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ABOGADOS

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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-077067- -00005-0000

Fecha: 2011-10-07 16:42:32 Dep. 2020 DIR.NUEVASOR
Tra. 11 PATENTEIYII Eva: 379 FASENACIONALII
Act. 523 RESPUESTA Folios: 51

Re: **PI.-ARENA PHARMACEUTICALS INC.-Solicitud de Patente de Invención en Fase Nacional PCT para "DERIVADOS DEL PIRIMIDINIL Y PIRIDINIL SUSTITUIDOS COMO MODULADORES DEL METABOLISMO Y EL TRATAMIENTO DE DESÓRDENES RELACIONADOS CON EL MISMO".- Clase C07D 401/14.-Expediente número 07-077.067.-**

1. Me refiero al auto dictado por ese Despacho notificado por fijación en lista de 15 de Julio de 2011.

2. Con el fin de responder a las objeciones expuestas por el Señor Examinador en su Concepto Técnico No. **1575** bajo los acápites de claridad, reivindicaciones relativas a un uso o un segundo uso y nivel inventivo, atentamente me permito presentar los siguientes argumentos técnicos y las siguientes modificaciones en el capítulo reivindicatorio de la solicitud, por medio de lo cual se superan completamente dichas objeciones.

3. **MODIFICACIONES A LA SOLICITUD**

Inicialmente me permito señalar ante ese Despacho que el solicitante ha decidido realizar las siguientes modificaciones en el capítulo reivindicatorio de la invención:

- Eliminar la posibilidad de que en la reivindicación 1 la variable R^4 represente un grupo C_{2-4} alquilil, así como la posibilidad de que los posibles grupos químicos representados por la variable R^5 puedan estar opcionalmente sustituidos con un grupo C_{2-4} alquilil;
- Eliminar la posibilidad de que en la reivindicación 1 la variable R^5 pueda representar un grupo de fórmula (A);
- En la reivindicación 20, eliminar la posibilidad de que la variable R^4 pueda representar un grupo $C\equiv CH$;

- Eliminar las reivindicaciones 23, 24, 25, 35, 50 a 62 y 112 a 124 actualmente presentadas y modificar la numeración del nuevo capítulo reivindicatorio de conformidad con lo anteriormente mencionado;
- Eliminar la posibilidad de que en la reivindicación 63 (nueva reivindicación 46) la variable R^4 represente un grupo C_{2-4} alquilil, así como la posibilidad de que los posibles grupos químicos representados por la variable R^5 puedan estar opcionalmente sustituidos con un grupo C_{2-4} alquilil;
- Eliminar la posibilidad de que en la reivindicación 63 (nueva reivindicación 46) la variable R^5 pueda representar un grupo de fórmula (A); y,
- En la reivindicación 76 (nueva reivindicación 59), eliminar la posibilidad de que la variable R^4 pueda representar un grupo $C\equiv CH$.

Finalmente y de conformidad con lo expuesto previamente, me permito manifestar antes ese Despacho que las modificaciones realizadas en el capítulo reivindicatorio de la solicitud de patente en cuestión de ninguna manera constituyen una ampliación en el alcance de la invención presentada originalmente, cumpliendo por lo tanto a cabalidad con las disposiciones de patentabilidad establecidas en el artículo 34 de la Decisión 486 de 2000.

4. CLARIDAD DE LA SOLICITUD

Ahora bien, el señor Examinador ha objetado la claridad del capítulo reivindicatorio aduciendo lo siguiente:

- ***"No se encuentran sustentados los solvatos e hidratos del compuesto de fórmula I y sus reivindicaciones dependientes en la descripción"***

Frente a éste particular me permito señalar que la persona medianamente versada en la materia reconoce y se encuentra en plena capacidad de poner en práctica los procesos experimentales de rutina que son requeridos para obtener los hidratos y solvatos de una molécula orgánica determinada.

Así, por ejemplo, es claro que para obtener los hidratos y solvatos de un compuesto orgánico es necesario poner en contacto una muestra de dicho compuesto con agua u otro solvente orgánico, de manera que una vez los hidratos o solvatos se han formado, éstos pueden ser fácilmente analizados mediante ensayos de rutina como análisis termogravimétrico, calorimetría de barrido diferencial, titulación Karl Fischer, difracciones de rayos-X (en polvo o de cristal sencillo), espectroscopía infrarroja, microscopía de luz polarizada, microscopía de platina caliente (ver por ejemplo la página 18, columna

derecha del artículo científico: Vippagunta et al., *Advanced Drug Delivery Reviews* 48 (2001) 3-26 (Anexo b) u otras técnicas de rutina para detectar y cuantificar la presencia de moléculas de hidratos o solvatos en una muestra.

Ahora bien, en este sentido es absolutamente claro que la exposición de un compuesto orgánico a agua o cualquier otro solvente se lleva a cabo a través de métodos experimentales simples, tales como permitir que la muestra entre en contacto con aire durante períodos de tiempo específicos, así como fluidificar y/o cristalizar las muestras a partir de una solución con agua u otro solvente. Otros, procedimientos típicos para obtener e identificar hidratos y solvatos son descritos en las páginas 202 a 209 del documento K. J. Guillory, *"Generation of Polymorphs, Hydrates, Solvates and Amorphous solids"*, en el libro titulado *"Polymorphism in Pharmaceutical Solids"*, ed., Harry G. Britain, Vol. 95. marcel Dekker, Inc., New York, 1999 (Anexo c).

Por lo tanto, debido a que la preparación de hidratos y solvatos implica el uso de métodos de laboratorio plenamente conocidos y que no requieren un esfuerzo excesivo, es claro que la inclusión dentro del alcance de la solicitud de patente en cuestión de los solvatos e hidratos de los compuestos revelados de ninguna manera implica una falta de claridad de la invención o una ampliación en el alcance de la solicitud presentada y soportada por la descripción. En consecuencia, atentamente me permito solicitar al señor Examinador la reconsideración de las objeciones realizadas a éste respecto.

Por último y aparte de lo señalado previamente, considero de gran importancia destacar ante ese Despacho que la Oficina Europea de Patentes ha reconocido la patentabilidad de los solvatos e hidratos de los compuestos revelados en la presente invención (ver patente EP 1 911 756).

- ***"Las reivindicaciones 57-62 y 118-124 se encuentran caracterizadas por el uso"***

En respuesta a lo anterior y de conformidad con lo mencionado previamente en el numeral 3 del presente memorial, el solicitante ha decidido eliminar las reivindicaciones 57 a 62 y 118 a 124 presentadas originalmente, con lo cual se superan completamente las objeciones realizadas por el señor Examinador a éste respecto.

- ***"Se sugiere restringir los compuestos de la solicitud presentada a aquellos que se encuentren sustentados en la descripción"***

Frente a éste particular, inicialmente me permito destacar ante ese Despacho que el solicitante ha decidido restringir drásticamente el alcance del capítulo reivindicatorio al limitar las definiciones para las variables R_4 y R_5 , tal y como fue descrito en el numeral 3 del presente memorial.

De otro lado, considero de gran importancia señalar que los compuestos químicos abarcados por el nuevo capítulo reivindicatorio de la solicitud encuentran pleno soporte en la descripción, específicamente en los ejemplos revelados por el solicitante en la Tabla A (páginas 27 a 46). Adicionalmente, es claro que en las páginas 95 a 137 de la descripción también se describen una serie de procedimientos experimentales que permiten sintetizar diversos compuestos representativos de la invención, tales como los compuestos 10, 20, 24, 27, 30, 31, 47, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 (ambos enantiómeros), 99, 100, 101, 102 y 103 de la Tabla A. Así mismo, me permito señalar que en las páginas 82 a 95, 137 y 138 de la descripción se describen en detalle una serie de ensayos biológicos relacionados con la respuesta de los compuestos de la invención frente a la proteína RUP3.

Ahora bien, con respecto al ejemplo 10 (páginas 137 a 139 de la descripción), es claro que los compuestos allí empleados fueron evaluados mediante un ensayo de dispersión de melanóforos, divulgándose los resultados experimentales obtenidos (valores EC_{50}) en la Tabla 3 de la descripción, donde se observa que algunos compuestos muestran una actividad EC_{50} menor a 20 μ L. Adicionalmente, es claro que las realizaciones de la invención están relacionadas con una serie de compuestos químicos que han demostrado presentar una capacidad de enlace a RPU3 cerca de 100 veces mayor a aquella mostrada por el receptor de corticotrofina liberador de factor-1.

Como consecuencia de lo anterior, me permito manifestar que el nuevo capítulo reivindicatorio de la solicitud de patente en cuestión cumple a cabalidad con las disposiciones de patentabilidad establecidas en el artículo 30 de la Decisión 486 de 2000, toda vez que es claro, conciso y encuentra pleno sustento en la descripción de la invención.

5. REIVINDICACIONES RELATIVAS A UN USO O A UN SEGUNDO USO

De otro lado, el señor Examinador ha objetado la patentabilidad de las reivindicaciones 50 a 56 y 112 a 117 aduciendo lo siguiente:

"El uso de las reivindicaciones 50-56 y 112-117 no es patentable de acuerdo con los Art. citados"

En respuesta a lo anterior y de conformidad con lo mencionado previamente en el numeral 3 del presente memorial, me permito manifestar que el solicitante ha decidido eliminar las reivindicaciones 50 a 56 y 112 a 117 presentadas originalmente, con lo cual se supera completamente la objeción realizada por el señor Examinador a éste respecto.

6. **OBJECIONES FRENTE AL NIVEL INVENTIVO DE LA SOLICITUD**

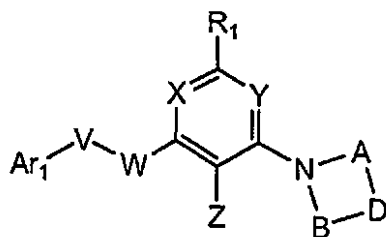
Finalmente, el señor Examinador ha objetado el nivel inventivo de las reivindicaciones 1 a 49, 57 a 111 y 118 a 124 basándose en las enseñanzas del siguiente documento:

(D1) → WO 2004/065380

En este sentido, el señor Examinador argumenta básicamente que la diferencia entre los compuestos de la invención definida en la reivindicación 1 y los compuestos enseñados en D1 consiste en la presencia específica de sustituyentes R^5 como C_{1-4} acilsulfonamida, C_{1-4} alcoxi y el grupo A. Sin embargo, de acuerdo con el señor Examinador, D1 ya resolvía el problema de obtener compuestos útiles como moduladores del metabolismo puesto que tienen una actividad ciclase IC50 de 0,05, 0,129 y 0,241 μ M, respectivamente, de tal forma que no se evidencia un efecto técnico inesperado en dicha actividad para los compuestos de la solicitud, en comparación con los de D1. Adicionalmente, el señor Examinador asevera que la reivindicación 1 es obvia porque el experto en la materia enfrentado al problema de "cómo modificar el compuesto conocido en D1 para obtener compuestos con una actividad de EC50 en el ensayo de melanóforos de menos de 10 μ L que sean útiles como moduladores del metabolismo", emplearía el grupo farmacofórico ya conocido en dicha anterioridad y variaría las diferentes sustituciones de acuerdo con su conocimiento medio en química orgánica, logrando los compuestos objeto de la invención bajo análisis.

Visto lo anterior y con el ánimo de demostrar ante ese Despacho que los compuestos químicos revelados en la solicitud de patente en cuestión presentan un inequívoco carácter inventivo frente a las enseñanzas del documento D1, atentamente me permito presentar ante ese Despacho las siguientes consideraciones técnicas:

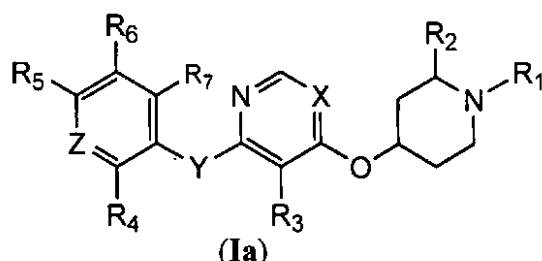
- (a) El documento D1 divulga compuestos que presentan la siguiente estructura química general:



Donde los posibles significados de las variables Ar_1 , V, W, X, Y, Z, R_1 , A, B y D se encuentran debidamente mencionados en las páginas 5 a 8 de dicha anterioridad.

De acuerdo con los autores de D1, los compuestos previamente señalados se caracterizan porque enlazan y modulan la actividad de la proteína RUP3 y por lo tanto son útiles en la profilaxis o tratamiento de desórdenes metabólicos y complicaciones de los mismos, incluyendo diabetes y obesidad.

- (b) Por su parte, en la solicitud de patente en cuestión se revelan compuestos que presentan la siguiente estructura química general:



donde los posibles significados de las variables Y, X, Z y R₁ a R₇ son los siguientes:

X es N o CR₈, donde R₈ es H o halógeno;

Y es NH u O;

Z es CH o N;

R₁ es carbo-C₁₋₆-alkoxi, oxadiazolilo o pirimidinilo

donde dicho carbo-C₁₋₆-alkoxi, oxadiazolilo y pirimidinilo están cada uno opcionalmente sustituidos con 1 o 2 sustituyentes seleccionados independientemente del grupo que consiste de C₁₋₄ alquilo, C₁₋₄ alkoxi y C₃₋₅ cicloalquilo;

R₂ es H o C₁₋₄ alquilo;

R₃ es C₁₋₄ alkoxi, O-C₂₋₄-alquinilo o hidroxilo;

R₄ es seleccionado del grupo que consiste de H, C₁₋₄ alkoxi, C₁₋₄ alquilo y halógeno;

R₅ es seleccionado del grupo que consiste de:

C₁₋₄ acilsulfonamida, C₁₋₄ alcoxi, C₁₋₄ alquilo, C₁₋₄ alquilamino, C₁₋₄ alquilsulfonilo, C₁₋₄ alquiltio, ciano, heterociclilo, di-C₁₋₄-dialquilamino y sulfonamida, donde dicho C₁₋₄ alcoxi, C₁₋₄ alquilo, C₁₋₄ alquilamino, C₁₋₄ alquilsulfonilo, C₁₋₄ alquiltio, di-C₁₋₄-dialquilamino y heterociclilo están cada uno opcionalmente sustituidos con 1 o 2 sustituyentes seleccionados independientemente del grupo que consiste de C₁₋₄ alcoxi, C₁₋₄ alquilcarboxamida, C₁₋₄ alquilsulfonil, C₃₋₅ cicloalquilo, C₃₋₅ cicloalquiloxi, di-C₁₋₄-alquilcarboxamida, hidroxil y fosfonooxi, donde dicha C₁₋₄ alquilcarboxamida está opcionalmente sustituida con hidroxilo;

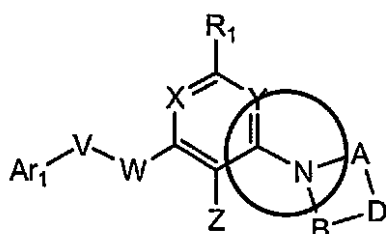
R₆ es H o halógeno; y

R₇ es H o C₁₋₄ alquilo.

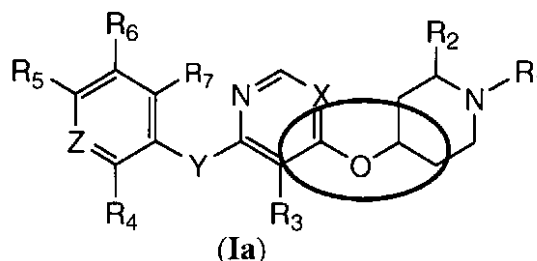
De acuerdo con los autores de la presente invención, los compuestos químicos previamente mencionados se caracterizan porque enlazan y modulan la actividad de la proteína RUP3 y por lo tanto son útiles en la profilaxis o tratamiento de desórdenes metabólicos y complicaciones de los mismos, incluyendo diabetes y obesidad.

(c) Ahora bien, a partir del análisis detallado de los compuestos químicos divulgados en D1 y en la solicitud de patente en cuestión, es claro que entre dichos compuestos existen las siguientes diferencias estructurales:

- i. Los compuestos enseñados en D1 no presentan un oxígeno como átomo enlazante al grupo piperidinilo. Contrario a lo anterior, los compuestos de la solicitud en cuestión presentan un átomo de oxígeno entre el grupo piperidinilo y el anillo piridinilo o pirimidinilo central:

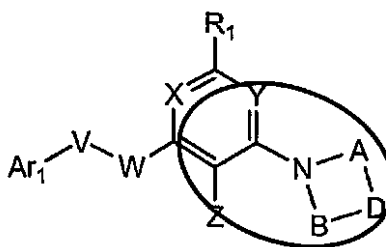


Estructura química general de los compuestos enseñados en D1

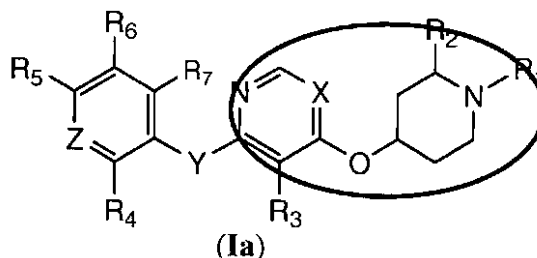


Estructura química general de los compuestos enseñados en la presente invención

- ii. Los compuestos enseñados en D1 tienen un grupo heterociclo N-A-B-D en el cual el átomo de nitrógeno está enlazado directamente al grupo arilo central. Contrario a esto, los compuestos revelados en la presente invención presentan un anillo piperidinilo en el que uno de los átomos de carbono está enlazado a un átomo de oxígeno, y éste último a su vez está enlazado al anillo piridinilo o pirimidinilo central:

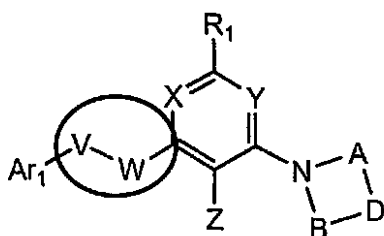


Estructura química general de los compuestos enseñados en D1

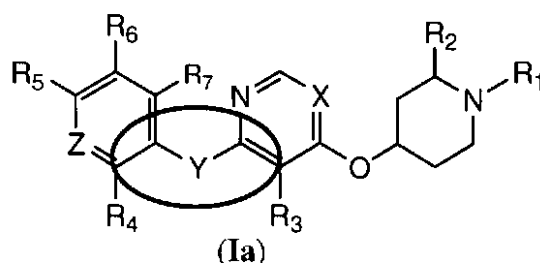


Estructura química general de los compuestos enseñados en la presente invención

- iii. Los compuestos enseñados en D1 presentan un grupo -W-, el cual es escogido entre NR_4 , O, S, S(O) , S(O)_2 o un enlace simple. Contrario a lo anterior, en la misma posición los compuestos de la presente invención presentan un grupo -Y- que únicamente puede representar un grupo -NH- ó un átomo de oxígeno:

