in order to participate in the reactions with electrophiles. It is very important to note that Johnson and co-workers very recently reported the viability of this approach in the synthesis of a variety of aromatic–aromatic cross-benzoin products **3** from aromatic acylphosphonates, with [18-crown-6/KCN] complex as catalyst in diethyl ether providing the optimal conditions (Scheme 1).⁹ Moreover Kurihara reported stoichiometric strong base deprotonation of α -cyanophosphates generating cyano-phosphate anions **1b** that react with a variety of electrophiles including aldehydes to provide **3**.¹⁰ However, they reported that cyano-phosphate anions **1b**

(1) For recent reviews, see: (a) Johnson, J. S. *Angew. Chem., Int. Ed.* 2004, 43, 1326–1328. (b) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* 2004, 37, 534–541. (c) Pohl, M.; Linggen, B.; Müller, M. *Chem. Eur. J.* 2002, 8, 5288–5295.

(2) (a) Enders, D.; Kalfass, U. *Angew. Chem., Int. Ed.* 2002, 41, 1743–1745 and references therein. (b) Dunkelmann, P.; Kolter-Jung, D.; Nitscho, A.; Demir, A. S.; Siegert, P.; Linggen, B.; Baumann, M.; Pohl, M.; Müller, M. *J. Am. Chem. Soc.* 2002, 124, 12084–12085. (c) Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc.* 2003, 125, 8432–8433. (d) Hachisu, Y.; Bode, J. W.; Suzuki, K. *Adv. Synth. Catal.* 2004, 346, 1097–1100. (e) Enders, D.; Oliver, N. *Synlett* 2004, 2111–2114.

(3) (a) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* 2004, 126, 8876–8877. (b) Road de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* 2005, 127, 6284–6289. (c) Enders, D.; Brouer, K.; Runsink, J.; Telos, J. H. *Helv. Chim. Acta* 1996, 79, 1899–1902. (d) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* 2004, 126, 2025–2035. (e) Mennen, S.; Blank, J.; Tan-Dubs, M. B.; Imbriglio, J. E.; Miller, S. *J. Chem. Commun.* 2005, 195–197. (f) Murry, J. E.; Frantz, D. E.; Schell, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* 2001, 123, 9696–9697.

(4) For examples of acylsilanes in benzoin synthesis, see: (a) Linghu, X.; Johnson, J. S. *Angew. Chem., Int. Ed.* 2003, 42, 2584–2586. (b) Linghu, X.; Potnick, J. R.; Johnson, J. S. *J. Am. Chem. Soc.* 2004, 126, 3070–3071. (c) Ricci, A.; Degl'Innocenti, A.; Chimichi, S.; Fioranza, M.; Rossini, G. *J. Org. Chem.* 1985, 50, 130–133. For application of benzils in benzoin synthesis, see: (d) Kuebrich, J. P.; Schowen, R. L. *J. Am. Chem. Soc.* 1971, 93, 1220–1223. (e) Demir, A. S.; Reis, Ö. *Tetrahedron* 2004, 60, 3803–3811.

(5) Stetter reaction with acylsilanes. For organocatalysis, see: (a) Mattson, A. E.; Bharadwaj, A. R.; Scheldt, K. A. *J. Am. Chem. Soc.* 2004, 126, 2314–2315. For metallophosphite catalysis, see: (b) Nahm, M. R.; Linghu, X.; Potnick, J. R.; Yates, C. M.; White, P. S.; Johnson, J. S. *Angew. Chem., Int. Ed.* 2005, 44, 2377–2379. For cyanide catalysis, see: (c) Degl'Innocenti, A.; Ricci, A.; Mordini, A.; Raginato, G.; Colotta, V. *Gazz. Chim. Ital.* 1987, 117, 646–648.

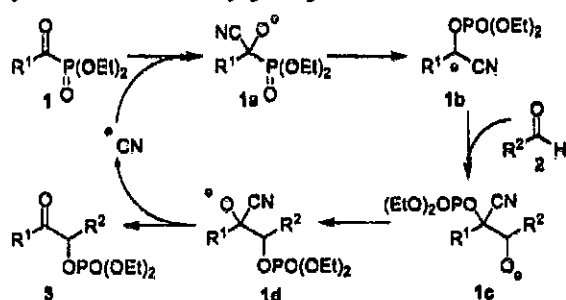
(6) (a) Brook, A. G. *Acc. Chem. Res.* 1974, 7, 77–84. (b) Moser, W. H. *Tetrahedron* 2001, 57, 2085–2084 and references therein.