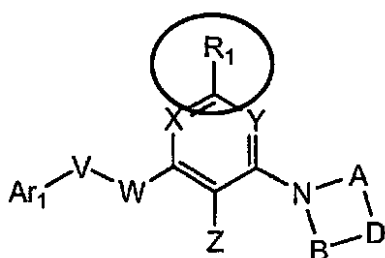


Estructura química general de los compuestos enseñados en D1

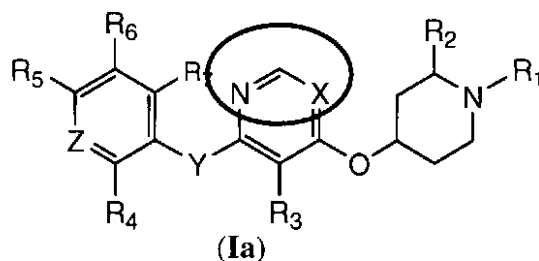


Estructura química general de los compuestos enseñados en la presente invención

- iv. Los compuestos enseñados en el documento D1 presentan un grupo R_1 que puede representar un grupo químico seleccionado entre una amplia variedad de posibilidades que incluyen H, alquencilo C_{2-6} , alcoxi C_{1-4} , alquilo C_{1-8} , alquilcarboxamida C_{1-4} , alquinil C_{2-6} , alquilsulfonamida C_{1-4} , alquilsulfinilo C_{1-4} , alquilsulfonilo C_{1-4} , alquiltio C_{1-4} , alquilureil C_{1-4} , amino, alquilamino C_{1-4} , dialquilamino C_{2-8} , carboxamida, ciano, cicloalquilo C_{3-6} , dialquilcarboxamida C_{2-6} , dialquilsulfonamida C_{2-6} , halógeno, haloalcoxi C_{1-4} , haloalquilo C_{1-4} , haloalquilsulfinilo C_{1-4} , haloalquilsulfonilo C_{1-4} , haloalquiltio C_{1-4} e hidroxilo. Contrario a lo anterior, en la misma posición los compuestos de la presente invención únicamente pueden presentar un átomo de hidrógeno:

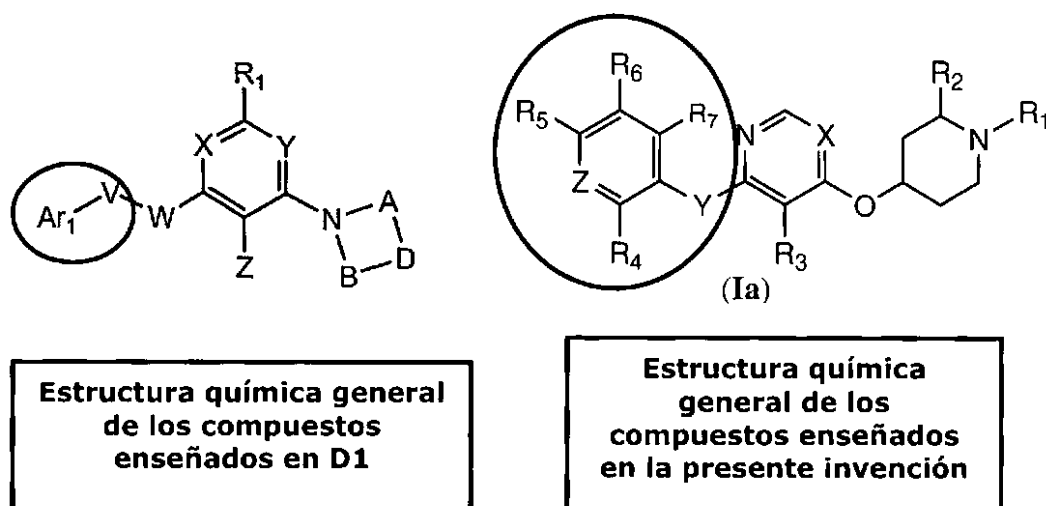


Estructura química general de los compuestos enseñados en D1



Estructura química general de los compuestos enseñados en la presente invención

- v. Finalmente, los compuestos enseñados en el documento D1 presentan un grupo Ar_1 que se selecciona entre un radical arilo y un radical heteroarilo opcionalmente sustituido con un amplio rango de posibles sustituyentes. Contrario a lo anterior, en la misma posición los compuestos revelados en la presente invención únicamente pueden presentar un grupo seleccionado entre fenilo y piridinilo:



- (d) Con base en lo señalado previamente, me permito manifestar ante ese Despacho que de ninguna manera es cierto que los compuestos revelados en la solicitud de patente en cuestión se diferencien de aquellos divulgados en el documento D1 únicamente por la presencia específica de sustituyentes R_5 como C_{1-4} acilsulfonamida, C_{1-4} alcoxi y el grupo A, tal como equivocadamente fue afirmado por el señor Examinador en su Concepto técnico.

Contrario a esto, se ha demostrado que los compuestos de la presente invención comprenden numerosas y marcadas diferencias estructurales con respecto a aquellos compuestos enseñados en el documento D1.

- (e) Por lo tanto, es claro que para la persona medianamente versada en la materia de ninguna manera podría haber sido evidente que luego de llevar a cabo todas las modificaciones estructurales necesarias para obtener los compuestos de la presente invención a partir de aquellos compuestos divulgados en D1 (insertar un átomo de oxígeno entre el grupo arilo central y el grupo piperidinilo, enlazar dicho grupo piperidinilo al anillo central a través de un átomo de carbono, limitar los posibles significados de la variable -W- en D1 a -NH- y O, limitar los posibles significados de la variable R_1 en D1 a tan sólo un átomo de hidrógeno y limitar los posibles significados de la variable Ar_1 en D1 a tan sólo un grupo fenilo o piridinilo), dichos novedosos

compuestos también se caractericen por presentar una fuerte actividad biológica como moduladores de la proteína RUP3, y que por lo tanto sean útiles en el tratamiento y prevención de desórdenes del metabolismo, tal y como se comprueba a partir de los datos experimentales divulgados por el solicitante en la Tabla 3 de la descripción.

Como consecuencia de lo anterior, me permito manifestar que la materia técnica revelada en la solicitud de patente en cuestión presenta un inequívoco carácter inventivo frente a las enseñanzas del documento D1, cumpliendo por lo tanto a cabalidad con las disposiciones de patentabilidad establecidas en el artículo 18 de la Decisión 486 de 2000.

7. **CONCLUSIÓN**

De conformidad con las modificaciones realizada en el capítulo reivindicatorio de la solicitud de patente en cuestión, es claro que dicho nuevo capítulo reivindicatorio cumple a cabalidad con las disposiciones de patentabilidad establecidas en los artículos 21 y 30 de la Decisión 486 de 2000, toda vez que no comprende usos o segundos usos, es claro, conciso y presenta pleno sustento en la descripción de la solicitud.

Así mismo, se ha demostrado a través de argumentos técnicos contundentes que los novedoso compuestos y composiciones químicas reveladas en la solicitud en cuestión presentan un inequívoco carácter inventivo frente a las enseñanzas del documento D1 señalado por el señor Examinador durante el análisis técnico llevado a cabo.

Por lo tanto, es claro que se han superado las objeciones presentadas por el señor Examinador en su Concepto Técnico, y por lo tanto, dicha invención es merecedora del privilegio de patente solicitado.

8. Anexo al presente memorial me permito presentar:

a) Copia del nuevo capítulo reivindicatorio de la solicitud, el cual está compuesto por 94 reivindicaciones y reemplaza al documento actualmente presentado;

b) Copia del documento Vippagunta et al., *Advanced Drug Delivery Reviews* 48 (2001) 3-26

c) Copia del documento K. J. Guillory, *"Generation of Polymorphs, Hydrates, Solvates and Amorphous solids"*, en el libro titulado "Polymorphism in Pharmaceutical Solids, ed., Harry G. Britain, Vol. 95. Marcel Dekker, Inc., New York, 1999.

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9. En vista de lo anterior, ruego a usted proceder a estudiar nuevamente la solicitud a la luz de los argumentos y modificaciones presentados y conceder el privilegio de patente solicitado.

Señor Superintendente,

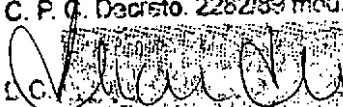

ALICIA LLORED A RICAURTE

T. P. 53.215

NOTARIA 41 DEL CÍRCULO DE BOGOTÁ D.C.
DEPARTAMENTO DE CUNDINAMARCA
REPÚBLICA DE COLOMBIA

El Notario 41 del círculo de Bogotá, da fe de que compareció personalmente Alicia Lloreda Ricaurte, identificada (c) con C.C. 39.690.713, cédula profesional de abogado No. 53.215 del Consejo Superior de la Judicatura, quien autentica la firma puesta por ella (el) mismo en este escrito.

(Art. 84 C. P. Q. Decreto. 2282/89 mod. 39)

 27 SET. 2011
Bogotá D.C.
ALICIA LLORED A RICAURTE
C.C. No. 39.690.713 de Usaquén

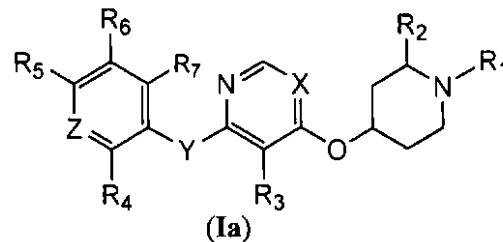




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VoBo

REIVINDICACIONES

1. Un compuesto de la Fórmula (Ia):



- 5 y sales, solvatos e hidratos farmacéuticamente aceptables del mismo; en donde:
 X es N o CR₈ donde R₈ es H o halógeno;
 Y es NH u O;
 Z es CH o N;
 R₁ es carbo-C₁₋₆-alkoxi, oxadiazolilo o pirimidinilo
 10 donde dicho carbo-C₁₋₆-alkoxi, oxadiazolilo y pirimidinilo están cada uno opcionalmente sustituidos con 1 o 2 sustituyentes seleccionados independientemente del grupo que consiste de C₁₋₄ alquilo, C₁₋₄ alkoxi y C₃₋₅ cicloalquilo;
 R₂ es H o C₁₋₄ alquilo;
 R₃ es C₁₋₄ alkoxi, O-C₂₋₄-alquinilo o hidroxilo;
 15 R₄ es seleccionado del grupo que consiste de H, C₁₋₄ alkoxi, C₁₋₄ alquilo y halógeno;
 R₅ es seleccionado del grupo que consiste de:
 C₁₋₄ acilsulfonamida, C₁₋₄ alcoxi, C₁₋₄ alquilo, C₁₋₄ alquilamino, C₁₋₄ alquilsulfonilo, C₁₋₄ alquiltio, ciano, heterociclilo, di-C₁₋₄-dialquilamino y sulfonamida,
 donde dicho C₁₋₄ alcoxi, C₁₋₄ alquilo, C₁₋₄ alquilamino, C₁₋₄ alquilsulfonilo, C₁₋₄
 20 alquiltio, di-C₁₋₄-dialquilamino y heterociclilo están cada uno opcionalmente sustituidos con 1 o 2 sustituyentes seleccionados independientemente del grupo que consiste de C₁₋₄ alcoxi, C₁₋₄ alquilcarboxamida, C₁₋₄ alquilsulfonil, C₃₋₅ cicloalquilo, C₃₋₅ cicloalquiloxi, di-C₁₋₄-alquilcarboxamida, hidroxil y fosfonooxi,
 donde dicha C₁₋₄ alquilcarboxamida está opcionalmente sustituida con hidroxilo;
 25 R₆ es H o halógeno; y
 R₇ es H o C₁₋₄ alquilo.

2. Un compuesto de acuerdo con la reivindicación 1 donde X es N.

- 30 3. Un compuesto de acuerdo con la reivindicación 1 donde X es CR₈.

4. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 3, donde R_8 es H o F.
- 5 5. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 4 donde Y es NH.
6. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 4 donde Y es O.
- 10 7. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 6 donde Z es CH.
8. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 6 donde Z es N.
- 15 9. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 8 donde R_1 es carbo- C_{1-6} -alcoxi opcionalmente sustituido con C_{3-5} cicloalquilo.
- 20 10. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 8 donde R_1 es seleccionado de $C(O)OCH_2CH_3$, $C(O)OCH(CH_3)_2$, $C(O)OCH(CH_3)(CH_2CH_3)$, $C(O)OCH_2$ -ciclopropilo y $C(O)OCH(CH_3)$ (ciclopropilo).
11. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 8 donde R_1 es oxadiazolilo opcionalmente sustituido con un grupo C_{1-4} alquilo.
- 25 12. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 8 donde R_1 es 5-isopropil-[1,2,4]oxadiazol-3-ilo.
13. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 8 donde R_1 es pirimidinilo opcionalmente sustituido con un grupo C_{1-4} alcoxi.
- 30 14. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 8 donde R_1 es 5-metoxi-pirimidin-2-ilo.
- 35 15. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 14 donde R_2 es H.

16. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 14 donde R_2 es CH_3 .

5 17. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 16 donde R_3 es C_{1-4} alcoxi.

18. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 16 donde R_3 es OCH_3 u OCH_2CH_3 .

10 19. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 16 donde R_3 es OH u $\text{O}-\text{C}\equiv\text{CH}$.

15 20. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 19 donde R_4 es seleccionado de H , OCH_3 , CH_3 , CH_2CH_3 , F y Cl .

20 21. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 20 donde R_5 es seleccionado de: $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{S}(\text{O})_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$, $\text{NHCH}_2\text{CH}_2\text{OH}$, ciano, $\text{CH}_2\text{CH}_2\text{OCH}_3$, $\text{CH}_2\text{CH}_2\text{OH}$, $\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{OH}$, $\text{CH}_2\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$, $\text{S}(\text{O})_2\text{NHC}(\text{O})\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{O-ciclopropilo}$, $\text{NHCH}_2\text{CH}_2\text{OCH}_3$, $\text{OCH}_2\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$, $\text{NHCH}_2\text{CH}(\text{CH}_3)\text{OH}$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$, $\text{NHCH}_2\text{CH}(\text{CH}_3)\text{S}(\text{O})_2\text{CH}_3$, $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}(\text{CH}_3)\text{S}(\text{O})_2\text{CH}_3$, 3-metanosulfonil-pirrolidin-1-ilo, 3-metanosulfonil-piperidin-1-ilo, $\text{CH}_2\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, 3-metanosulfonil-azetidin-1-ilo, $\text{CH}_2\text{C}(\text{O})\text{NHCH}_2\text{CH}_2\text{OH}$, $\text{SCH}_2\text{CH}_2\text{OH}$, $\text{S}(\text{O})_2\text{CH}_2\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$, $\text{S}(\text{O})_2\text{CH}_2\text{CH}_3$, $\text{NHCH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$, $\text{S}(\text{O})_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{OCH}_2\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$ y $\text{S}(\text{O})_2\text{NH}_2$.

25 22. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 20 donde R_5 es seleccionado de $\text{OCH}_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{S}(\text{O})_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$, $\text{NHCH}_2\text{CH}_2\text{OH}$, ciano, $\text{CH}_2\text{CH}_2\text{OH}$, $\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{OH}$, $\text{CH}_2\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$, $\text{S}(\text{O})_2\text{NHC}(\text{O})\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{S}(\text{O})_2\text{CH}_2\text{CH}_3$, $\text{NHCH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$, amino, NHCH_2CH_3 , $\text{NHCH}(\text{CH}_3)_2$ y $\text{NHCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$.

30 23. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 22 donde R_6 es H .

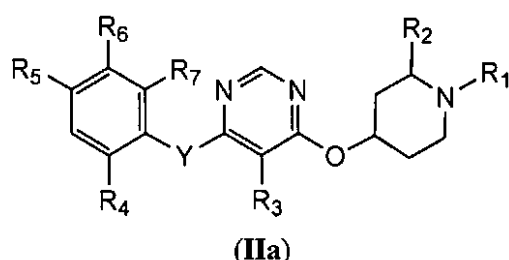
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24. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 22 donde R_6 es F.

25. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 24 donde R_7 es H.

26. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 24 donde R_7 es CH_3 .

27. Un compuesto de acuerdo con la reivindicación 1, seleccionado de compuestos que tienen la Fórmula (IIa), y sales, solvatos e hidratos farmacéuticamente aceptables del mismo:



donde:

Y es NH u O;

R_1 es carbo- C_{1-6} -alcoxi opcionalmente sustituido con C_{3-5} cicloalquilo;

R_2 es H o CH_3 ;

R_3 es C_{1-4} alcoxi;

R_4 es seleccionado de H, OCH_3 , CH_3 , CH_2CH_3 , F y Cl;

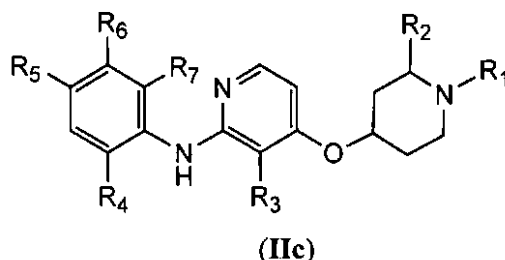
R_5 es seleccionado de:

$OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$,
 $NHCH_2CH_2OH$, ciano, $CH_2CH_2OCH_3$, CH_2CH_2OH , $CH_2CH_2CH(CH_3)OH$,
 $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O -ciclopropilo,
 $NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$,
 $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$,
 $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-metanosulfonyl-pirrolidin-1-ilo, 3-metanosulfonyl-
piperidin-1-ilo, $CH_2C(O)N(CH_3)_2$, 3-metanosulfonyl-azetidin-1-ilo,
 $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH , $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$,
 $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$,
 $OCH_2CH_2CH_2OP(O)(OH)_2$ y $S(O)_2NH_2$;

R_6 es H o F; y

R_7 es H o CH_3 .