(7) Clark, C. T.; Milgram, B. C.; Scheldt, K. *Org. Lett.* 2004, 6, 3977–3980.

(8) (a) Hammerschmidt, F.; Schneyder, E.; Zbiral, E. *Chem. Ber.* 1980, 113, 3891–3897. (b) Fitch, S.; Moodritzer, K. *J. Am. Chem. Soc.* 1962, 84, 1876. (c) Ruel, R.; Bouvier, J.-P.; Young, R. N. *J. Org. Chem.* 1995, 60, 5209–5213. Cyanide anion promoted phosphonate–phosphate rearrangement of acetylphosphonate in aqueous medium was reported; see: (d) Hall, L. A. R.; Stephens, C. W.; Drysdale, J. J. *J. Am. Chem. Soc.* 1957, 79, 1768–1769.

(9) Bausch, C. C.; Johnson, J. S. *Adv. Synth. Catal.* 2005, 347, 1207–1211.

SCHEME 1. Mechanism of Cross-Benzoin Reaction via Cyanide Ion Promoted Generation of Acyl Anions from Acylphosphonates



with electron-rich aromatic and aliphatic groups are not useful in this particular transformation. Herein, we report our preliminary results in the realization of this idea utilizing acylphosphonates **1** as the acyl anion precursors and aldehydes **2** as electrophiles in the presence of a cyanide catalyst to provide cross-benzoin products **3** (Scheme 1).¹¹ Acylphosphonates are readily available on a multigram scale from acyl chlorides and trialkyl phosphites via Arbuzov reaction without need to use any special condition or apparatus.¹²

We initially investigated the reaction of benzoylphosphonate with *p*-anisaldehyde catalyzed by 10% KCN in the presence of phase transfer catalysts (Bu_4NBr or 18-crown-6) in various solvents and observed very slow or no conversion in many solvents at ambient temperature. Although heating provided varying degrees of conversions in different solvents, reaction in DMF provided a smooth and fast transformation into the desired product **3a** in 93% yield at ambient temperature without using a phase transfer catalyst (Table 1, entry 1).

Next, we investigated the scope of this reaction for the synthesis of typical aromatic-aromatic benzoin. Reaction of benzoylphosphonate with various aromatic aldehydes furnished the expected products in good to excellent yields (Table 1, entries 1–8). Heterocyclic aldehydes provided the expected products **3e** and **3g**, albeit contaminated with isomeric benzoin **3f** and **3h** (Table 1, entries 5–8). This concurrent regioisomerization process was also pointed out by Johnson and co-workers.⁹ Whereas lowering the temperature (0 °C) provided the expected products without isomer contamination, increasing the catalyst load (30%) quickly furnished the isomeric products. In this way the synthesis of both isomeric benzoin was possible from the same starting materials. Formation of isomeric benzoin is presumably due to the basic cyanide-catalyzed isomerization of the expected benzoin. In fact, the treatment of isolated pure **3g** with catalytic DBU under the same reaction conditions afforded **3h** with complete conversion. To understand the scope of the

TABLE 1. Synthesis of Aromatic-Aromatic Benzoin^a

entry	R ¹	R ²	Product	Yield (%) ^b
1	Ph	4-OMePh		93
2	Ph	4-FPh		83
3	Ph	3,5-(OMe) ₂ Ph		88
4	Ph	1-naphthyl		87
5	Ph	2-furyl		81
6	Ph	2-furyl		85
7	Ph	2-thienyl		86
8	Ph	2-thienyl		89
9	4-FPh	Ph		87
10	4-FPh	4-OMePh		93
11	4-OMePh	Ph		91
12	4-OMePh	4-FPh		94