28. Un compuesto de acuerdo con la reivindicación 1, seleccionado de compuestos que tienen la Fórmula (IIc), y sales, solvatos e hidratos farmacéuticamente aceptables del mismo:



donde:

R_1 es carbo- C_{1-6} -alcoxi opcionalmente sustituido con C_{3-5} cicloalquilo;

R_2 es H o CH_3 ;

R_3 es C_{1-4} alcoxi;

R_4 es seleccionado de: H, OCH_3 , CH_3 , CH_2CH_3 , F y Cl;

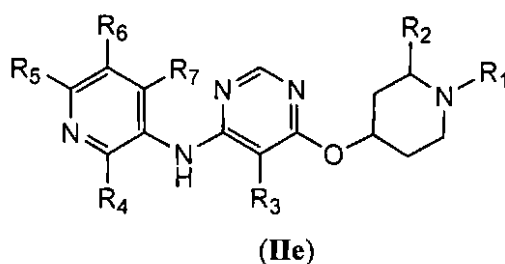
R_5 es seleccionado de:

$\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{S}(\text{O})_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$,
 $\text{NHCH}_2\text{CH}_2\text{OH}$, ciano, $\text{CH}_2\text{CH}_2\text{OCH}_3$, $\text{CH}_2\text{CH}_2\text{OH}$, $\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{OH}$,
 $\text{CH}_2\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$, $\text{S}(\text{O})_2\text{NHC}(\text{O})\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{O-ciclopropilo}$,
 $\text{NHCH}_2\text{CH}_2\text{OCH}_3$, $\text{OCH}_2\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$, $\text{NHCH}_2\text{CH}(\text{CH}_3)\text{OH}$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$,
 $\text{CH}_2\text{CH}_2\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$, $\text{NHCH}_2\text{CH}(\text{CH}_3)\text{S}(\text{O})_2\text{CH}_3$,
 $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}(\text{CH}_3)\text{S}(\text{O})_2\text{CH}_3$, 3-metanosulfonil-pirrolidin-1-ilo, 3-metanosulfonil-
piperidin-1-ilo, $\text{CH}_2\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, 3-metanosulfonil-azetidin-1-ilo,
 $\text{CH}_2\text{C}(\text{O})\text{NHCH}_2\text{CH}_2\text{OH}$, $\text{SCH}_2\text{CH}_2\text{OH}$, $\text{S}(\text{O})_2\text{CH}_2\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$, $\text{S}(\text{O})_2\text{CH}_2\text{CH}_3$,
 $\text{NHCH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$, $\text{S}(\text{O})_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{OCH}_2\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$,
 $\text{OCH}_2\text{CH}_2\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$ y $\text{S}(\text{O})_2\text{NH}_2$;

R_6 es H o F; y

R_7 es H o CH_3 .

29. Un compuesto de acuerdo con la reivindicación 1, seleccionado de compuestos que tienen la Fórmula (IIe), y sales, solvatos e hidratos farmacéuticamente aceptables del mismo:



donde:

R₁ es carbo-C₁₋₆-alcoxi opcionalmente sustituido con C₃₋₅ cicloalquilo;

R₂ es H o CH₃;

R₃ es C₁₋₄ alcoxi;

R₄ es seleccionado de H, OCH₃, CH₃, CH₂CH₃, F y Cl;

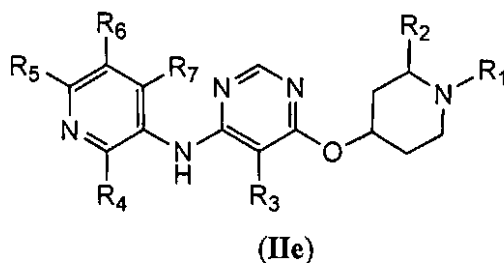
R₅ es seleccionado de:

OCH₂CH₂CH₃, OCH₂CH₂CH₂OH, S(O)₂CH₃, CH₂CH₂S(O)₂CH₃,
 NHCH₂CH₂OH, ciano, CH₂CH₂OCH₃, CH₂CH₂OH, CH₂CH₂CH(CH₃)OH,
 CH₂CH₂OP(O)(OH)₂, S(O)₂NHC(O)CH₂CH₃, CH₂CH₂O-ciclopropilo,
 NHCH₂CH₂OCH₃, OCH₂CH₂S(O)₂CH₃, NHCH₂CH(CH₃)OH, CH₂CH₂CH₂OH,
 CH₂CH₂CH₂OP(O)(OH)₂, NHCH₂CH(CH₃)S(O)₂CH₃,
 N(CH₃)CH₂CH(CH₃)S(O)₂CH₃, 3-metanosulfonyl-pirrolidin-1-ilo, 3-metanosulfonyl-
 piperidin-1-ilo, CH₂C(O)N(CH₃)₂, 3-metanosulfonyl-azetidin-1-ilo,
 CH₂C(O)NHCH₂CH₂OH, SCH₂CH₂OH, S(O)₂CH₂CH₂OP(O)(OH)₂, S(O)₂CH₂CH₃,
 NHCH₂CH(OH)CH₂OH, S(O)₂CH₂CH₂OH, OCH₂CH₂OP(O)(OH)₂,
 OCH₂CH₂CH₂OP(O)(OH)₂ y S(O)₂NH₂;

R₆ es H o F; y

R₇ es H o CH₃.

30. Un compuesto de acuerdo con la reivindicación 1, seleccionado de compuestos que tienen la Fórmula (IIe), y sales, solvatos e hidratos farmacéuticamente aceptables del mismo:



donde:

R₁ es carbo-C₁₋₆-alcoxi opcionalmente sustituido con C₃₋₅ cicloalquilo;

R_2 es H o CH_3 ;

R_3 es C_{1-4} alcoxi;

R_4 es seleccionado de: H, OCH_3 , CH_3 , CH_2CH_3 , F y Cl;

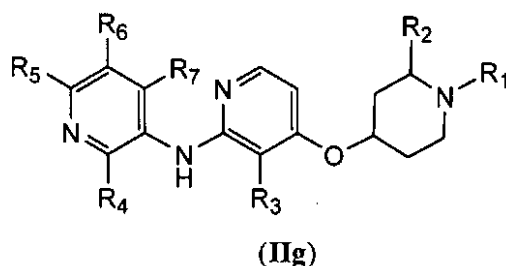
R_5 es seleccionado de:

$OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, ciano, CH_2CH_2OH , $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, $CH_2CH_2CH_2OH$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$ y $S(O)_2NH_2$;

R_6 es H o F; y

R_7 es H o CH_3 .

31. Un compuesto de acuerdo con la reivindicación 1, seleccionado de compuestos que tienen la Fórmula (IIg), y sales, solvatos e hidratos farmacéuticamente aceptables del mismo:



donde:

R_1 es carbo- C_{1-6} -alcoxi opcionalmente sustituido con C_{3-5} cicloalquilo;

R_2 es H o CH_3 ;

R_3 es C_{1-4} alcoxi;

R_4 es seleccionado de: H, OCH_3 , CH_3 , CH_2CH_3 , F y Cl;

R_5 es seleccionado de:

$OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, ciano, $CH_2CH_2OCH_3$, CH_2CH_2OH , $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O -ciclopropilo, $NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-metanosulfonil-pirrolidin-1-ilo, 3-metanosulfonil-piperidin-1-ilo, $CH_2C(O)N(CH_3)_2$, 3-metanosulfonil-azetidin-1-ilo, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH , $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$ y $S(O)_2NH_2$;

R_6 es H o F; y

R₇ es H o CH₃.

32. Un compuesto de acuerdo con la reivindicación 1 seleccionado del grupo que consiste de:

- 5 isopropil éster del ácido 4-[6-(4-Metanosulfonil-2-metoxi-fenilamino)-5-metoxi-pirimidin-4-iloxi]-piperidina-1-carboxílico;
- isopropil éster del ácido 4-{5-Metoxi-6-[6-(2-metoxi-etil)-2-metil-piridin-3-ilamino]-pirimidin-4-iloxi}-piperidina-1-carboxílico;
- 10 1-ciclopropil-etil éster del ácido 4-{6-[6-(2-Metanosulfonil-etil)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;
- isopropil éster del ácido 4-[6-(2-Fluoro-4-metanosulfonil-fenilamino)-5-metoxi-pirimidin-4-iloxi]-piperidina-1-carboxílico;
- isopropil éster del ácido 4-[6-(4-Ciano-2-fluoro-fenilamino)-5-metoxi-pirimidin-4-iloxi]-piperidina-1-carboxílico;
- 15 isopropil éster del ácido 4-{6-[6-(2-Hidroxi-etil)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;
- isopropil éster del ácido 4-{6-[6-(2-Metanosulfonil-etil)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;
- isopropil éster del ácido 4-{5-Metoxi-6-[6-(2-metoxi-etilamino)-2-metil-piridin-3-ilamino]-pirimidin-4-iloxi}-piperidina-1-carboxílico;
- 20 isopropil éster del ácido 4-{6-[6-(2-Metanosulfonil-etoxi)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;
- isopropil éster del ácido 4-{6-[6-(2-Hidroxi-propilamino)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;
- 25 isopropil éster del ácido 4-{6-[6-(3-Hidroxi-propil)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico
- isopropil éster del ácido 4-{5-metoxi-6-[2-metil-6-(3-fosfonooxi-propil)-piridin-3-ilamino]-pirimidin-4-iloxi}-piperidina-1-carboxílico;
- isopropil éster del ácido 4-{6-[6-(2-Metanosulfonil-etilamino)-2-metoxi-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;
- 30 isopropil éster del ácido 4-{6-[6-(2-Metanosulfonil-propilamino)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;
- isopropil éster del ácido 4-[6-(6-Dimetilcarbamoilmetil-2-metil-piridin-3-ilamino)-5-metoxi-pirimidin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-(6-{2-Fluoro-4-[(2-hidroxi-etilcarbamoil)-metil]-fenilamino}-5-metoxi-pirimidin-4-iloxi)-piperidina-1-carboxílico;

isopropil éster del ácido 4-{6-[6-(2-Metanosulfonil-etilamino)-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;

5 isopropil éster del ácido 4-{6-[2-Fluoro-4-(2-hidroxi-etilsulfanil)-fenilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{6-[6-(2,3-Dihidroxi-propilamino)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;

10 isopropil éster del ácido 4-{6-[6-(2,3-Dihidroxi-propilamino)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{6-[6-(2-Hidroxi-etoxi)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{5-Metoxi-6-[2-metil-6-(2-fosfonooxi-etoxi)-piridin-3-ilamino]-pirimidin-4-iloxi}-piperidina-1-carboxílico;

15 isopropil éster del ácido 4-{6-[6-(3-Hidroxi-propoxi)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-ácido carboxílico; y

isopropil éster del ácido 4-{5-Metoxi-6-[2-metil-6-(3-fosfonooxi-propoxi)-piridin-3-ilamino]-pirimidin-4-iloxi}-piperidina-1-carboxílico;

o sales, solvatos e hidratos farmacéuticamente aceptables del mismo.

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33. Un compuesto de acuerdo con la reivindicación 1 seleccionado del grupo que consiste de:

isopropil éster del ácido 4-[2-(2-Fluoro-4-propoxi-fenilamino)-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

25 isopropil éster del ácido 4-{2-[2-Fluoro-4-(2-hidroxi-etil)-fenilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-[5-Fluoro-2-(2-fluoro-4-metanosulfonil-fenilamino)-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

30 isopropil éster del ácido 4-{2-[2-Etil-4-(2-metanosulfonil-etil)-fenilamino]-3-metoxi-piridin-4-iloxi}-2-metil-piperidina-1-carboxílico;

isopropil éster del ácido 4-{5-Fluoro-2-[6-(2-hidroxi-etoxi)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[2-Fluoro-4-(2-metanosulfonil-etil)-fenilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(2-Hidroxi-etilamino)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-[2-(4-Ciano-2-fluoro-fenilamino)-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

5 isopropil éster del ácido 4-[2-(2-Cloro-4-ciano-fenilamino)-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(2-Metanosulfonil-etil)-2-metoxi-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

10 isopropil éster del ácido 4-{2-[6-(2-Metanosulfonil-etil)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(2-Hidroxi-etil)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(3-Hidroxi-butil)-2-metoxi-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

15 isopropil éster del ácido 4-{2-[2-Fluoro-4-(2-hidroxi-etoxi)-fenilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{3-Etoxi-2-[2-fluoro-4-(2-fosfonooxi-etil)-fenilamino]-piridin-4-iloxi}-piperidina-1-carboxílico;

20 isopropil éster del ácido 4-[3-Metoxi-2-(2-metoxi-4-propionilsulfamoil-fenilamino)-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-[2-(2,5-Difluoro-4-propoxi-fenilamino)-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

(2-Fluoro-4-metanosulfonil-fenil)-{4-[1-(5-isopropil-[1,2,4]oxadiazol-3-il)-piperidin-4-iloxi]-3-metoxi-piridin-2-il}-amina;

25 (2-Fluoro-4-metanosulfonil-fenil)-{3-metoxi-4-[1-(5-metoxi-pirimidin-2-il)-piperidin-4-iloxi]-piridin-2-il}-amina;

isopropil éster del ácido 4-{2-[6-(2-Ciclopropoxi-etil)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

30 isopropil éster del ácido 4-[2-(2-Cloro-4-metanosulfonil-fenilamino)-5-fluoro-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-[3-Etoxi-2-(4-metanosulfonil-2-metoxi-fenilamino)-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-[2-(5-Fluoro-2-metil-4-propoxi-fenilamino)-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(2-Metanosulfonil-etil)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-[2-(2-Fluoro-4-metanosulfonil-fenilamino)-3-hidroxi-piridin-4-iloxi]-piperidina-1-carboxílico;

5 isopropil éster del ácido 4-[2-(2-Cloro-4-propoxi-fenilamino)-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-{3-Metoxi-2-[2-metil-6-(2-fosfonooxi-etil)-piridin-3-ilamino]-piridin-4-iloxi}-piperidina-1-carboxílico;

10 isopropil éster del ácido 4-{2-[6-(2-Metanosulfonil-etilamino)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-(2-{6-[(2-Metanosulfonil-etil)-metil-amino]-2-metil-piridin-3-ilamino}-3-metoxi-piridin-4-iloxi)-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(3-Metanosulfonil-pirrolidin-1-il)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

15 isopropil éster del ácido 4-[2-(3-Metanosulfonil-6'-metil-3,4,5,6-tetrahidro-2H-[1,2']bipiridinil-5'-ilamino)-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(3-Metanosulfonil-azetidin-1-il)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

20 isopropil éster del ácido 4-[3-etiniloxi-2-(2-fluoro-4-metanosulfonil-fenilamino)-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[2-Fluoro-4-(2-fosfonooxi-etanosulfonil)-fenilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

sec-butil éster del ácido 4-[2-(4-Etanosulfonil-2-fluoro-fenilamino)-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

25 isopropil éster del ácido 4-{2-[6-(2,3-Dihidroxi-propilamino)-4-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(2-Hidroxi-etilsulfanil)-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

30 isopropil éster del ácido 4-{2-[2-Fluoro-4-(2-hidroxi-etanosulfonil)-fenilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(2-Hidroxi-etoxi)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{3-Metoxi-2-[2-metil-6-(2-fosfonooxi-etoxi)-piridin-3-ilamino]-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(3-Hidroxi-propoxi)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{3-Metoxi-2-[2-metil-6-(3-fosfonooxi-propoxi)-piridin-3-ilamino]-piridin-4-iloxi}-piperidina-1-carboxílico;

5 isopropil éster del ácido 4-[3-Metoxi-2-(2-metoxi-4-sulfamoil-fenilamino)-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[2-Fluoro-4-(3-fosfonooxi-propil)-fenilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

10 isopropil éster del ácido 4-{2-[6-(2-Hidroxi-etil)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{3-Metoxi-2-[2-metil-6-(2-fosfonooxi-etil)-piridin-3-ilamino]-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(3-Hidroxi-propil)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico; e

15 isopropil éster del ácido 4-{3-Metoxi-2-[2-metil-6-(3-fosfonooxi-propil)-piridin-3-ilamino]-piridin-4-iloxi}-piperidina-1-carboxílico;

o sales, solvatos e hidratos farmacéuticamente aceptables del mismo.

20 34. Un compuesto de acuerdo con la reivindicación 1 que es: 1-ciclopropil-etil éster del ácido (S)-4-{6-[6-(2-metanosulfonil-etil)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidin-1-carboxílico, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

25 35. Un compuesto de acuerdo con la reivindicación 1 que es:
(2-fluoro-4-metanosulfonil-fenil)-{4-[1-(5-isopropil-[1,2,4]oxadiazol-3-il)-piperidin-4-iloxi]-3-metoxi-piridin-2-il}-amina, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

30 36. Un compuesto de acuerdo con la reivindicación 1 que es:
isopropil éster del ácido 4-[6-(2-fluoro-4-metanosulfonil-fenilamino)-5-metoxi-pirimidin-4-iloxi]piperidina-1-carboxílico, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

35 37. Un compuesto de acuerdo con la reivindicación 1 que es:

isopropil éster del ácido 4-[6-(4-ciano-2-fluoro-fenilamino)-5-metoxi-pirimidin-4-iloxi]-piperidina-1-carboxílico, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

- 5 38. Un compuesto de acuerdo con la reivindicación 1 que es:
 isopropil éster del ácido 4-{6-[6-(2-hidroxi-etil)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.
- 10 39. Un compuesto de acuerdo con la reivindicación 1 que es:
 isopropil éster del ácido 4-{6-[6-(2-metanosulfonil-etil)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.
- 15 40. Un compuesto de acuerdo con la reivindicación 1 que es:
 isopropil éster del ácido 4-{2-[6-(2-metanosulfonil-etil)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.
- 20 41. Un compuesto de acuerdo con la reivindicación 1 que es:
 isopropil éster del ácido 4-[6-(6-dimetilcarbamoilmetil-2-metil-piridin-3-ilamino)-5-metoxi-pirimidin-4-iloxi]-piperidina-1-carboxílico, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.
- 25 42. Un compuesto de acuerdo con la reivindicación 1 que es:
 isopropil éster del ácido 4-{6-[6-(2-hidroxi-etoxi)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.
- 30 43. Un compuesto de acuerdo con la reivindicación 1 que es:
 isopropil éster del ácido 4-[6-(6-metanosulfonil-2-metil-piridin-3-ilamino)-5-metoxi-pirimidin-4-iloxi]-piperidina-1-carboxílico, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

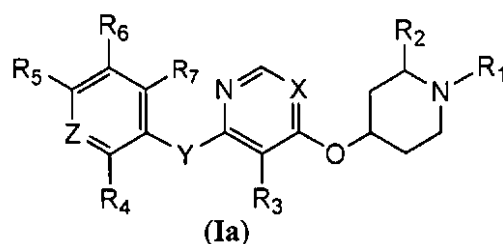
44. Una composición farmacéutica que comprende al menos un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 43 y un portador farmacéuticamente aceptable.

45. Un método de producir una composición farmacéutica que comprende mezclar al menos un compuesto de una cualquiera de las reivindicaciones 1 a 43 y un portador farmacéuticamente aceptable.