^a Reactions were carried out on a 1 mmol scale (1.1 equiv of aldehyde) with concentrations of 0.5 M in the presence of 10% KCN at room temperature except for entries 5 and 7 at 0 °C and entries 6, 8, 11, and 12 with 30% KCN. ^b Isolated yields.

method in synthesizing all of the isomers of a given pair of a donor and acceptor, we examined the reaction of substituted acylphosphonates. Whereas the reaction of 4-*F*-benzoylphosphonate proceeded smoothly to give disubstituted cross-benzoin **3i** and **3j** in very good yields (Table 1, entries 9–10), electron-rich 4-MeO-benzoylphosphonate reacted very slowly under the usual reaction conditions. Gratifyingly, simply increasing the catalyst load (30% KCN) resulted in a smooth transformation providing **3k** and **3l** in very good yields (Table 1, entries 11 and 12).

(10) For examples of stoichiometric generation of acyl anion equivalents from α -cyanophosphates and their reactions, see: (a) Kurihara, T.; Santo, K.; Harusawa, S.; Yoneda, R.; *Chem. Pharm. Bull.* **1987**, *35*, 4777–4788. (b) Schrader, T. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 917–919.

(11) This mechanistic picture is based on the well-known benzoin reaction mechanism and its congeners; see refs 1, 4, and 9.

(12) (a) Berlin, K. D.; Taylor, H. A. *J. Am. Chem. Soc.* **1964**, *86*, 3862–3866. (b) Maeda, H.; Takahashi, K.; Ohmori, H. *Tetrahedron* **1998**, *54*, 12233–12242.

TABLE 2. Synthesis of Aromatic-Aliphatic and Aliphatic-Aromatic Benzoin^a

$\text{R}^1-\text{P}(\text{OEt})_2 + \text{R}^2-\text{CHO} \xrightarrow[\text{solvent}]{\text{cat.}} \text{R}^1-\text{CH}(\text{R}^2)-\text{COP}(\text{OEt})_2$				
entry	R ¹	R ²	Product	Yield (%) ^b
1	Ph	cyclohexyl		87
2	4-FPh	cyclohexyl		81
3	4-OMePh	cyclohexyl		85
4	Ph	benzyloxymethyl		81
5	4-FPh	benzyloxymethyl		75
6	4-OMe	benzyloxymethyl		77
7	cyclohexyl	Ph		64
8	(CH ₃) ₃ C	Ph		87

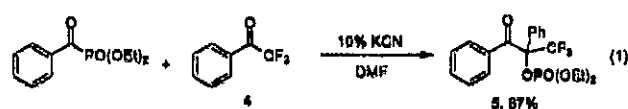
^a For entries 1–6, reactions were carried out in premixed DMF solution of 20% CsF and 30% TMSCN (see Supporting Information for details). For entries 7 and 8, 2 equiv of aldehyde with 30% KCN and 30% 18-crown-6 in toluene (5 mL, 0.2 M) was heated to 100 °C. ^b Isolated yields.

After establishing the utility of acylphosphonates in aromatic–aromatic cross-benzoin synthesis, we investigated their potential in the incorporation of aliphatic moieties into the benzoin structure and started with the reactions of aroylphosphonates with aliphatic aldehydes. Although the initial reactions with the KCN catalyst provided the expected benzoin, yields were low with considerable side product(s) contamination. Later we found that the DMF solution of premixed CsF (20%) and TMSCN (30%) was superior to KCN in terms of conversion rates and product purity. In fact the reaction of aroylphosphonates with cyclohexanecarboxaldehyde and benzyloxyacetaldehyde furnished the products in good yields (Table 2, entries 1–6).

The use of both KCN and CsF + TMSCN in DMF failed to give good yields in reactions between aliphatic acylphosphonates and aromatic aldehydes. Presumably the highly enolizable nature of aliphatic acylphosphonates resulted in the protonation of the critical acyl anion equivalent, and hence the presumed catalytic cycle failed (Scheme 1). We found that the use of 30% KCN and 30% 18-crown-6 in refluxing toluene provided better yields (Table 2, entries 7 and 8). Although we examined the reactions of a wide range of aliphatic acylphosphonates 1 (R¹ = cyclohexyl, isopropyl, methyl) and aromatic aldehydes 2 (R² = Ph, 4-OMePh, 4-FPh) to obtain aliphatic–aromatic

benzoin in the 60–70% yield range, the formation of a protonation product (15–20%) was unavoidable. The separation of this product to obtain pure products proved to be highly problematic. When reaction was carried out with nonenolizable trimethylacetylphosphonate, good yield of the corresponding benzoin was obtained smoothly in toluene (Table 2, entry 8). Last, the syntheses of aliphatic–aliphatic cross-benzoin 3 (R¹ = cyclohexyl, isopropyl, methyl and R² = cyclohexyl, isopropyl, methyl) were very sluggish, providing only <20% estimated yields.

Prompted by the success of acylphosphonates as acyl anion precursors in benzoin condensation, we carried out preliminary experiments to further study the potential of these entities. Catalytic intermolecular coupling of aldehydes and ketones has not been realized so far.^{2c–e} Thus, we examined the reaction of benzoylphosphonate with potent electrophile 2,2,2-trifluoroacetophenone 4, which furnished the expected coupling product 5 in 87% yield (eq 1). The same reaction with acetophenone only provided poor yields together with the recovered starting materials.



In conclusion, we have shown that acylphosphonates are a new generation of potent acyl anion precursors that undergo nucleophile-promoted phosphonate–phosphate rearrangement to provide the corresponding acyl anion equivalents as reactive intermediates. Compared to laborious synthesis of acylsilanes, they are readily available on a multigram scale from the corresponding carboxylic acids or aldehydes, which offers an atom- and time-efficient access to acyl anions. They add a new and highly practical method to the toolbox of synthetic chemists. Current work is directed toward further understanding the nature and reactivity of acylphosphonates as acyl anion precursors in reactions with various electrophiles and development of enantioselective version of the presented reaction.

Experimental Section

General Procedures for Cyanide-Catalyzed Cross-Benzoin Reactions. Reactions were carried out according to different procedures depending on the nature of the substrates. Briefly, reactions between aromatic acylphosphonates were carried out in DMF with 10% KCN catalysis (Method A), and slight modifications in temperature (0 °C, Method B) or catalyst load (30% KCN, Method C) were made to optimize yields. Reactions between aromatic acylphosphonates and aliphatic aldehydes were carried out in DMF with CsF + TMSCN catalysis (Method D), and reactions between aliphatic acylphosphonates and aromatic aldehydes were carried out in toluene with 30% KCN and 30% 18-crown-6 as catalyst system (Method E). Representative procedures are as follows.

Representative Example for Method A: Diethyl 2-(4-fluorophenyl)-1-(4-methoxyphenyl)-2-oxoethyl phosphonate (3j). The title compound was prepared according to Method A using 260 mg (1 mmol) of acylphosphonate, 149.8 mg (1.1 mmol) of *p*-methoxybenzaldehyde, 6.5 mg (10%, 0.1 mmol) KCN, and 2 mL of DMF. After 25 min at ambient temperature, the crude product was purified by flash chromatography with 1:3 petroleum ether/ether to afford 368 mg (93%) of the product as a

colorless oil: IR (film) 2986, 2839, 1698, 1601, 1512, 1461, 1443, 1257, 1177, 1159, 1044, 986 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.16 (2H, t, $J = 7.0$ Hz), 1.33 (3H, t, $J = 6.7$ Hz), 3.76 (3H, s), 3.88–3.96 (2H, m), 4.14–4.26 (2H, m), 6.58 (1H, d, $J = 7.8$ Hz), 6.89 (2H, d, $J = (8.7$ Hz), 7.05 (2H, m), 7.41 (2H, d, $J = 8.7$ Hz), 7.94–7.98 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 16.2 (d, $J = 6.9$ Hz), 16.3 (d, $J = 6.9$ Hz), 55.6, 64.2 (d, $J = 6.3$ Hz), 65.0 (d, $J = 6.0$ Hz), 80.0 (d, $J = 4.8$ Hz), 114.9, 116.1 (d, $J = 22.0$ Hz), 127.1, 130.0, 131.1 (d, $J = 2.9$ Hz), 132 (d, $J = 9.2$ Hz), 160.8, 166.1 (d, $J = 255$ Hz), 192.4 (d, $J = 4.7$ Hz); ^{31}P NMR (161 MHz, CDCl_3) δ -1.19. Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{FO}_6\text{P}$: C, 57.58; H, 5.69. Found: C, 57.31; H, 5.32.