46. Una composición que comprende:

(a) un inhibidor de dipeptidil peptidasa IV (DPP-IV); y

(b) un compuesto seleccionado entre compuestos de la Fórmula (Ia) y sales, solvatos e hidratos farmacéuticamente aceptables de los mismos:



donde:

X es N o CR₈ donde R₈ es H o halógeno;

Y es NH u O;

Z es CH o N;

R₁ es carbo-C₁₋₆-alkoxi, oxadiazolilo o pirimidinilo

donde dicho carbo-C₁₋₆-alkoxi, oxadiazolilo y pirimidinilo están cada uno opcionalmente sustituidos con 1 o 2 sustituyentes seleccionados independientemente de C₁₋₄ alquilo, C₁₋₄ alcoxilo y C₃₋₅ cicloalquilo;

R₂ es H o C₁₋₄ alquilo;

R₃ es C₁₋₄ alcoxilo, O-C_{2,4}-alquinilo o hidroxilo;

R₄ es seleccionado de H, C₁₋₄ alcoxilo, C₁₋₄ alquilo y halógeno;

cada:

R₅ es seleccionado de:

C₁₋₄ acilsulfonamida, C₁₋₄ alcoxilo, C₁₋₄ alquilo, C₁₋₄ alquilamino, C₁₋₄ alquilsulfonilo, C₁₋₄ alquiltio, ciano, heterociclilo, di-C₁₋₄-dialquilamino y sulfonamida,

donde dicho C₁₋₄ alcoxilo, C₁₋₄ alquilo, C₁₋₄ alquilamino, C₁₋₄ alquilsulfonilo, C₁₋₄ alquiltio, di-C₁₋₄-dialquilamino y heterociclilo están cada uno opcionalmente sustituidos con 1 o 2 sustituyentes seleccionados independientemente de C₁₋₄ alcoxilo, C₁₋₄ alquilcarboxamida,

C₁₋₄ alquilsulfonil, C₃₋₅ cicloalquilo, C₃₋₅ cicloalquiloxi, di-C₁₋₄-alquilcarboxamida, hidroxilo y fosfonooxi,

donde dicha C₁₋₄ alquilcarboxamida está opcionalmente sustituida con hidroxilo;

R₆ es H o halógeno; y

R₇ es H o C₁₋₄ alquilo.

47. Una composición de acuerdo con la reivindicación 46 donde X es N.

48. Una composición de acuerdo con las reivindicaciones 46 o 47 donde Y es NH.

49. Una composición de acuerdo con las reivindicaciones 46 o 47 donde Y es O.

50. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 49 donde Z es CH.

51. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 49 donde Z es N.

52. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 51 donde R₁ es carbo-C₁₋₆-alcoxi opcionalmente sustituido con C₃₋₅ cicloalquilo.

53. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 51 donde: R₁ es seleccionado de C(O)OCH₂CH₃, C(O)OCH(CH₃)₂, C(O)OCH(CH₃)(CH₂CH₃), C(O)OCH₂-ciclopropilo y C(O)OCH(CH₃)(ciclopropilo).

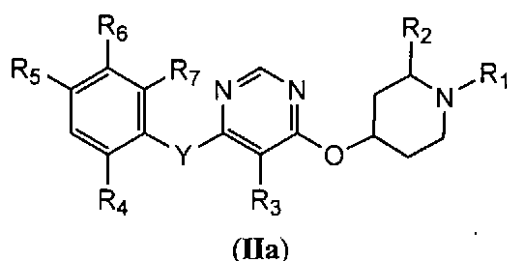
54. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 51 donde R₁ es oxadiazolilo opcionalmente sustituido con un grupo C₁₋₄ alquilo.

55. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 51 donde R₁ es pirimidinilo opcionalmente sustituido con un grupo C₁₋₄ alcoxi.

56. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 55 donde R₂ es H.

57. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 56 donde R_3 es C_{1-4} alcoxi.
58. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 56 donde R_3 es OCH_3 u OCH_2CH_3 .
59. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 58 donde R_4 es seleccionado de H, OCH_3 , CH_3 , CH_2CH_3 , F y Cl.
60. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 59 donde R_5 es seleccionado de: $OCH_2CH_2CH_3$, $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, ciano, $CH_2CH_2OCH_3$, CH_2CH_2OH , $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, CH_2CH_2O -ciclopropilo, $NHCH_2CH_2OCH_3$, $OCH_2CH_2S(O)_2CH_3$, $NHCH_2CH(CH_3)OH$, $CH_2CH_2CH_2OH$, $CH_2CH_2CH_2OP(O)(OH)_2$, $NHCH_2CH(CH_3)S(O)_2CH_3$, $N(CH_3)CH_2CH(CH_3)S(O)_2CH_3$, 3-metanosulfonil-pirrolidin-1-ilo, 3-metanosulfonil-piperidin-1-ilo, $CH_2C(O)N(CH_3)_2$, 3-metanosulfonil-azetidin-1-ilo, $CH_2C(O)NHCH_2CH_2OH$, SCH_2CH_2OH , $S(O)_2CH_2CH_2OP(O)(OH)_2$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, $S(O)_2CH_2CH_2OH$, $OCH_2CH_2OP(O)(OH)_2$, $OCH_2CH_2CH_2OP(O)(OH)_2$ y $S(O)_2NH_2$.
61. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 59 donde R_5 es seleccionado de $OCH_2CH_2CH_2OH$, $S(O)_2CH_3$, $CH_2CH_2S(O)_2CH_3$, $NHCH_2CH_2OH$, ciano, CH_2CH_2OH , $CH_2CH_2CH(CH_3)OH$, $CH_2CH_2OP(O)(OH)_2$, $S(O)_2NHC(O)CH_2CH_3$, $CH_2CH_2CH_2OH$, $S(O)_2CH_2CH_3$, $NHCH_2CH(OH)CH_2OH$, amino, $NHCH_2CH_3$, $NHCH(CH_3)_2$ y $NHCH(CH_3)CH_2CH_3$.
62. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 61 donde R_6 es H.
63. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 62 donde R_7 es H.

64. Una composición de acuerdo con la reivindicación 46, en donde el compuesto es seleccionado de compuestos que tienen la Fórmula (IIa), y sales, solvatos e hidratos farmacéuticamente aceptables del mismo:



donde:

Y es NH u O;

R₁ es carbo-C₁₋₆-alcoxi opcionalmente sustituido con C_{3,5} cicloalquilo;

R₂ es H o CH₃;

R₃ es C₁₋₄ alcoxi;

R₄ es seleccionado de H, OCH₃, CH₃, CH₂CH₃, F y Cl;

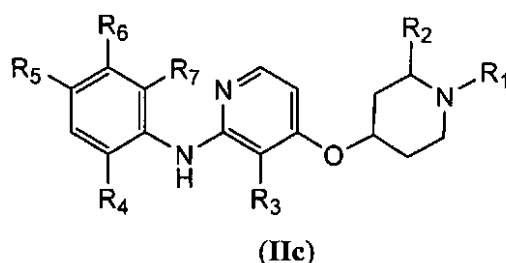
R₅ es seleccionado de:

OCH₂CH₂CH₃, OCH₂CH₂CH₂OH, S(O)₂CH₃, CH₂CH₂S(O)₂CH₃,
 NHCH₂CH₂OH, ciano, CH₂CH₂OCH₃, CH₂CH₂OH, CH₂CH₂CH(CH₃)OH,
 CH₂CH₂OP(O)(OH)₂, S(O)₂NHC(O)CH₂CH₃, CH₂CH₂O-ciclopropilo,
 NHCH₂CH₂OCH₃, OCH₂CH₂S(O)₂CH₃, NHCH₂CH(CH₃)OH, CH₂CH₂CH₂OH,
 CH₂CH₂CH₂OP(O)(OH)₂, NHCH₂CH(CH₃)S(O)₂CH₃,
 N(CH₃)CH₂CH(CH₃)S(O)₂CH₃, 3-metanosulfonyl-pirrolidin-1-ilo, 3-metanosulfonyl-
 piperidin-1-ilo, CH₂C(O)N(CH₃)₂, 3-metanosulfonyl-azetidin-1-ilo,
 CH₂C(O)NHCH₂CH₂OH, SCH₂CH₂OH, S(O)₂CH₂CH₂OP(O)(OH)₂, S(O)₂CH₂CH₃,
 NHCH₂CH(OH)CH₂OH, S(O)₂CH₂CH₂OH, OCH₂CH₂OP(O)(OH)₂,
 OCH₂CH₂CH₂OP(O)(OH)₂ y S(O)₂NH₂;

R₆ es H o F; y

R₇ es H o CH₃.

65. Una composición de acuerdo con la reivindicación 46, en donde el compuesto es seleccionado de compuestos que tienen la Fórmula (IIc), y sales, solvatos e hidratos farmacéuticamente aceptables del mismo:



donde:

R₁ es carbo-C₁₋₆-alcoxi opcionalmente sustituido con C₃₋₅ cicloalquilo;

R₂ es H o CH₃;

R₃ es C₁₋₄ alcoxi;

R₄ es seleccionado de: H, OCH₃, CH₃, CH₂CH₃, F y Cl;

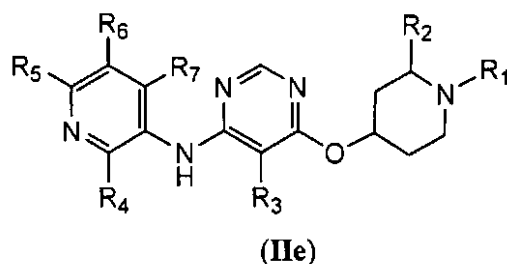
R₅ es seleccionado de:

OCH₂CH₂CH₃, OCH₂CH₂CH₂OH, S(O)₂CH₃, CH₂CH₂S(O)₂CH₃,
 NHCH₂CH₂OH, ciano, CH₂CH₂OCH₃, CH₂CH₂OH, CH₂CH₂CH(CH₃)OH,
 CH₂CH₂OP(O)(OH)₂, S(O)₂NHC(O)CH₂CH₃, CH₂CH₂O-ciclopropilo,
 NHCH₂CH₂OCH₃, OCH₂CH₂S(O)₂CH₃, NHCH₂CH(CH₃)OH, CH₂CH₂CH₂OH,
 CH₂CH₂CH₂OP(O)(OH)₂, NHCH₂CH(CH₃)S(O)₂CH₃,
 N(CH₃)CH₂CH(CH₃)S(O)₂CH₃, 3-metanosulfonil-pirrolidin-1-ilo, 3-metanosulfonil-
 piperidin-1-ilo, CH₂C(O)N(CH₃)₂, 3-metanosulfonil-azetidin-1-ilo,
 CH₂C(O)NHCH₂CH₂OH, SCH₂CH₂OH, S(O)₂CH₂CH₂OP(O)(OH)₂, S(O)₂CH₂CH₃,
 NHCH₂CH(OH)CH₂OH, S(O)₂CH₂CH₂OH, OCH₂CH₂OP(O)(OH)₂,
 OCH₂CH₂CH₂OP(O)(OH)₂ y S(O)₂NH₂;

R₆ es H o F; y

R₇ es H o CH₃.

66. Una composición de acuerdo con la reivindicación 46, en donde el compuesto es seleccionado de compuestos que tienen la Fórmula (IIe), y sales, solvatos e hidratos farmacéuticamente aceptables del mismo:



donde:

R₁ es carbo-C₁₋₆-alcoxi opcionalmente sustituido con C₃₋₅ cicloalquilo;

R_2 es H o CH_3 ;

R_3 es C_{1-4} alcoxi;

R_4 es seleccionado de H, OCH_3 , CH_3 , CH_2CH_3 , F y Cl;

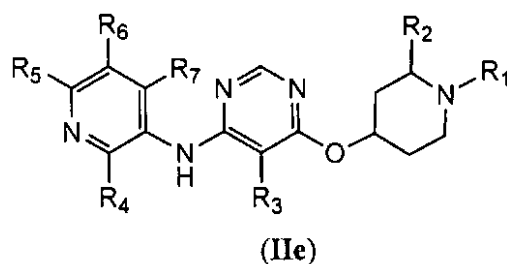
R_5 es seleccionado de:

5 $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{S(O)}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{S(O)}_2\text{CH}_3$,
 $\text{NHCH}_2\text{CH}_2\text{OH}$, ciano, $\text{CH}_2\text{CH}_2\text{OCH}_3$, $\text{CH}_2\text{CH}_2\text{OH}$, $\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{OH}$,
 $\text{CH}_2\text{CH}_2\text{OP(O)}(\text{OH})_2$, $\text{S(O)}_2\text{NHC(O)CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{O-ciclopropilo}$,
 $\text{NHCH}_2\text{CH}_2\text{OCH}_3$, $\text{OCH}_2\text{CH}_2\text{S(O)}_2\text{CH}_3$, $\text{NHCH}_2\text{CH}(\text{CH}_3)\text{OH}$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$,
 $\text{CH}_2\text{CH}_2\text{CH}_2\text{OP(O)}(\text{OH})_2$, $\text{NHCH}_2\text{CH}(\text{CH}_3)\text{S(O)}_2\text{CH}_3$,
10 $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}(\text{CH}_3)\text{S(O)}_2\text{CH}_3$, 3-metanosulfonil-pirrolidin-1-ilo, 3-metanosulfonil-
piperidin-1-ilo, $\text{CH}_2\text{C(O)N}(\text{CH}_3)_2$, 3-metanosulfonil-azetidin-1-ilo,
 $\text{CH}_2\text{C(O)NHCH}_2\text{CH}_2\text{OH}$, $\text{SCH}_2\text{CH}_2\text{OH}$, $\text{S(O)}_2\text{CH}_2\text{CH}_2\text{OP(O)}(\text{OH})_2$, $\text{S(O)}_2\text{CH}_2\text{CH}_3$,
 $\text{NHCH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$, $\text{S(O)}_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{OCH}_2\text{CH}_2\text{OP(O)}(\text{OH})_2$,
 $\text{OCH}_2\text{CH}_2\text{CH}_2\text{OP(O)}(\text{OH})_2$ y $\text{S(O)}_2\text{NH}_2$;

15 R_6 es H o F; y

R_7 es H o CH_3 .

67. Una composición de acuerdo con la reivindicación 46, en donde el compuesto es
seleccionado de compuestos que tienen la Fórmula (IIe), y sales, solvatos e hidratos
20 farmacéuticamente aceptables del mismo:



donde:

R_1 es carbo- C_{1-6} -alcoxi opcionalmente sustituido con C_{3-5} cicloalquilo;

R_2 es H o CH_3 ;

25 R_3 es C_{1-4} alcoxi;

R_4 es seleccionado de: H, OCH_3 , CH_3 , CH_2CH_3 , F y Cl;

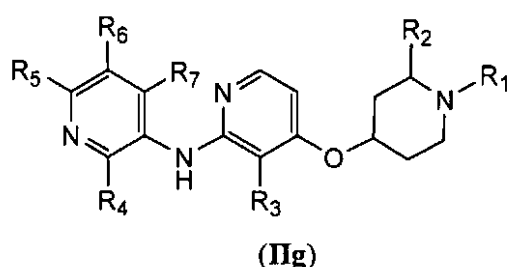
R_5 es seleccionado de:

$\text{OCH}_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{S(O)}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{S(O)}_2\text{CH}_3$, $\text{NHCH}_2\text{CH}_2\text{OH}$, ciano,
 $\text{CH}_2\text{CH}_2\text{OH}$, $\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{OH}$, $\text{CH}_2\text{CH}_2\text{OP(O)}(\text{OH})_2$, $\text{S(O)}_2\text{NHC(O)CH}_2\text{CH}_3$,
30 $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{S(O)}_2\text{CH}_2\text{CH}_3$, $\text{NHCH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$ y $\text{S(O)}_2\text{NH}_2$;

R_6 es H o F; y

R_7 es H o CH_3 .

68. Una composición de acuerdo con la reivindicación 46, en donde el compuesto es seleccionado de compuestos que tienen la Fórmula (IIg), y sales, solvatos e hidratos farmacéuticamente aceptables del mismo:



donde:

R_1 es carbo- C_{1-6} -alcoxi opcionalmente sustituido con C_{3-5} cicloalquilo;

R_2 es H o CH_3 ;

R_3 es C_{1-4} alcoxi;

R_4 es seleccionado de: H, OCH_3 , CH_3 , CH_2CH_3 , F y Cl;

R_5 es seleccionado de:

$\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{S}(\text{O})_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$,
 $\text{NHCH}_2\text{CH}_2\text{OH}$, ciano, $\text{CH}_2\text{CH}_2\text{OCH}_3$, $\text{CH}_2\text{CH}_2\text{OH}$, $\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{OH}$,
 $\text{CH}_2\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$, $\text{S}(\text{O})_2\text{NHC}(\text{O})\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{O-ciclopropilo}$,
 $\text{NHCH}_2\text{CH}_2\text{OCH}_3$, $\text{OCH}_2\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$, $\text{NHCH}_2\text{CH}(\text{CH}_3)\text{OH}$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$,
 $\text{CH}_2\text{CH}_2\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$, $\text{NHCH}_2\text{CH}(\text{CH}_3)\text{S}(\text{O})_2\text{CH}_3$,
 $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}(\text{CH}_3)\text{S}(\text{O})_2\text{CH}_3$, 3-metanosulfonil-pirrolidin-1-ilo, 3-metanosulfonil-
piperidin-1-ilo, $\text{CH}_2\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, 3-metanosulfonil-azetidin-1-ilo,
 $\text{CH}_2\text{C}(\text{O})\text{NHCH}_2\text{CH}_2\text{OH}$, $\text{SCH}_2\text{CH}_2\text{OH}$, $\text{S}(\text{O})_2\text{CH}_2\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$, $\text{S}(\text{O})_2\text{CH}_2\text{CH}_3$,
 $\text{NHCH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$, $\text{S}(\text{O})_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{OCH}_2\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$,
 $\text{OCH}_2\text{CH}_2\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$ y $\text{S}(\text{O})_2\text{NH}_2$;

R_6 es H o F; y

R_7 es H o CH_3 .

69. Una composición de acuerdo con la reivindicación 46, en donde el compuesto es seleccionado de los siguientes compuestos y sales, solvatos e hidratos farmacéuticamente aceptables del mismo:

isopropil éster del ácido 4-[6-(4-Metanosulfonil-2-metoxi-fenilamino)-5-metoxi-pirimidin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-{5-Metoxi-6-[6-(2-metoxi-etil)-2-metil-piridin-3-ilamino]-pirimidin-4-iloxi}-piperidina-1-carboxílico;

1-ciclopropil-etil éster del ácido 4-{6-[6-(2-Metanosulfonil-etil)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;

5 isopropil éster del ácido 4-[6-(2-Fluoro-4-metanosulfonil-fenilamino)-5-metoxi-pirimidin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-[6-(4-Ciano-2-fluoro-fenilamino)-5-metoxi-pirimidin-4-iloxi]-piperidina-1-carboxílico;

10 isopropil éster del ácido 4-{6-[6-(2-Hidroxi-etil)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{6-[6-(2-Metanosulfonil-etil)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{5-Metoxi-6-[6-(2-metoxi-etilamino)-2-metil-piridin-3-ilamino]-pirimidin-4-iloxi}-piperidina-1-carboxílico;

15 isopropil éster del ácido 4-{6-[6-(2-Metanosulfonil-etoxi)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{6-[6-(2-Hidroxi-propilamino)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;

20 isopropil éster del ácido 4-{6-[6-(3-Hidroxi-propil)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{5-metoxi-6-[2-metil-6-(3-fosfonooxi-propil)-piridin-3-ilamino]-pirimidin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{6-[6-(2-Metanosulfonil-etilamino)-2-metoxi-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;

25 isopropil éster del ácido 4-{6-[6-(2-Metanosulfonil-propilamino)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-[6-(6-Dimetilcarbamoilmetil-2-metil-piridin-3-ilamino)-5-metoxi-pirimidin-4-iloxi]-piperidina-1-carboxílico;

30 isopropil éster del ácido 4-(6-{2-Fluoro-4-[(2-hidroxi-etilcarbamoil)-metil]-fenilamino}-5-metoxi-pirimidin-4-iloxi)-piperidina-1-carboxílico;

isopropil éster del ácido 4-{6-[6-(2-Metanosulfonil-etilamino)-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{6-[2-Fluoro-4-(2-hidroxi-etilsulfanil)-fenilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{6-[6-(2,3-Dihidroxi-propilamino)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{6-[6-(2-Hidroxi-etoxi)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico;

5 isopropil éster del ácido 4-{5-Metoxi-6-[2-metil-6-(2-fosfonooxi-etoxi)-piridin-3-ilamino]-pirimidin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{6-[6-(3-Hidroxi-propoxi)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-ácido carboxílico; y

10 isopropil éster del ácido 4-{5-Metoxi-6-[2-metil-6-(3-fosfonooxi-propoxi)-piridin-3-ilamino]-pirimidin-4-iloxi}-piperidina-1-carboxílico.