Representative Example for Method B: Diethyl 2-oxo-2-phenyl-1-(thiophen-2-yl)ethyl phosphate (3g). The title compound was prepared according to Method B using 242 mg (1 mmol) of acylphosphonate, 123 mg (1.1 mmol) of 2-thiophenecarboxaldehyde, 6.5 mg (10%, 0.1 mmol) KCN, and 2 mL of DMF. After 30 min at 0 $^\circ\text{C}$, the crude product was purified by flash chromatography with 1:3 petroleum ether/ether to afford 305 mg (86%) of the product as a pale yellow oil: IR (film) 2968, 1695, 1516, 1443, 1435, 1282 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.20 (3H, dt, $J = 1, 7$ Hz), 1.31 (3H, dt, $J = 1, 7.9$ Hz), 3.9–4.05 (2H, m), 4.1–4.25 (2H, m), 6.9 (1H, dj, $J = 7.9$ Hz), 6.96 (1H, dd, $J = 3.6, 5.1$ Hz), 7.17 (1H, dd, $J = 1.1, 3.6$ Hz), 7.36 (1H, dd, $J = 1.1, 5.1$ Hz), 7.4–7.44 (2H, m), 7.51–7.57 (1H, m), 7.95–7.9 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 15.73 (d, $J = 7.3$ Hz), 15.85 (d, $J = 6.8$ Hz), 63.9 (d, $J = 6.3$ Hz), 64.3 (d, $J = 5.9$ Hz), 74.7 (d, $J = 4.2$ Hz), 127.2, 128.2, 128.6, 128.7, 128.9, 133.6, 134.0, 136.6 (d, $J = 6.2$ Hz), 192.2 (d, $J = 4.8$ Hz); ^{31}P NMR (161 MHz, CDCl_3) δ -2.61. Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{O}_6\text{PS}$: C, 54.23; H, 5.40. Found: C, 54.05; H, 5.26.

Representative Example for Method C: Diethyl 1-(4-fluorophenyl)-2-(4-methoxyphenyl)-2-oxoethyl phosphate (3l). The title compound was prepared according to Method C using 272 mg (1 mmol) of acylphosphonate, 136.5 mg (1.1 mmol) of *p*-fluorobenzaldehyde, 19.5 mg KCN (30%, 0.3 mmol), and 2 mL of DMF. After 6 h at ambient temperature, the crude product was purified by flash chromatography with 1:3 petroleum ether/ether to afford 372 mg (94%) of the product as a colorless oil: IR (film) 2993, 1693, 1601, 1511, 1261, 1173, 1037, 986 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.18 (3H, t, $J = 7.1$ Hz), 1.33 (3H, t, $J = 7.1$ Hz), 3.84 (3H, s), 3.89–3.98 (2H, m), 4.14–4.24 (2H, m), 6.60 (1H, d, $J = 8.1$ Hz), 6.9 (2H, d, $J = 8.8$ Hz), 7.06 (2H, m), 7.45–7.55 (2H, m), 7.93 (2H, d, $J = 8.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 15.8 (d, $J = 7.1$ Hz), 16.0 (d, $J = 7.0$ Hz), 55.4, 63.9 (d, $J = 6.2$ Hz), 63.9 (d, $J = 6$ Hz), 78.8 (d, $J = 4.9$ Hz), 114, 116 (d, $J = 22.1$ Hz), 130 (d, $J = 8.2$ Hz), 131.3, 163.1 (d, $J = 251$ Hz), 163.9, 191.7 (d, $J = 4.9$ Hz); ^{31}P NMR (161 MHz,

CDCl_3) δ -2.30. Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{FO}_6\text{P}$: C, 57.58; H, 5.59. Found: C, 57.52; H, 5.61.

Representative Example for Method D: 3-(Benzyloxy)-1-oxo-1-phenylpropan-2-yl diethyl phosphate (3p). The title compound was prepared according to Method D using 242 mg (1 mmol) of acylphosphonate, 165 mg (1.1 mmol) of benzyloxyacetaldehyde, 30 mg CsF (20%), 29.7 mg TMSO (30%), and 2 mL of DMF. After 5–10 min at ambient temperature, the crude product was purified by flash chromatography with 1:3 petroleum ether/ether to afford 318 mg (81%) of the product as a colorless oil: IR (film) 2950, 2354, 1692, 1695, 1515, 1451 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.1–1.23 (6H, m), 3.8–3.83 (2H, m), 3.96–4.09 (4H, m), 4.43–4.52 (2H, m), 5.74–5.79 (1H, m), 7.14–7.23 (5H, m), 7.36–7.41 (2H, m), 7.49–7.53 (1H, m), 7.86–7.89 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 15.9 (d, $J = 2.76$ Hz), 16.0 (d, $J = 2.79$ Hz), 64.12 (d, $J = 6.0$ Hz), 64.2 (d, $J = 6.0$ Hz), 70.4 (d, $J = 6.1$ Hz), 73.4, 77.9 (d, $J = 5.4$ Hz), 127.6, 127.8, 128.3, 128.8, (d, $J = 3.0$ Hz), 133.6, 134.9, 137.3, 194.8 (d, $J = 3.0$ Hz); ^{31}P NMR (161 MHz, CDCl_3) δ -2.27. Anal. Calcd for $\text{C}_{20}\text{H}_{25}\text{O}_6\text{P}$: C, 61.22; H, 6.42. Found: C, 61.42; H, 6.64.

Representative Example for Method E: 2-Cyclohexyl-2-oxo-1-phenylethyl diethyl phosphate (3t). The title compound was prepared according to Method E using 248 mg (1 mmol) of acylphosphonate, 212.2 mg (2 mmol) of benzaldehyde, 18.5 mg KCN (30%, 0.3 mmol), 79 mg (30%, 0.3 mmol) of 18-crown-6, and 5 mL of toluene. After 6 h at 100 $^\circ\text{C}$, the crude product was purified by flash chromatography with 1:3 petroleum ether/ether to afford 227 mg (64%) of the product as a colorless oil: IR (film) 2926, 1692, 1655, 1512, 1450, 1280, 1229, 1031 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.16 (3H, dt, $J = 0.9, 7.2$ Hz), 1.34 (3H, dt, $J = 0.9, 6.9$ Hz), 1.10–1.45 (5H, m), 1.60–1.83 (5H, m), 2.50 (1H, m), 3.84–3.94 (2H, m), 4.11–4.21 (2H, m), 5.75 (1H, d, $J = 8.1$ Hz), 7.30–7.40 (5H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 15.9 (2C, m), 25.2, 25.6, 25.7, 28.0, 29.3, 29.7, 46.7, 64.1 (2C, m), 81.9 (d, $J = 5.2$ Hz), 127.9, 128.9, 129.3, 134.5, 207.2; ^{31}P NMR (161 MHz, CDCl_3) δ -2.44. Anal. Calcd for $\text{C}_{18}\text{H}_{27}\text{O}_6\text{P}$: C, 61.01; H, 7.68. Found: C, 61.24; H, 7.52.

Acknowledgment. This work was supported by Middle East Technical University and Turkish Academy of Sciences.

Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO051811U

REFINEMENT OF THE LEAD STRUCTURE

Determination of the Pharmacophore

Once a lead compound has been discovered for a particular therapeutic use, the next step is to determine the pharmacophore for this compound. The pharmacophore of a drug molecule is that portion of the molecule containing the essential organic functional groups that directly interact with the receptor active site and, therefore, confers on the molecule the biological activity of interest. Because drug-receptor interactions can be very specific, the pharmacophore may constitute a small portion of the molecule. It has been found on several occasions that what seem to be very complex molecules can be reduced to simpler structures with retention of the desired biological action. An example of this is the narcotic analgesic morphine, which is a tetracyclic compound with five chiral centers. Not only would simplification of the structure possibly provide molecules with fewer side effects, a reduction in the number of chiral centers would greatly simplify the synthesis of morphine derivatives and, thereby, decrease cost. Figure 2.30 shows how the morphine structure has been simplified in the search for compounds with fewer deleterious side effects, such as respiratory depression and addiction potential. Within each class are analogues that are less potent, equipotent, and many times more potent than morphine. It can be readily seen from the figure that the pharmacophore of morphine must consist of a tertiary alkylamine that is at least four atoms away from an aromatic ring. A more detailed discussion of the chemistry and pharmacology of morphine can be found in Chapter 24.