70. Una composición de acuerdo con la reivindicación 46, en donde el compuesto es seleccionado de los siguientes compuestos y sales, solvatos e hidratos farmacéuticamente aceptables del mismo:

15 isopropil éster del ácido 4-[2-(2-Fluoro-4-propoxi-fenilamino)-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[2-Fluoro-4-(2-hidroxi-etil)-fenilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

20 isopropil éster del ácido 4-[5-Fluoro-2-(2-fluoro-4-metanosulfonil-fenilamino)-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[2-Etil-4-(2-metanosulfonil-etil)-fenilamino]-3-metoxi-piridin-4-iloxi}-2-metil-piperidina-1-carboxílico;

isopropil éster del ácido 4-{5-Fluoro-2-[6-(2-hidroxi-etoxi)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

25 isopropil éster del ácido 4-{2-[2-Fluoro-4-(2-metanosulfonil-etil)-fenilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(2-Hidroxi-etilamino)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

30 isopropil éster del ácido 4-[2-(4-Ciano-2-fluoro-fenilamino)-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-[2-(2-Cloro-4-ciano-fenilamino)-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(2-Metanosulfonil-etil)-2-metoxi-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(2-Metanosulfonil-etil)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(2-Hidroxi-etil)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

5 isopropil éster del ácido 4-{2-[6-(3-Hidroxi-butil)-2-metoxi-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[2-Fluoro-4-(2-hidroxi-etoxi)-fenilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

10 isopropil éster del ácido 4-{3-Etoxi-2-[2-fluoro-4-(2-fosfonooxi-etil)-fenilamino]-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{3-Metoxi-2-(2-metoxi-4-propionilsulfamoil-fenilamino)-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-[2-(2,5-Difluoro-4-propoxi-fenilamino)-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

15 (2-Fluoro-4-metanosulfonil-fenil)-{4-[1-(5-isopropil-[1,2,4]oxadiazol-3-il)-piperidin-4-iloxi]-3-metoxi-piridin-2-il}-amina;

(2-Fluoro-4-metanosulfonil-fenil)-{3-metoxi-4-[1-(5-metoxi-pirimidin-2-il)-piperidin-4-iloxi]-piridin-2-il}-amina;

20 isopropil éster del ácido 4-{2-[6-(2-Ciclopropoxi-etil)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-[2-(2-Cloro-4-metanosulfonil-fenilamino)-5-fluoro-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-[3-Etoxi-2-(4-metanosulfonil-2-metoxi-fenilamino)-piridin-4-iloxi]-piperidina-1-carboxílico;

25 isopropil éster del ácido 4-[2-(5-Fluoro-2-metil-4-propoxi-fenilamino)-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(2-Metanosulfonil-etil)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

30 isopropil éster del ácido 4-[2-(2-Fluoro-4-metanosulfonil-fenilamino)-3-hidroxi-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-[2-(2-Cloro-4-propoxi-fenilamino)-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-{3-Metoxi-2-[2-metil-6-(2-fosfonooxi-etil)-piridin-3-ilamino]-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(2-Metanosulfonil-etilamino)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-(2-{6-[(2-Metanosulfonil-etil)-metil-amino]-2-metil-piridin-3-ilamino}-3-metoxi-piridin-4-iloxi)-piperidina-1-carboxílico;

5 isopropil éster del ácido 4-{2-[6-(3-Metanosulfonil-pirrolidin-1-il)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-[2-(3-Metanosulfonil-6'-metil-3,4,5,6-tetrahidro-2H-[1,2']bipiridinil-5'-ilamino)-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

10 isopropil éster del ácido 4-{2-[6-(3-Metanosulfonil-azetidin-1-il)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-[3-etiniloxi-2-(2-fluoro-4-metanosulfonil-fenilamino)-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[2-Fluoro-4-(2-fosfonooxi-etanosulfonil)-fenilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

15 sec-butil éster del ácido 4-[2-(4-Etanosulfonil-2-fluoro-fenilamino)-3-metoxi-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(2,3-Dihidroxi-propilamino)-4-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

20 isopropil éster del ácido 4-{2-[6-(2-Hidroxi-etilsulfanil)-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[2-Fluoro-4-(2-hidroxi-etanosulfonil)-fenilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(2-Hidroxi-etoxi)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

25 isopropil éster del ácido 4-{3-Metoxi-2-[2-metil-6-(2-fosfonooxi-etoxi)-piridin-3-ilamino]-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(3-Hidroxi-propoxi)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

30 isopropil éster del ácido 4-{3-Metoxi-2-[2-metil-6-(3-fosfonooxi-propoxi)-piridin-3-ilamino]-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-[3-Metoxi-2-(2-metoxi-4-sulfamoil-fenilamino)-piridin-4-iloxi]-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[2-Fluoro-4-(3-fosfonooxi-propil)-fenilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{2-[6-(2-Hidroxi-etil)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico;

isopropil éster del ácido 4-{3-Metoxi-2-[2-metil-6-(2-fosfonooxi-etil)-piridin-3-ilamino]-piridin-4-iloxi}-piperidina-1-carboxílico;

5 isopropil éster del ácido 4-{2-[6-(3-Hidroxi-propil)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico; e

isopropil éster del ácido 4-{3-Metoxi-2-[2-metil-6-(3-fosfonooxi-propil)-piridin-3-ilamino]-piridin-4-iloxi}-piperidina-1-carboxílico.

10 71. Una composición de acuerdo con la reivindicación 46, en donde el compuesto es seleccionado de los siguientes compuestos y sales, solvatos e hidratos del mismo:

1-ciclopropil-etil éster del ácido (S)-4-{6-[6-(2-metanosulfonil-etil)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico,

(2-fluoro-4-metanosulfonil-fenil)-{4-[1-(5-isopropil-[1,2,4]oxadiazol-3-il)-piperidin-4-iloxi]-3-metoxi-piridin-2-il}-amina.

15 isopropil éster del ácido 4-[6-(2-fluoro-4-metanosulfonil-fenilamino)-5-metoxi-pirimidin-4-iloxi]-piperidina-1-carboxílico.

isopropil éster del ácido 4-[6-(4-ciano-2-fluoro-fenilamino)-5-metoxi-pirimidin-4-iloxi]-piperidina-1-carboxílico.

20 isopropil éster del ácido 4-{6-[6-(2-hidroxi-etil)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico.

isopropil éster del ácido 4-{6-[6-(2-metanosulfonil-etil)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico.

25 isopropil éster del ácido 4-{2-[6-(2-metanosulfonil-etil)-2-metil-piridin-3-ilamino]-3-metoxi-piridin-4-iloxi}-piperidina-1-carboxílico.

isopropil éster del ácido 4-[6-(6-dimetilcarbamoilmetil-2-metil-piridin-3-ilamino)-5-metoxi-pirimidin-4-iloxi]-piperidina-1-carboxílico.

isopropil éster del ácido 4-{6-[6-(2-hidroxi-etoxi)-2-metil-piridin-3-ilamino]-5-metoxi-pirimidin-4-iloxi}-piperidina-1-carboxílico.

30 72. Una composición de acuerdo con la reivindicación 46, en donde el compuesto es seleccionado del siguiente compuesto y sales, solvatos e hidratos del mismo:

isopropil éster del ácido 4-[6-(6-metanosulfonil-2-metil-piridin-3-ilamino)-5-metoxi-pirimidin-4-iloxi]-piperidina-1-carboxílico.

73. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 72, en donde dicho inhibidor de dipeptidil peptidasa IV es seleccionado entre:

valina-pirrolidida,

3-(L-isoleucil)tiазolidina,

1-[2-[5-cianopiridin-2-il)amino]etilamino]acetil-2-ciano-(S)-pirrolidina (NVP-DPP728),

3(R)-Amino-1-[3-(trifluorometil)-5,6,7,8-tetrahidro[1,2,4]triazolo[4,3-a]pirazin-7-il]-4-(2,4,5-trifluorofenil)butan-1-ona (MK-0431),

(1-[[3-hidroxi-1-adamantil)amino]acetil]-2-ciano-(S)-pirrolidina (LAF237),

(1S,3S,5S)-2-[2(S)-Amino-2-(3-hidroxiadamantan-1-il)acetil]-2-azabicyclo[3.1.0]hexano-3-carbonitrilo (BMS-477118), y

[1-[2(S)-Amino-3-metilbutiril]pirrolidin-2(R)-il]ácido borónico (PT-100).

74. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 71, en donde dicho inhibidor de dipeptidil peptidasa IV es 3(R)-Amino-1-[3-(trifluorometil)-5,6,7,8-tetrahidro [1,2,4] triazolo [4,3-a] pirazin-7- il]-4-(2,4,5-trifluorofenil)butan-1-ona (MK-0431).

75. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 71, en donde dicho inhibidor de dipeptidil peptidasa IV es (1-[[3-hidroxi-1-adamantil)amino]acetil]-2-ciano-(S)-pirrolidina (LAF237).

76. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 71, en donde dicho inhibidor de dipeptidil peptidasa IV es (1S,3S,5S)-2-[2(S)-Amino-2-(3-hidroxiadamantan-1-il)acetil]-2-azabicyclo[3.1.0]hexano-3-carbonitrilo (BMS-477118).

77. Un método para preparar una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 76, el método comprende mezclar dicho inhibidor de dipeptidil peptidasa IV (DPP-IV) y dicho compuesto.

78. Una composición de acuerdo con una cualquiera de las reivindicaciones 46 a 76, que además comprende un portador farmacéuticamente aceptable.

79. Un método para preparar una composición de acuerdo con la reivindicación 78, el método comprende mezclar dicho inhibidor de dipeptidil peptidasa IV (DPP-IV), dicho compuesto, y dicho portador farmacéuticamente aceptable.

5 80. Una composición de acuerdo con la reivindicación 46, en donde:

el compuesto es seleccionado del siguiente compuesto y sales, solvatos e hidratos farmacéuticamente aceptables del mismo:

isopropil éster del ácido 4-[6-(6-metanosulfonil-2-metil-piridin-3-ilamino)-5-metoxi-pirimidin-4-iloxi]-piperidina-1-carboxílico; y

10 dicho inhibidor de dipeptidil peptidasa IV es 3(R)-Amino-1-[3-(trifluorometil)-5,6,7,8-tetrahidro[1,2,4]triazolo[4,3-a]pirazin-7-il]-4-(2,4,5-trifluorofenil)butan-1-ona (MK-0431).

15 81. Un método para preparar una composición de acuerdo con la reivindicación 80, el método comprende mezclar dicho inhibidor de dipeptidil peptidasa IV (DPP-IV) y dicho compuesto.

82. Una composición de acuerdo con la reivindicación 80, que además comprende un portador farmacéuticamente aceptable.

20 83. Un proceso para preparar una composición de acuerdo con la reivindicación 82, el método comprende mezclar dicho inhibidor de dipeptidil peptidasa IV (DPP-IV), dicho compuesto, y dicho portador farmacéuticamente aceptable.

25 84. Un proceso de acuerdo con la reivindicación 83, que además comprende el paso de preparar una forma de dosificación unitaria de la composición.

85. Una composición de acuerdo con la reivindicación 46, en donde:

30 el compuesto es seleccionado del siguiente compuesto y sales, solvatos e hidratos farmacéuticamente aceptables del mismo:

isopropil éster del ácido 4-[6-(6-metanosulfonil-2-metil-piridin-3-ilamino)-5-metoxi-pirimidin-4-iloxi]-piperidina-1-carboxílico; y

35 dicho inhibidor de dipeptidil peptidasa IV es (1-[[3-hidroxi-1-adamantil)amino]acetil]-2-ciano-(S)-pirrolidina (LAF237).

86. Un método para preparar una composición de acuerdo con la reivindicación 85, el método comprende mezclar dicho inhibidor de dipeptidil peptidasa IV (DPP-IV) y dicho compuesto.

5 87. Una composición de acuerdo con la reivindicación 85, que además comprende un portador farmacéuticamente aceptable.

10 88. Un método para preparar una composición de acuerdo con la reivindicación 87, el método comprende mezclar dicho inhibidor de dipeptidil peptidasa IV (DPP-IV), dicho compuesto, y dicho portador farmacéuticamente aceptable.

89. Un método de acuerdo con la reivindicación 88, que además comprende el paso de preparar una forma de dosificación unitaria de la composición.

15 90. Una composición de acuerdo con la reivindicación 46, en donde:
el compuesto es seleccionado del siguiente compuesto y sales, solvatos e hidratos farmacéuticamente aceptables del mismo:
isopropil éster del ácido 4-[6-(6-metanosulfonil-2-metil-piridin-3-ilamino)-5-metoxi-pirimidin-4-iloxi]-piperidina-1-carboxílico; y
20 dicho inhibidor de dipeptidil peptidasa IV es (1S,3S,5S)-2-[2(S)-Amino-2-(3-hidroxiadamantan-1-il)acetil]-2-azabicyclo[3.1.0]hexano-3-carbonitrilo (BMS-477118).

25 91. Un método para preparar una composición de acuerdo con la reivindicación 90, el método comprende mezclar dicho inhibidor de dipeptidil peptidasa IV (DPP-IV) y dicho compuesto.

92. Una composición de acuerdo con la reivindicación 90, que además comprende un portador farmacéuticamente aceptable.

30 93. Un método para preparar una composición de acuerdo con la reivindicación 92, el método comprende mezclar dicho inhibidor de dipeptidil peptidasa IV (DPP-IV), dicho compuesto, y dicho portador farmacéuticamente aceptable.

94. Un método de acuerdo con la reivindicación 93, que además comprende el paso de preparar una forma de dosificación unitaria de la composición.



Crystalline solids

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Abstract

Many drugs exist in the crystalline solid state due to reasons of stability and ease of handling during the various stages of drug development. Crystalline solids can exist in the form of polymorphs, solvates or hydrates. Phase transitions such as polymorph interconversion, desolvation of solvate, formation of hydrate and conversion of crystalline to amorphous form may occur during various pharmaceutical processes, which may alter the dissolution rate and transport characteristics of the drug. Hence it is desirable to choose the most suitable and stable form of the drug in the initial stages of drug development. The current focus of research in the solid-state area is to understand the origins of polymorphism at the molecular level, and to predict and prepare the most stable polymorph of a drug. The recent advances in computational tools allow the prediction of possible polymorphs of the drug from its molecular structure. Sensitive analytical methods are being developed to understand the nature of polymorphism and to characterize the various crystalline forms of a drug in its dosage form. The aim of this review is to emphasize the recent advances made in the area of prediction and characterization of polymorphs and solvates, to address the current challenges faced by pharmaceutical scientists and to anticipate future developments. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Crystallinity; Polymorphs; Hydrates; Solvates; Formulation; Drug substance; Phase transformation; Characterization

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1. Introduction

Most organic and inorganic compounds of pharmaceutical relevance can exist in one or more crystalline forms. When applied to solids, the adjective, *crystalline*, implies an ideal crystal in which the structural units, termed *unit cells*, are repeated regularly and indefinitely in three dimensions in space. The unit cell has a definite orientation and shape defined by the translational vectors, a , b , and c , and hence has a definite volume, V , that contains the atoms and molecules necessary for generating the crystal. Each crystal can be classified as a member of one of seven possible crystal systems or crystal classes that are defined by the relationships between the individual dimensions, a , b , and c , of the unit cell and between the individual angles, α , β , and γ of the unit cell [1,2]. The structure of a given crystal may be assigned to one of the seven crystal systems, to one of the 14 Bravais lattices, and to one of the 230 space groups [1]. All the 230 possible space groups, their symmetries, and the symmetries of their diffraction patterns are compiled in the International Tables for Crystallography [3].

The common crystalline forms found for a given drug substance are polymorphs and solvates. Crystalline polymorphs have the same chemical composition but different internal crystal structures and, therefore, possess different physico-chemical properties. The different crystal structures in polymorphs arise when the drug substance crystallizes in different crystal packing arrangements and/or different conformations. The occurrence of polymorphism is quite common among organic molecules, and a large number of polymorphic drug compounds have been noted and catalogued [4–7].

Solvates, also known as pseudopolymorphs, are

crystalline solid adducts containing solvent molecules within the crystal structure, in either stoichiometric or nonstoichiometric proportions, giving rise to unique differences in the physical and pharmaceutical properties of the drug. If the incorporated solvent is water, a solvate is termed a hydrate. Adducts frequently crystallize more easily because two molecules often can pack together with less difficulty than single molecules. While no definite explanations can be given, possible reasons include adduct symmetry, adduct-induced conformation changes, and the ability to form hydrogen bonds through the solvent molecules [2,8,9]. Desolvated solvates are produced when a solvate is desolvated and the crystal retains the structure of the solvate [10]. Desolvated solvates are less ordered than their crystalline counterparts and are difficult to characterize, because analytical studies indicate that they are unsolvated materials (or anhydrous crystal forms) when, in fact, they have the structure of the solvated crystal form from which they were derived [11].

Because different crystalline polymorphs and solvates differ in crystal packing, and/or molecular conformation as well as in lattice energy and entropy, there are usually significant differences in their physical properties, such as density, hardness, tabletability, refractive index, melting point, enthalpy of fusion, vapor pressure, solubility, dissolution rate, other thermodynamic and kinetic properties and even color [12]. Differences in physical properties of various solid forms have an important effect on the processing of drug substances into drug products [13], while differences in solubility may have implications on the absorption of the active drug from its dosage form [14], by affecting the dissolution rate and possibly the mass transport of the molecules. These concerns have led to an increased regulatory

interest in understanding the solid-state properties and behavior of drug substances. For approval of a new drug, the drug substance guideline of the US Food and Drug Administration (FDA) states that "appropriate" analytical procedures need to be used to detect polymorphs, hydrates and amorphous forms of the drug substance and also stresses the importance of controlling the crystal form of the drug substance during the various stages of product development [11]. It is very important to control the crystal form of the drug during the various stages of drug development, because any phase change due to polymorph interconversions, desolvation of solvates, formation of hydrates and change in the degree of crystallinity can alter the bioavailability of the drug. When going through a phase transition, a solid drug may undergo a change in its thermodynamic properties, with consequent changes in its dissolution and transport characteristics [15].