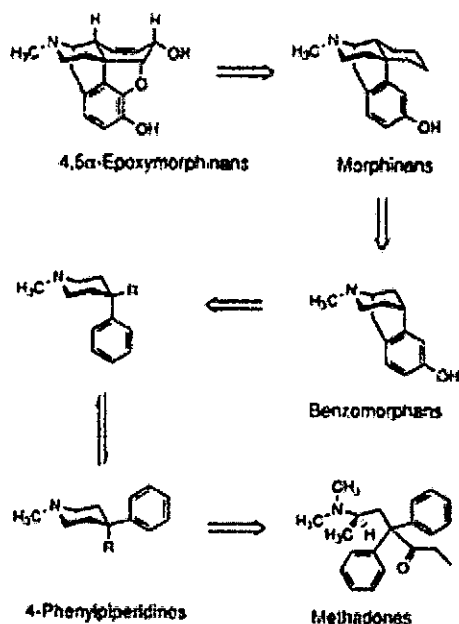
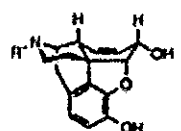


Fig. 2.30. Morphine pharmacophore and its relationship to analgesic derivatives.

Alterations in Alkyl Chains: Chain Length, Branching, and Rings

Alterations in alkyl chains, such as increasing or decreasing chain length (homologation), branching, and changing ring size, can have profound effects on the potency and pharmacologic activity of the molecule. Simply changing the length of an alkyl chain by one CH_2 unit or branching the chain will alter the lipophilic character of the molecule and, therefore, its properties of absorption, distribution, and excretion. If the alkyl chain is directly involved in the receptor interaction, then chain length and branching can alter the binding characteristics. Molecules that are conformationally flexible may become less flexible if branching is introduced at a key position of an alkyl chain. Changes in conformation will affect the spatial relationship of functional groups in the molecule, thereby influencing receptor binding. Changes as small as one CH_2 unit may seem trivial at first, but in many instances, such small changes are important aspects in the design of analogues.

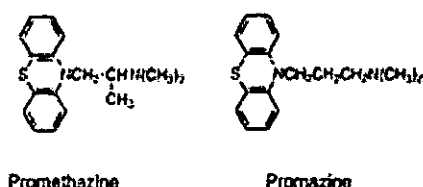
An example in which simply increasing hydrocarbon chain length has significant effects not only on potency but also on the agonistic or antagonistic action of a molecule is provided by a series of N-alkyl morphine analogues (Fig. 2.31). In this series, going from $\text{R}=\text{CH}_3$ (morphine) to $\text{R}=\text{CH}_2\text{CH}_2\text{CH}_3$ (N-propylnormorphine) produces a pronounced decrease in agonist activity and an increase in antagonist activity. When $\text{R}=\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ (N-butylnormorphine), the compound is totally devoid of agonist or antagonist activity (i.e., the compound is inactive), but further increases in chain length ($\text{R}=\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ and $\text{R}=\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$) produce compounds with increasing potency as agonists. When R is β -phenylethyl, the compound is a full agonist, with a potency approximately 14-fold that of morphine (28,29).



R	Pharmacological activity
$-\text{CH}_3$	Analgesic (morphine)
$-\text{CH}_2\text{CH}_3$	Opioid agonist activity decreased
$-\text{CH}_2\text{CH}_2\text{CH}_3$	Opioid antagonist activity increased
$-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	Inactive as opioid agonist or antagonist
$-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	Opioid antagonist activity increased
$-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	
$-\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$	14X potency of morphine

Fig. 2.31. Effect of alkyl chain length on activity of morphine.