Various pharmaceutical processes during drug development significantly influence the final crystalline form of the drug in the dosage form. The various effects of pharmaceutical processing on drug polymorphs, solvates and phase transitions have been described in detail by Brittain and Fiese [16] and will be discussed in later chapters. Briefly, processes such as lyophilization and spray drying may lead to the formation of the amorphous form of drug, which tends to be less stable and more hygroscopic than the crystalline product. Also, processing stresses, such as drying, grinding, milling, wet granulation, oven drying and compaction, are reported to accelerate the phase transitions in pharmaceutical solids. The degree of polymorphic conversion will depend on the relative stability of the phases in question, and on the type and degree of mechanical processing applied. Keeping these factors in mind, it is desirable and usual to choose the most stable polymorphic form of the drug in the beginning and to control the crystal form and the distributions in size and shape of the drug crystals during the entire process of development. The presence of a metastable form during processing or in the final dosage form often leads to instability of drug release as a result of phase transformation [17].

Crystallization plays a critical role in controlling the crystalline form and the distribution in size and shape of the drug. The significance of crystallization

mechanisms and kinetics in directing crystallization pathways of pharmaceutical solids and the factors affecting the formation of crystals have been reviewed in detail by various researchers [12,18,19]. A crystalline phase is created as a consequence of molecular aggregation processes in solution that lead to the formation of nuclei, which achieve a certain size during the nucleation phase to enable growth into macroscopic crystals to take place during the growth phase. The factors affecting the rate and mechanisms by which crystals are formed are: solubility, supersaturation, rate at which supersaturation and desupersaturation occur, diffusivity, temperature, and the reactivity of surfaces towards nucleation. The various forces responsible for holding the organic crystalline solids together, such as nonbonded interactions and hydrogen bonding, have been discussed in detail by Byrn et al. [2] and Etter [20].

Various analytical methods are being currently used to characterize the crystalline form of the drug during the various steps of processing and development. These methods have been reviewed recently in detail by many authors [7,10,21–25]. The single most valuable piece of information about the crystalline solid, including the existence of polymorphs and solvates, is the molecular and crystalline structure, which is determined by single-crystal X-ray diffractometry [2]. Powder X-ray diffractometry provides a "fingerprint" of the solid phase and may sometimes be used to determine crystal structure. Once the existence of polymorphism (or solvate formation) is definitely established by single-crystal and powder X-ray diffractometry, spectral methods, such as Fourier transform infrared absorption (FTIR) spectroscopy, Fourier transform Raman scattering (FT Raman) spectroscopy, solid-state nuclear magnetic resonance (SSNMR) spectroscopy, ultraviolet and visible (UV-Vis) and/or fluorescence spectroscopy [23] may be employed for further characterization. Of special significance are thermal methods, such as differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and optical microscopy using a hot stage [24]. These methods are almost always employed for further characterization. Modulated (temperature) differential scanning calorimetry (MDSC) in combination with DSC and optical microscopy are able to identify the glass

transition of amorphous forms with much greater clarity and allow unique insights into the glass transitional and polymorphic behavior of drug substances [26].

Because solid-state NMR spectroscopy can be used to study crystalline solids, as well as pharmaceutical dosage forms, this powerful method is finding increasing application in deducing the nature of polymorphic variations [27], such as variations in hydrogen bonding network and molecular conformations among polymorphs [28,29] and for the determination of molecular conformations and mobility of drugs in mixtures and dosage forms [2]. Solid-state ^{13}C -NMR in conjunction with the techniques, known as high power proton decoupling, cross polarization (CP), and magic-angle spinning (MAS) offers information not obtained readily by other techniques. Recently, two-dimensional ^{13}C -solid-state NMR spectroscopy has been used to study the three conformational polymorphs of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile [30]. Use of two-dimensional NMR and total suppression of spinning side bands (TOSS) pulse sequences allowed the separation of isotropic and anisotropic chemical shifts for the three forms. This is a very powerful method for analyzing differences in the chemical environment and is finding increased application in the study of conformational polymorphism.

With advances in analytical methods, the current focus of research in the solid-state area is to understand polymorphism and pseudopolymorphism at the molecular level. Knowledge of the crystal packing arrangements and the various intermolecular forces involved in the different packing arrangements will help in the prediction and preparation of the most stable polymorphs of a given compound well in advance, to avoid surprises during product development. A current emphasis is on the development of software to predict crystal structures of polymorphs from molecular structures. A thorough understanding of the physicochemical properties of polymorphs and solvates (hydrates) is of primary importance to the selection of a suitable crystalline form and development of a successful pharmaceutical product. Bray et al. [31] have shown that, by thorough characterization of four different crystalline forms of L-738,167, a fibrinogen receptor antagonist by various analytical

techniques, it was possible to determine the suitability of one or two forms for the development of pharmaceutical oral dosage forms.

The present review aims to emphasize the recent advances made in the area of prediction and characterization of polymorphs and solvates, attempts to address the current challenges and problems faced by pharmaceutical scientists and intends to anticipate future development. This review does not attempt to provide solutions to the problems but attempts to review comprehensively the advances made in recent years to help address these problems.

2. Recent advances in the identification, prediction and characterization of polymorphs

2.1. Types of polymorphism

Based on differences in the thermodynamic properties, polymorphs are classified as either enantiotropes or monotropes, depending upon whether one form can transform reversibly to another or not. In an enantiotropic system, a reversible transition between polymorphs is possible at a definite transition temperature below the melting point. In a monotropic system, no reversible transition is observed between the polymorphs below the melting point. Four useful rules have been developed by Burger and Ramburger [32,33] to determine qualitatively the enantiotropic or monotropic nature of the relationship between polymorphs. These rules are the heat of transition rule, heat of fusion rule, infrared rule and density rule.

If, by use of the above rules, it is established that the polymorphs of a particular drug are enantiotropic or monotropic, then the next goal is to define the thermodynamically stable (or metastable) domain of each crystalline phase of a substance as a function of temperature. The plot of the Gibbs free energy difference, ΔG , against the absolute temperature, T , gives the most complete and quantitative information on the stability relationship of polymorphs [22], with the most stable polymorph having the lowest Gibbs free energy. The ΔG between the polymorphs may be obtained using several techniques operating at

different temperatures, such as solubility [34] and intrinsic dissolution rate. Yu [35] has derived thermodynamic equations to calculate ΔG between two polymorphs and its temperature slope from the melting data. This method is essentially an extension of the heat of fusion rule, which is based on statistical mechanics. Extrapolating ΔG to zero gives an estimate of the transition temperature, from which the existence of monotropy or enantiotropy is inferred. The integration of different types of data provides the ΔG vs. T curve over a wide temperature range and allows the consistency between techniques to be checked [22]. Another approach to establish the order of stability among various polymorphs has been studied using pressure versus temperature plots, e.g., for sulfanilamide and piracetam [36]. This approach is based upon Ostwald's principle of least vapor pressure, according to which the stable polymorph exhibits the lowest vapor pressure. The accuracy of this approach to establish the stability hierarchy among the polymorphs has been shown to be very much dependent on the accuracy of the experimental data.

In recent years, the main focus of research has been the characterization of polymorphs arising from structural differences in the crystal lattice. It has been established for some time that organic molecules are capable of forming different crystal lattices through two different mechanisms. One of the mechanisms is termed *packing polymorphism*, and represents instances where conformationally relatively rigid molecules can be assembled into different three-dimensional structures through the invocation of different intermolecular mechanisms. The other mechanism is termed *conformational polymorphism* and arises when a nonconformationally rigid molecule can be folded into different arrangements, which subsequently can be packed into alternative crystal structures. The distinction between *packing polymorphism* and *conformational polymorphism* is somewhat artificial because different packing arrangements impose different conformations on the molecules, however slight, and different conformations will inevitably pack differently. The structural aspects associated with polymorphs have been reviewed recently [2], as have the analogous features of solvate and hydrate systems [9]. In the next

section, the results of some more recent investigations are discussed.

2.2. Packing polymorphism

An investigation into the structures and charge densities of two polymorphs of *p*-nitrophenol has been performed with the aim of deducing the different modes of inter-molecular hydrogen bonding that lead to the formation of the two structures shown in Fig. 1a and b [37]. A detailed analysis of the charge density of the two forms indicates charge migration from the benzene ring region to the nitro and hydroxyl groups that accompanies the transformation of one form into the other. In addition, polarization of the oxygen lone-pair electrons was found to be substantially larger in the crystal forms than in the free molecule, resulting in considerably larger dipole moments in the solid state.

During the study of a new crystal form (form I) of

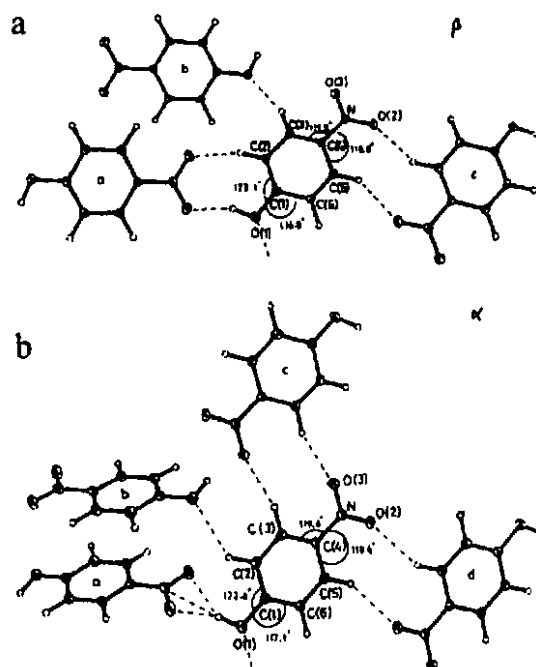


Fig. 1. Molecular packing diagrams of the (a) β polymorph of *p*-nitrophenol, (b) α polymorph of *p*-nitrophenol, showing 50% probability displacement ellipsoids ([37], reproduced with the permission of the American Chemical Society).

chlordiazepoxide, it was found that the heat of transition between the two forms (forms I and II) is rather modest, and kinetic factors permit the existence of the metastable phase [38]. Both structures contain four crystallographically independent molecules linked in dimers through hydrogen bonding, but the dimers are packed differently to yield the two crystal forms. Because the dimers in the fundamental units are spaced differently in the two forms, it was proposed that the solid-state enantiotropic transformation entailed rearrangement of the dimer units.

A different approach has been taken during an evaluation of the different structures formed by sulfathiazole [39]. Using a graph set approach to classify the known structural differences and similarities among the various forms, it became possible to identify packing motifs common to three of the four crystal structures. Fig. 2 shows the unit cells of the polymorphs I, II, III and IV, where molecules are paired as hydrogen-bonded dimers. At the end of the process, the authors were able to deduce possible links between the observed patterns of hydrogen bonding, processes of nucleation, and the crystal growth observed from a number of solvent systems. Interestingly, the analysis did not indicate a relationship between the appearance of a particular polymorph from solution and the growth of its fastest

growing surface. Rather, it appeared as if the different solvents affected the process of polymorph formation through their effects on nucleation of the various forms.

2.3. Conformational polymorphism

The conformational polymorphism of the two forms of piroxicam pivalate has been studied in detail [40]. This compound is distinctive in that the high-melting form (polymorph 1) contains an unanticipated array of associated molecules bound as centrosymmetric dimers through hydrogen bonding, with the amido nitrogen atom acting as the donor and the pyridine nitrogen as the acceptor (Scheme 1, structure I). The low-melting form (polymorph 2) contains molecules of two distinct conformational states coexisting in the same crystal (Fig. 3), but linked through different hydrogen bonding arrangements. This latter finding represents another unusual aspect of the crystallography of the substance.

The inclusion of different solvent molecules in a crystal lattice can lead to the existence of different packing patterns, and has also been found to influence the molecular conformation of paroxetine hydrochloride in two solvate forms [41]. One form

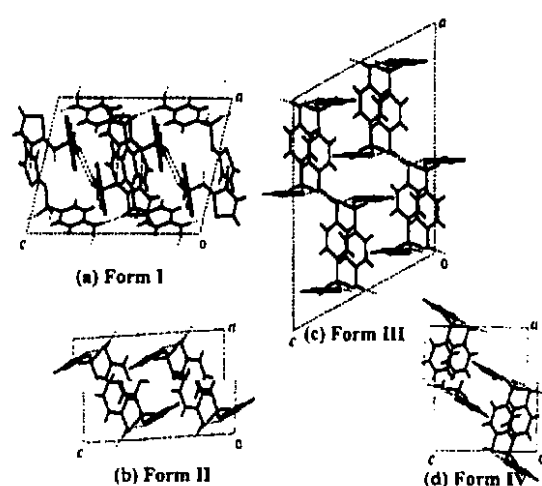
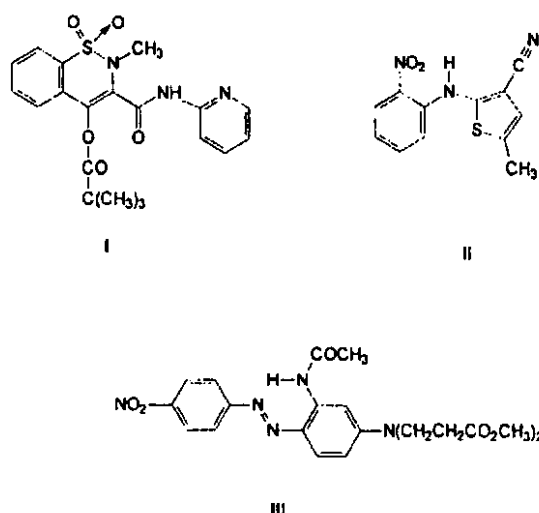


Fig. 2. Unit cells of four polymorphs (I, II, III and IV) of sulfathiazole showing hydrogen bonds, with the dimer structure clearly discernible ([39], reproduced with the permission of the Royal Society of Chemistry).



Scheme 1. Molecular structure of piroxicam pivalate (I) [40], 5-methyl-2-[2-(nitrophenyl)amino]-3-thiophenecarbonitrile (II) [30], 2'-acetamido-4'-(N,N-bis(2-methylcarbonyl)ethyl)amino-4-nitroazobenzene (III) [48].

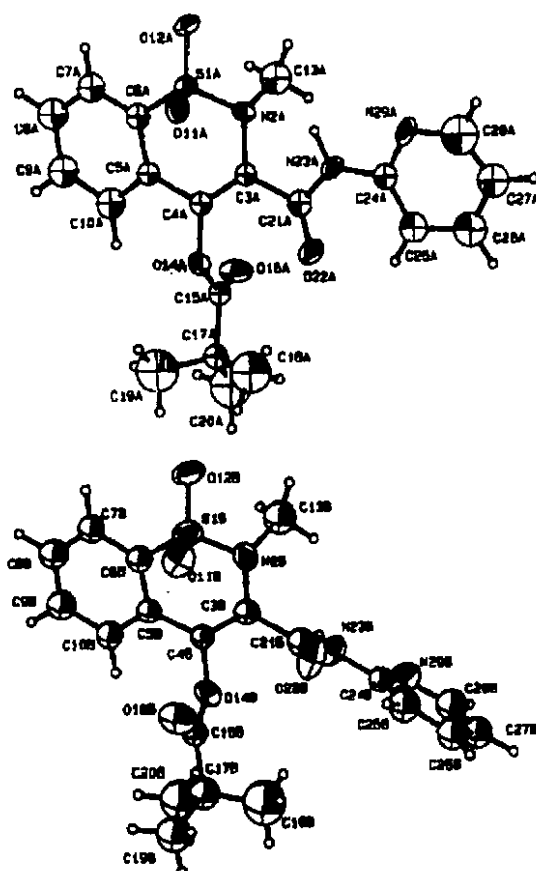


Fig. 3. Conformations of the two independent molecules of piroxicam pivalate (I) in polymorph 2. Thermal ellipsoids are drawn at the 40% probability level, and H atoms are shown as spheres of arbitrary size ([40], reproduced with the permission of the American Pharmaceutical Association).

was obtained as a hemihydrate, and the other as the solvate of isopropanol (2-propanol). In the unit cell of the hemihydrate, one finds two protonated paroxetine and two chloride ions together with one water molecule. Interestingly, the two paroxetine molecules are conformationally nonequivalent, and exhibit a number of different bond angles and torsion angles. In the other form, the unit cell contains one protonated paroxetine molecule, one chloride ion, and one isopropanol molecule disordered along a molecular channel. Furthermore, the conformation of the paroxetine molecule in the isopropanol solvate is different from either molecular conformation observed in the

hemihydrate phase. Crystals of the isopropanol solvate decomposes in the open air at room temperature, because the isopropanol molecules are released easily through the channel. The hemihydrate is relatively stable.

In an impressive fundamental study, the polymorphism of 5-methyl-2-[2-(nitrophenyl)amino]-3-thiophenecarbonitrile (Scheme 1, structure II) has been catalogued [42,43] and discussed in detail [2]. This compound was crystallized as six solvent-free polymorphs, each of which differed in the mode of packing and in molecular conformation. The different conformers yielded sufficient perturbations on the respective molecular orbital so that a variety of crystal colors (red, orange, and yellow) were observed. To obtain a more detailed evaluation of the relative stability, the authors considered a partitioning of polymorphic energy differences into lattice and conformational contributions, and were able to deduce general trends that appeared valid in the absence of hydrogen bonding. The act of crystallization was found to feature an interplay of opposing forces, with perpendicular molecular conformations being favored in fluid solutions, while a preference for planar/high dipole conformers existed in most crystal forms, as shown in Fig. 4 [42]. The unusual polymorphism displayed by this system may result from one or more of the following factors: the preference for perpendicular conformations in solutions, the preference for planar/high dipole conformers in crystals, the formation of inter- and intramolecular hydrogen bonds, and the thermodynamic tendency towards low energy and high entropy.