Branching of alkyl chains also can produce drastic changes in potency and pharmacologic activity. If the mechanism of action is closely related to the lipophilicity of the molecule, then branching of a hydrocarbon chain will result in a less lipophilic compound and significantly altered biological effect. This decrease in lipophilicity as the result of hydrocarbon chain branching results from the chain becoming more compact and, therefore, produces less disruption of the hydrogen-bonding network of water. If the hydrocarbon chain is directly involved in receptor interactions, then branching can produce major changes in pharmacologic activity. For example, consider the phenothiazines promethazine and promazine:



The primary pharmacologic activity of promethazine is that of an antihistamine, whereas promazine is an antipsychotic. The only difference between the two is the alkylamine side chain. In the case of promethazine, it contains a isopropylamine side chain, whereas promazine has a n-propylamine. In this case, the small change of one carbon atom from a branched to a linear hydrocarbon radically alters the pharmacologic activity.

Position isomers of substituents on aromatic rings also may possess different pharmacologic properties. Substituents on aromatic rings can alter the electron distribution throughout the ring, which in turn can affect how the ring interacts with the receptor. Ring substituents also may influence the conformation of a flexible molecule, especially if they are located *ortho* to flexible side chains and can participate in steric or electronic intramolecular interactions (e.g., hydrogen; ion-dipole, or ion-ion bonds). Ring substituents influence the conformations of adjacent substituents via steric interactions and may significantly affect receptor interactions. Aromatic methoxy groups *ortho* to two other substituents take on a conformation perpendicular to the plane of the aromatic ring in hallucinogenic phenylalkylamines (Fig. 2.32) and can explain the lack of hallucinogenic activity in these compounds (30).

FUNCTIONAL GROUP MODIFICATION: ISOSTERISM AND BIOISOSTERISM

Isosterism

When a lead compound is first discovered for a particular disease state, it often lacks the required potency and pharmacokinetic properties suitable for making it a viable clinical candidate. These may include undesirable side effects, physicochemical properties, other factors

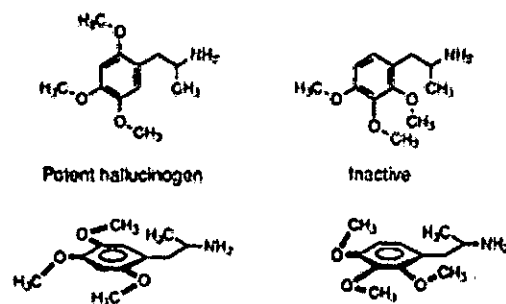


Fig. 2.32. Effect of positional isomers on structural conformation and biological activity.

that affect oral bioavailability (see Chapter 9), and adverse metabolic or excretion properties. These undesirable properties could be the result of specific functional groups in the molecule. The medicinal chemist therefore must modify the compound to reduce or eliminate these undesirable features without losing the desired biological activity. Replacement or modification of functional groups with other groups having similar properties is known as "isosteric replacement," or "bioisosteric replacement."

In 1919, Langmuir (31,32) first developed the concept of chemical isosterism to describe the similarities in physical properties among atoms, functional groups, radicals, and molecules. The similarities among atoms described by Langmuir primarily resulted from the fact that these atoms contained the same number of valence electrons and came from the same columns within the periodic table. This concept was limited to elements in adjacent rows and columns, inorganic molecules, ions, and small organic molecules, such as diazomethane and ketene. Table 2.7 shows a comparison of the physical properties of N_2O and CO_2 to illustrate Langmuir's concept.

To account for similarities between groups with the same number of valence electrons but different numbers of atoms, Grimm (33) developed his hydride displacement law. This is not a "law" in the strict sense but, rather, more an illustration of similar physical properties among closely related functional groups. Table 2.8 presents an example of hydride displacement. Descending diagonally from left to right in the table, hydrogen atoms are progressively added to maintain the same number of

Table 2.7. Comparison of Physical Properties of N_2O and CO_2

Property	N_2O	CO_2
Viscosity at 20°C	148×10^{-6}	148×10^{-6}
Density of liquid at 10°C	0.856	0.858
Refractive index of liquid, D line 16°C	1.193	1.190
Dielectric constant of liquid at 0°C	1.593	1.582
Solubility in alcohol at 15°C	3.250	3.130