2.4. Phase transformations in the solid state

Studies of phase transformations in the solid state are important, because the sudden appearance or disappearance of a crystalline form can threaten process development, and can lead to serious pharmaceutical consequences if the transformation occurs in the dosage forms. Hence, an understanding of the kinetics and mechanism of phase transformations is of practical importance. The rearrangement of molecules into a new structure during phase transformation may or may not involve a solvent or vapor phase. To explain the mechanism of solid–solid

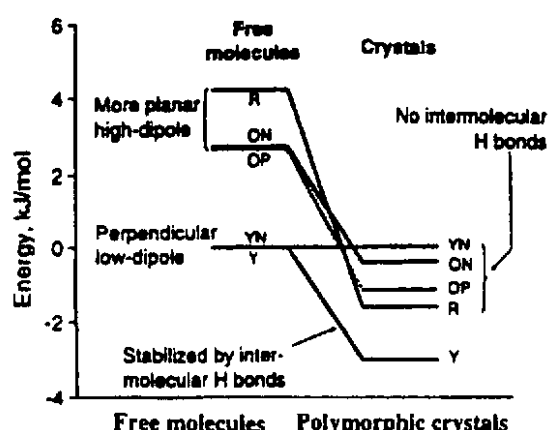


Fig. 4. Comparison of conformational energies and crystal energies of the various polymorphs of 5-methyl-2-[2-(nitrophenyl)amino]-3-thiophenecarbonitrile (II). Form R (red prisms, m.p. 106.2°C), form Y (yellow prisms, m.p. 109.8°C), form OP (orange plates, m.p. 112.7°C), form ON (orange needles, m.p. 114.8°C), form YN (yellow needles, m.p. not measurable) ([42], reproduced with the permission of the American Chemical Society).

physical transition, four steps have been proposed: (a) molecular loosening in the initial phase; (b) formation of an intermediate solid solution; (c) nucleation of the new solid phase and (d) growth of the new phase [2]. In an interesting study, Skwierczynski [44] has proposed a two-environment model to describe the decomposition reaction kinetics of a crystalline solid, aspartame. The decomposition reaction of aspartame is a simple unimolecular thermally-induced aminolysis and the reaction proceeds under anhydrous conditions, i.e., water is not a reactant [45]. This model links the chemistry of the solid-state reaction with the molecular mobility of the reactant as the reaction proceeds. The advantage of this model is that it can be used to determine the shelf life of a product from kinetic data gathered at elevated temperatures. Apart from solid–solid physical transformations, solution-mediated physical transformations among polymorphs are also known to occur in processes, such as wet granulation and during dissolution testing.

While the majority of studies have probed the equilibrium properties of polymorphic and solid-state solvated systems, relatively few have been concerned with the dynamics of phase transformation. Byrn et

al. [2] have reviewed briefly the aspect of polymorphic interconversions and the factors affecting the transformations. In one study, the contribution of hydrogen bonding to the $\alpha \rightarrow \beta$ phase change of resorcinol has been detailed [46]. The α form is more stable than the β form at room temperature, but is less dense than the β form. The transition of $\alpha \rightarrow \beta$ at an estimated transition temperature of 337 ± 1 K is accompanied by an increase in crystal density, with the structure shifting from an open array of molecules (linked through hydrogen bonding) to a denser structure resembling molecular crystals. Through the use of a simple potential model, it was concluded that, during the phase transformation, the energy of the hydrogen bonds decreases along with the extent of such bonding. The energy liberated by this process is almost offset by the enhanced Van der Waals energies associated with the increase in crystal density, and consequently the transition enthalpy is rather small. Accompanying the shifts in hydrogen bonding is a number of effective proton transfers, altering the covalent and ionic portions of the crystal. It was also learned that the increase in entropy produced from the redistribution of protons was of the same order of magnitude as the entropy of the phase transition.

A number of spectroscopic techniques have been used to study the processes associated with a polymorphic transition of 2-(2,4-dinitrobenzyl)-3-methylpyridine [47]. The two interconverting structures coexisted over a temperature range of at least 8–9°C. The phase change was associated with a molecular tautomerization that translated through the collective changes of a large number of molecules, yielding domains having definite short-range order. The slowly evolving spectroscopy that took place above the transition temperature was interpreted as the annealing of domains into a long-range ordered system. The process of phase transformation appeared to consist of an initial fast redistribution of the mole ratio of the coexisting phases, followed by a much slower process involving a macroscopic relaxation of the system. Although local thermodynamic equilibrium was thought to exist in individual domains, the magnitude noted for the temperature range of the phase transition was proposed to arise from nonequilibrium conditions existing among the various types of domain.

A combination of solid-state ^{15}N -NMR spectroscopy and X-ray crystallography was used to study polymorphic transitions in an azobenzene dyestuff, 2'-acetamido-4'-[*N,N*-bis(2-methoxycarbonylethyl)amino]-4-nitroazobenzene (Scheme 1, structure III) [48]. This work established that the structure of one polymorph was disordered, and that the process of phase transformation entailed a crankshaft-type motion of the azo linkage. The ORTEP plots of the two molecular conformations for the X-ray structure determination of structure III at 293 K are shown in Fig. 5. Selective polarization inversion and band shape-fitting experiments were used to deduce the thermodynamic parameters of the exchange process.

Raman spectroscopy was used to study the effect of pressure on the phase transitions in hexamethylbenzene and hexa(methyl- d_3)benzene [49]. The form II $\rightarrow$ form III transition of the partially deuterated substance was found to take place at a lower pressure relative to that of the analogous hexamethylbenzene compound, which was attributed to differences in the energies of the intramolecular methyl torsional vibration in the two crystal forms. In another study performed by the same group, the effects of both temperature and pressure on the phase transitions of tetrafluoro-1,4-benzoquinone were considered [50]. In this system, the changes in en-

vironmental conditions were found to influence a number of intermolecular and intramolecular vibrational modes, yielding conformational changes that in turn produced the observed phase transitions.

2.5. Prediction of polymorphs

The main challenge in managing the phenomenon of multiple solid forms of a drug is the inability to predict the number of forms that can be expected in a given case. This prediction would involve quantification of the myriad intermolecular forces within any proposed crystal structure as well as the ability to postulate the likely packing modes for a given molecule in all its configurations [10]. Accurate theoretical prediction of polymorphs from studies of molecular dynamics and crystal structure generation would be of outstanding importance in drug research [36].

More research is now being directed towards developing computational tools to understand the nature of polymorphism and to predict polymorphic forms at an early stage in the drug development process. The recent developments in computational chemistry allow the prediction of possible polymorphic forms based only on the molecular structure of the drug. The Polymorph Predictor, from Molecular Simulations, is currently the only commercial software package that can predict the possible polymorphs of an organic compound from its molecular structure [51]. The package developed by Karfunkel and co-workers [52–54] uses a Monte Carlo simulated annealing approach to generate thousands of possible crystal packing alternatives for a given molecule. Each of the unique crystal structures is then subjected to a lattice energy minimization to obtain the relative stability ranking of the various packing possibilities and the resulting lowest-energy structures are the potential polymorphs. This method has been successfully employed to generate known polymorphs of primidone (Fig. 6A and B) and progesterone, starting from the molecular structures alone [55]. It has also been used to predict polymorphs for a range of small molecules and to predict unknown polymorphic structures of 4-amidinoin-danone guanyldiazide, a selective inhibitor of *S*-adenosylmethionine decarboxylase [56], and of aspirin [57].

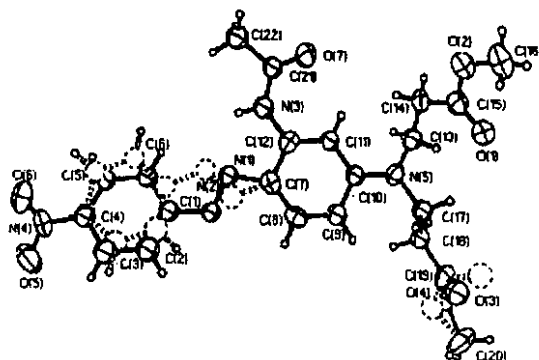


Fig. 5. ORTEP plots of the two molecular conformations (1 and 2) for the X-ray structure determination of 2'-acetamido-4'-[*N,N*-bis(2-methoxycarbonylethyl)amino]-4-nitroazobenzene (Scheme 1 Structure) at 293 K. Thermal ellipsoids are shown at 30% for clarity, with conformer 2 being represented by the solid lines and Conformer 1 by the dotted lines ([48], reproduced with the permission of the American Chemical Society).

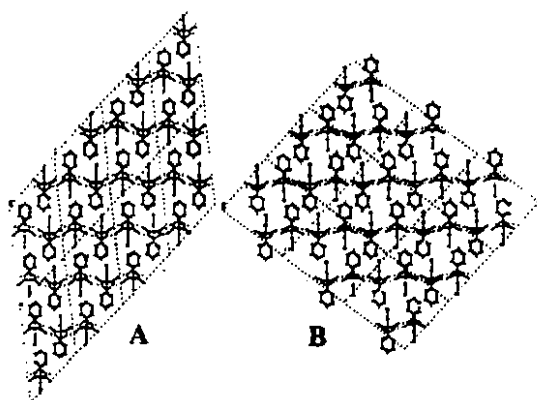


Fig. 6. Comparison of the crystal structure of primidone A (A) versus the most likely packing arrangement, frame 7 (B) ([55], reproduced with the permission of Elsevier Science).

The theoretical predictions of lattice energies, entropies, morphologies and polymorphs should stimulate experimental activities and vice versa. The current crystal-modeling efforts have the potential of producing more quantitative tools for bridging structures and properties, which could help in creating solid forms with desired properties [22]. There are many limitations in using computational methods for predicting polymorphs theoretically. The first limitation is that the *ab initio* screening is useful only for nonionic rigid molecules. For more complex systems, the method is very useful for generating plausible crystal structures, but it is not accurate enough to determine which of these possible structures can actually be crystallized [58]. In addition, the limitations in computer power can restrict the use of this method for predicting polymorphs of complex molecules. An issue of concern is that the existing methods only predict the lattice energies, which relate to internal energies or enthalpies of the crystals. However, the relative thermodynamic stability of polymorphs is determined by the Gibbs free energy, which is a linear function of both enthalpy and entropy. Predictions of the relative stability of polymorphs will be more accurate when the entropies, as well as lattice energies, are considered. Application of molecular dynamics may enable the entropies to be calculated. Hence, no general method is currently available for the prediction or interpretation of the properties of complicated polymorphic or pseudopolymorphic systems.

2.6. Directing the crystallization of specific polymorphs

Complementing the different computational methods for predicting the stable polymorphs of a given compound, various experimental methods are also being employed extensively to control the type of polymorph formed during the crystallization process. Many studies have reported the role of additives in controlling the outcome of the crystallization process. Some of the preselected additives are capable of inhibiting the nucleation and/or growth of the unwanted polymorphs. For the first time, the role of reaction by-products in controlling polymorph appearance of a drug has been reported [59]. This drug is sulfathiazole that is known to exist as polymorphs, forms I, II, III and IV, that differ in the hydrogen-bond network. Form I was found to be different from the other three forms as a result of a different hydrogen bonding at the aniline moiety of the molecule. From studies of the hydrogen-bonding pattern, it was predicted that the ethamido derivative of sulfathiazole could selectively control the formation of form I over other forms by entering the growing face of form I without disrupting the structure (Fig. 7a). Because a similar effect was not possible with the other forms, incorporation of the ethamido derivative in the other forms should inhibit their growth (Fig. 7b). Experimentally, it was shown that the ethamido by-product stabilized form I over the other polymorphs. This study clearly shows that the combination of crystal morphology and the hydrogen-bond network analysis of the different polymorphs offer a new and powerful approach to understanding and controlling polymorph appearance and stability in the presence of additives.

A similar approach was also applied to stabilize a metastable α conformational polymorph of L-glutamic acid using additives [60]. Methods such as DREIDING and TRIPOS force fields were used to select appropriate additives which could mimic the α and β conformations. Four additives were chosen for this study of which two were present exclusively in the β conformation and theoretically should selectively inhibit the crystallization of the β phase and thus stabilize the metastable α phase. Experimentally, it was proven that the additives, by virtue of their conformation, were able to selectively inhibit the

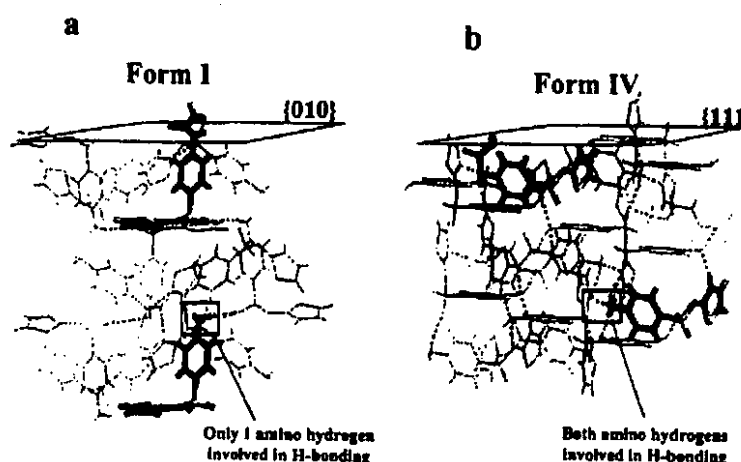


Fig. 7. Possible binding interaction of ethamidosulfamide in the fastest growing faces of (a) form I and (b) form IV of sulfathiazole ([59], reproduced with the permission of Elsevier Science).

appearance of the stable β polymorph of L-glutamic acid by interfering with either the nucleation rates or the growth rates and thus stabilize the metastable form. These studies demonstrate clearly that the molecular packing and intermolecular hydrogen bonds are the main features, which make possible the conformational discrimination. The use of conformational mimicry to stabilize the metastable structures of conformational polymorphs now offers a powerful tool for the prediction and development of robust processes for the control of polymorphic systems.

2.7. Characterization of polymorphs using a combination of analytical techniques

The common techniques often fail to differentiate definitively between two structurally similar polymorphs. Hence more advanced techniques or a combination of techniques need to be used to avoid errors of interpretation and in the identification of polymorphs [24]. Combinations of techniques are being employed currently for the characterization of crystalline pharmaceutical solids. For example, conventional single-crystal X-ray diffractometry and polarized microscopy were of no use in distinguishing the two forms I and II of roxifiban, a very promising cardiovascular drug, because of the relatively small crystallite sizes of the polymorphs. Hence, transmission electron microscopy (TEM) and

synchrotron X-ray diffraction techniques were employed to characterize the unit cells of the two forms. By coupling the highly resolved synchrotron powder X-ray diffraction data shown in Fig. 8, with in-

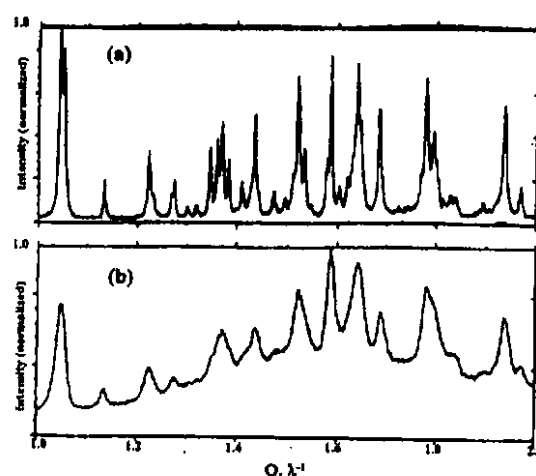


Fig. 8. A partial comparison of (a) a synchrotron pattern of polymorph II of roxifiban, collected using a wavelength of 1.00006 $\text{\AA}$ with (b) a conventional X-ray diffraction pattern using $\text{CuK}\alpha$ radiation in a region where there are many overlapping peaks. The patterns are plotted as a function of $Q = 2\pi/d = 4\pi \sin \theta/\lambda$ to remove the effects of different wavelengths ([61], reproduced with the permission of the American Pharmaceutical Association).

formation obtained from TEM diffraction patterns, the unit cell parameters of the two forms of roxifiban were determined [61]. Similarly, the three modifications, I, II and III, of the nonsteroidal antiinflammatory drug, tiaprofenic acid, could not be distinguished by the two traditional spectroscopic methods, FTIR and FT-Raman spectroscopy. The modifications can only be distinguished by a combination of thermoanalytical and powder X-ray diffractometric methods [62].

Another example, to which a combination of techniques has been successfully applied to identify the various conformational polymorphs of a drug, is the characterization of the solid forms of neotame [29]. Neotame, *N*-(3,3-dimethylbutyl)-L-aspartyl-L-phenylalanine methyl ester, a new high-potency sweetener exists in the following phase-pure crystalline forms: monohydrate, the most stable crystalline form of neotame under ambient conditions, a methanol + water solvate [63], a methanol solvate [64], an amorphous anhydrate [29] and a crystalline anhydrate (form A; [65]). The authors conducted a systematic study of the conversion of the monohydrate under vacuum to a mixture of anhydrate forms followed by the reconversion of the anhydrate to the monohydrate upon exposure to moisture under ambient conditions. No significant changes were observed in the powder X-ray diffraction patterns during part of the reconversion process, suggesting that no change in lattice structure had occurred. However, the solid-state ^{13}C -CP-MAS NMR spectra, indicated the presence of several forms of neotame during the reconversion (Fig. 9). This discrepancy in the results between the two techniques was attributed to the conformational change of neotame molecules during reconversion, without significant change in unit cell parameters. This example indicates that both solid-state ^{13}C -CP-MAS NMR spectroscopy and powder X-ray diffractometry are needed to analyze mixtures of solid forms of conformationally flexible molecules, such as neotame.

A combination of solid-state ^{13}C -NMR spectroscopy and single crystal X-ray diffractometry also has been used to examine the solid-state tautomerism of acetohexamide [66,67]. Polymorphism of the anti-diabetic drug acetohexamide has been investigated by numerous techniques. On the basis of FTIR data, form A of acetohexamide has been proposed to exist

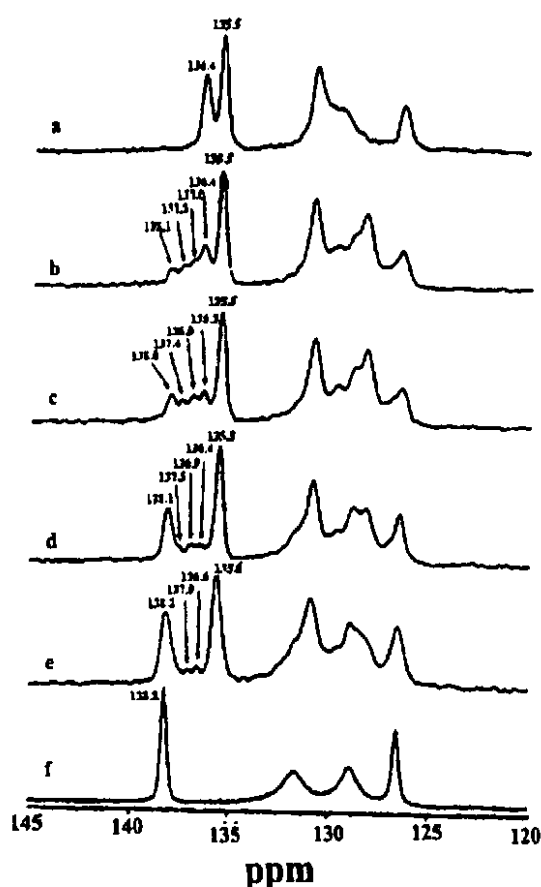


Fig. 9. Resonance signal of the phenyl carbon (C-15) attached to the side chain in the ^{13}C -CP-MAS NMR spectra of neotame anhydrate: (a) sample generated by placing the original monohydrate under vacuum (~ 1 Torr) for 3 days; (b–e) sample after being sealed in a jar for 2, 4, 6 and 8 days, respectively; (f) sample after being exposed to a relative humidity environment of 84% for 12 days ([29], reproduced with the permission of the American Chemical Society).

in the enol-tautomeric state, whereas form B has been proposed to be in the keto-tautomeric state. Using NMR and crystal structure data it was firmly established that both these acetohexamide polymorphic forms are present in the keto-form. Hence the combination of solid-state NMR spectroscopy and X-ray crystallography provided strong evidence that both forms of acetohexamide exist in the keto-tautomeric state and are truly polymorphic.

3. Recent advances in the identification and characterization of hydrates and solvates

3.1. Introduction to solvates and hydrates

It has been estimated that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates [68]. The water molecule, because of its small size, can easily fill structural voids and because of its multidirectional hydrogen bonding capability, is also ideal for linking a majority of drug molecules into stable crystal structures [2]. The mere presence of water in a system is not a sufficient reason to expect hydrate formation, because some compounds, though they are soluble in water, do not form hydrates. It is the activity of water in the medium that determines whether a given hydrate structure will form. Solvates may be formed when a pure organic solvent or a mixture of solvents is used as the solvent for crystallizing the compound. Guillory [69] has discussed the various methods of preparation of hydrates and solvates in detail. Because solvates behave similarly to hydrates, common analytical techniques can be used for characterization of solvates and hydrates.

3.2. Structural aspects

Crystalline hydrates, based on their structure may be classified into three categories. The first category (class 1) are the isolated site hydrates, where the water molecules are isolated from direct contact with other water molecules by intervening drug molecules, e.g., cephadrine dihydrate. The second category (class 2) are channel hydrates where the water molecules included in the lattice lie next to other water molecules of adjoining unit cells along an axis of the lattice, forming channels through the crystal, e.g., ampicillin trihydrate. The channel hydrates can be subclassified into two subcategories. One category comprises the expanded-channel or nonstoichiometric hydrates, which may take up additional moisture in the channels when exposed to high humidity and for which the crystal lattice may expand or contract as the hydration or dehydration proceeds effecting changes in the dimensions of unit cells, e.g. cromolyn sodium. The other subcategory comprises

the planar hydrates, which are channel hydrates in which water is localized in a two-dimensional order, or plane, e.g., sodium ibuprofen. The third category (class 3) of crystalline hydrates are the ion-associated hydrates, in which the metal ions are coordinated with water, e.g., citalopram calcium [8,9].

In this section, some examples of nonstoichiometric hydrates and their characterization will be discussed in detail because these forms pose a special challenge in dosage form development due to unpredictability of water content in the crystals. Following the work of Cox et al. [70] the unusual water uptake and formation of nonstoichiometric hydrates of cromolyn sodium was reinvestigated using single crystal X-ray diffractometry, PXRD, as well as by molecular modeling [71]. Cromolyn sodium, an antiasthmatic drug, exists as two liquid crystalline phases and a crystalline hydrate phase that sorbs and liberates water continuously and reversibly to give a continuous range of nonstoichiometric hydrates [70]. The changes in the PXRD patterns of the crystalline hydrate phase of cromolyn sodium in response to the surrounding relative humidity (RH) were explained in the light of the molecular and crystal structure of cromolyn sodium. Single crystal X-ray diffractometry indicated the space group for cromolyn sodium as *P*1, a chiral space group, even though the molecule itself is achiral. The crystal structure of cromolyn sodium with five or six water molecules per cromolyn sodium molecule, solved at room temperature by Hamodrakas et al. [72], revealed the positions of only one sodium ion and two water molecules and showed that the second sodium ion and the other water molecules are disordered. Recently, the single crystal structure of cromolyn sodium at 76% RH, with 6.44 molecules of water was solved at 173 K by Chen et al. [71]. This work showed that the second undetermined sodium ion is disordered over three sites and that four of the eight water positions are partially occupied. Comparison of the crystal structures determined by Hamodrakas et al. [72] and Chen et al. [71] indicated that the cromolyn anion is flexible. In particular, the bond and torsional angles of the 2-hydroxypropane linking the two cyclic moieties, changed to accommodate lattice expansion or contraction resulting from water sorption and desorption by the crystals. As water is taken up, the relative occupancies of the sites of the

second sodium ion and that of water molecules change. As a result, the triclinic structure with $\alpha > 90^\circ$ approaches the monoclinic form with $\alpha \approx 90^\circ$. To summarize, the presence of large water channels, the flexibility of the 2-hydroxypropane link, the disorder of the second sodium ion (Fig. 10) and the disorder of the surrounding water molecules in the crystal lattice explain the reversible and nonstoichiometric water sorption and desorption by cromolyn sodium. This study emphasizes the importance of the detailed single crystal structure in explaining many unusual physico-chemical properties of drug hydrates.

The muscarinic agonist, LY297802 tartarate (i.e., (+)-3-[3-(butylthio)-1,2,5-thiadiazol-4-yl]-1-azabicyclo[2.2.2]octane monohydrogentartrate), was also found to exhibit an unusual tendency to form nonstoichiometric hydrates of variable, but specific composition, ranging from 0 to 0.5 mol of water [73]. Solid-state ^{13}C -NMR spectroscopy, in conjunction with moisture sorption analysis and X-ray crystallography was used to provide unique insights into nonstoichiometric moisture sorption behavior. The PXRD patterns of the drug exposed to different RH values (0 to 75%), indicated neither a peak shift nor the presence of any new peaks, suggesting that

the anhydrous and the hydrated forms of the drug are isomorphic. Fig. 11 shows the significant changes in the SSNMR peaks on exposure to different relative humidities and temperature, indicating that water incorporated into the crystal lattice changes the local chemical environment and causes the observed NMR changes. The incorporation of water into the crystal lattice of the drug was also confirmed by X-ray crystallography. The considerable hygroscopicity of the drug was rationalized in terms of the similar crystal structures of the hydrated and nonhydrated forms, and hence no significant structural modifications are needed for the reabsorption of water into the solids. The rates of dehydration and rehydration are largely determined by the size of the water channels and the strength of the hydrogen-bonding interactions that bind the water molecules in the channels.

Another interesting study with different solvated forms of L-lysine monohydrochloride (LH) was conducted by Bandyopadhyay et al. [74]. LH was found to form: a pure methanol solvate at water activity, $a_w < 0.34$, with methanol activity, $a_m > 0.7$; a dihydrate at $a_w > \sim 0.65$ with $a_m < 0.45$; and mixed solvates at intermediate values of a_w and a_m . It was found that the dihydrate and the mono-

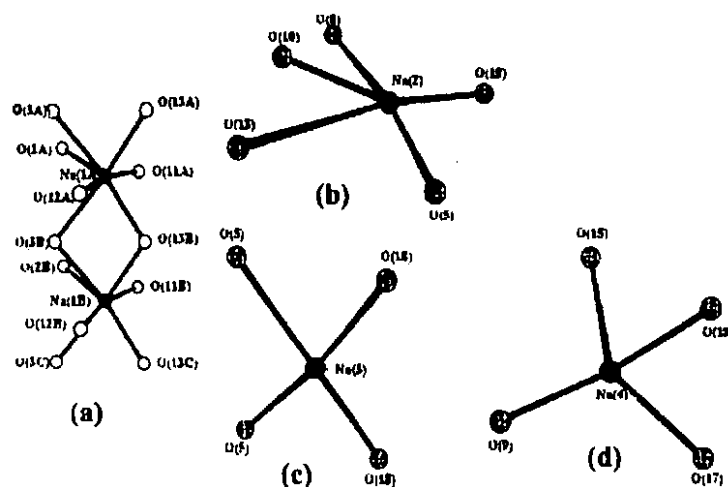


Fig. 10. In hydrated cromolyn sodium, coordination environment of: (a) the first (ordered) sodium ion, Na(1), shown in two neighboring unit cells (A and B); and the second (disordered) sodium ion at the three partially occupied sites, (b) Na(2), (c) Na(3), and (d) Na(4). The striped circles represent the sodium sites. The open circles represent the oxygen atoms coordinated to Na(1). The dotted (gray) circles represent the oxygen atoms coordinated to Na(2), Na(3), or Na(4) ([71], reproduced with the permission of the American Pharmaceutical Association).

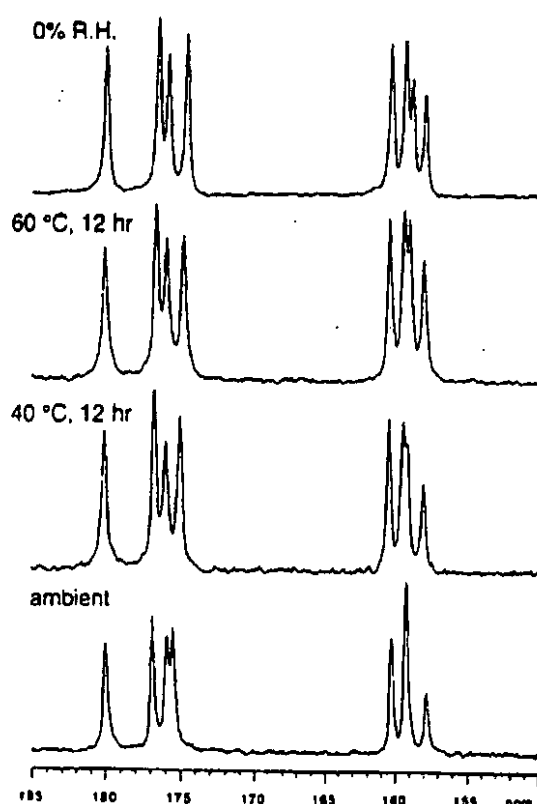


Fig. 11. Solid-state ^{13}C -NMR spectra of LY297802 tartrate ((+)-3-[3-(butylthio)-1,2,5-thiadiazol-4-yl]-1-azabicyclo[2.2.2]octane monohydrate) after storage at 0% humidity and before and after drying at elevated temperatures ([73], reproduced with the permission of the American Pharmaceutical Association).

methanol solvated forms of LH possessed similar crystal structures, similar PXRD patterns, but differed in the crystal habit. The crystal structures of LH hydrate and methanol solvate indicate that one molecule of methanol in the methanol solvate occupies approximately the same volume as the two water molecules in the dihydrate. During dehydration in the presence of methanol in the crystallization medium, the loss of one or more water molecules from the crystal lattice was compensated by the gradual uptake of methanol into the crystal structure to satisfy the hydrogen bonding pattern within the lattice with minor rearrangements, giving rise to mixed solvates. The similarities of the crystal lattices of the dihydrate and monomethanol solvate explain the similarity of the PXRD patterns.

3.3. Phase transformation of hydrates and solvates

Phase changes due to hydration/dehydration and solvation/desolvation of pharmaceutical compounds during processing or in the final product may result in an unstable system that would effect the bioavailability of drug from solid dosage forms. Various types of phase changes are possible in solid-state hydrated or solvated systems in response to changes in environmental conditions, such as relative humidity, temperature and pressure. For example, some hydrated compounds may convert to an amorphous phase upon dehydration and some may convert from a lower to a higher state of hydration yielding forms with lower solubility. Alternatively, a kinetically favored but thermodynamically unstable form may be converted during pharmaceutical processing to a more stable and less soluble form [8]. The phase transitions in hydrates and solvates can occur at various stages of dosage form development. Morris [9] has discussed the behavior of hydrates during processing, handling and storage of formulations in detail.

The phase transformations associated with exposure to water, such as during solubility measurements, wet granulation processes, dissolution studies and accelerated stability tests are likely to occur via solution mediation. Solution mediated phase transformations depend upon the solution phase to provide the mobility necessary to rearrange in the most stable form and hence are much faster than solid-state transformations. The rate of a solution-mediated transformation is proportional to the solubility of the species involved. Temperature, pressure and relative humidity may increase the rate of phase transformation of hydrates by inducing mobility in the system.

Solution-mediated phase transformations have been reported for many hydrate systems, such as theophylline crystals [17], eprosartan mesylate [75] and nedocromil sodium [76]. Ghosh and Grant [77] have addressed a common problem associated with the characterization of solvates which centers around the determination of solubilities of solvates and of nonsolvates that undergo phase transformation in the presence of an interacting solvent, such as solvation of nonsolvates in the solvent of crystallization or the desolvation of solvates in water. A thermodynamic cycle analogous to Hess's law but based on free

energies has been developed to predict the theoretical solubilities of 1,2-dialkyl-3-hydroxy-4-pyridones, which form 1:1 formic acid solvates in the presence of formic acid, and of the 1:1 formic acid solvates which produce the corresponding unsolvated compounds in the presence of water. A good correlation was obtained between the solubility values measured by the standard extrapolation method and that calculated by means of the thermodynamic cycle.

Apart from identifying and characterizing the phases during various stages of drug development, it is very important to gain an understanding of the dehydration/hydration mechanisms and kinetics. Many models have been developed to account for the dehydration kinetics of the crystalline hydrates [78]. Nucleation is the most significant phenomenon in determining the transformation kinetics, that is, the rate of formation of a new phase [8]. The dehydration kinetics to some extent will also depend upon the class of the hydrate system to which the drug belongs, particle size and morphology. The practical applications of understanding the dehydration kinetics, as indicated by Morris [9], are mainly the determination of the conditions for allowable exposure of bulk drug substances during development and processing, proper packaging, allowable temperature ranges for shipping, storage, and labeling of the final product, and the initial selection of a form for development.

3.4. Prediction of the formation of hydrates and solvates

Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available

for predicting the crystal structures of hydrates and solvates.

3.5. Characterization of hydrates and solvates

The common methods for the characterization of hydrates and solvates are polarized light microscopy and hot stage microscopy, DSC, TGA, Karl Fischer titrimetry, single-crystal X-ray diffractometry, powder X-ray diffractometry, and infrared spectroscopy. These methods have been reviewed in detail [21] and will also be discussed in detail in later chapters.

Pressure DSC is gaining increasing popularity in the study of solvates and hydrates where dehydration reactions occur above or near the boiling point of water. Using conventional DSC, it is very difficult to measure the heats of dehydration and heat of vaporization separately, but if one conducts DSC experiments at elevated pressures, the two processes may be completely separated. The advantage of using pressure DSC is that the pressure can be precisely controlled and the solids can be subjected to a controlled temperature program while under substantially elevated temperatures. The influence of elevated pressures on the solid-state behavior of carbamazepine dihydrate was studied by Han and Suryanarayanan [79]. In Fig. 12 it is shown that pressure DSC can separate the dehydration and vaporization endotherms of carbamazepine dihydrate during its conversion to the anhydrate form. Also the technique permitted the water liberated on dehydration to remain in intimate contact with the anhydrous phase formed which could significantly influence its solid-state properties.

The combined physical analytical techniques of thermogravimetry and infrared spectroscopy (TG/IR) can permit identification of the solvent incorporated into the crystal lattice. This combined technique has been used to study formulated products, such as capsules and tablets [80].

4. Current challenges and future directions

4.1. Origins of the challenges

A series of flow charts and decision trees have been presented and discussed [11,22] that can be

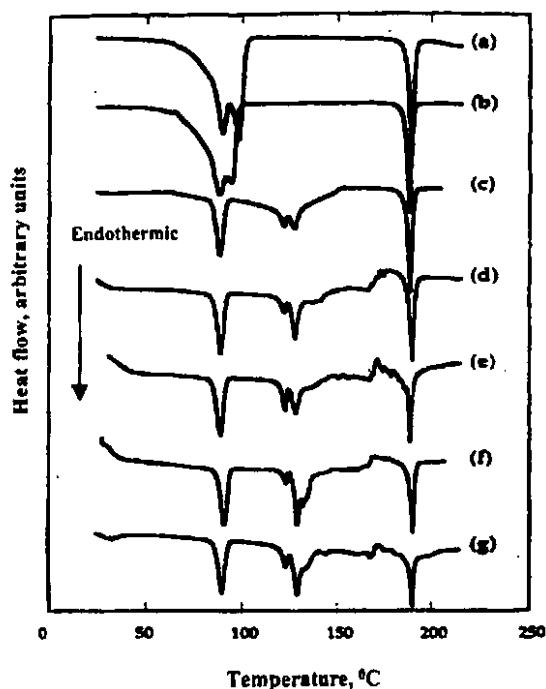


Fig. 12. Differential scanning calorimetry (DSC) curves of carbamazepine dihydrate at different pressures: (a) at atmospheric pressure in a conventional DSC cell, (b) at atmospheric pressure in a pressure DSC (PDSC) cell, (c) 100 p.s.i., (d) 200 p.s.i., (e) 300 p.s.i., (f) 400 p.s.i., and (g) 600 p.s.i. (1 p.s.i. = 6.9 kPa) ([79], reproduced with the permission of Elsevier Science).

used by investigators to characterize the polymorphs and solvates of compounds under development or for registration with regulatory authorities. Due to the complex and nonconventional behavior of various organic drug molecules, there are many opportunities for research and development in the area of characterization of polymorphs and solvates. Some of the problems which are commonly encountered during characterization of crystalline solids and which need to be addressed are: disorder in the crystal lattice due to pharmaceutical processing leading to conversion of a crystalline phase to an amorphous material or phase conversion from one form to the other; quantitating the amount of single polymorph in a mixture of polymorphs; identifying the solid form of the active ingredient in the formulated product, particularly when the drug is a minor component in the presence of numerous other materials (excipi-

ents); and the issues of disappearing polymorphs and the appearance of new polymorphs. In the following sections we will address some of these issues and some of the studies that have addressed these problems.

4.2. Phase transformations during processing

The effects of pharmaceutical processing on the crystalline state of drug polymorphs and solvates have been discussed recently by Brittain and Fiese [16]. Exposure to changes in temperature, pressure, relative humidity and comminution are encountered during processes such as drying, granulation, milling and compression. The stresses applied to crystals during pharmaceutical processing can cause defects in their crystal lattices, and contribute to lattice disorder, thus affecting the physical properties of the resulting powder [81]. This problem has been discussed in detail by Byrn et al. [10]. Arising from different degrees of crystalline disorder, the difficulty in reproducing materials with the same properties is a major concern in the pharmaceutical industry.

Milling, the last processing step in the production of bulk drug substance to reduce particle size, is often accompanied by a decrease in crystallinity due to the creation of lattice defects, beginning at the surface. The defects created by mechanical activation of the solid on the surface can migrate, transform, and change their number and nature. If the defects in the mechanically activated crystal heal to produce a crystal lattice different from the initial lattice, then a polymorphic transformation has taken place. Milling-induced polymorphic changes have been observed for many small drug molecules, such as fostedil, chloramphenicol palmitate, indomethacin and phenylbutazone [16]. Polymorphic transformation of the dipeptide sweetener, aspartame hemihydrate, can occur during milling [82]. Polymorph II of aspartame hemihydrate was found to transform to form I during ball-milling or on heating for 30 min at 160°C in the presence of steam as shown in the X-ray diffraction pattern (Fig. 13). The susceptibility of form II of aspartame hemihydrate to transform to form I has been attributed to the less symmetric crystal structure of form II compared to that of form I as studied by spectroscopic methods.

Some authors, such as Hüttenrauch [81] have

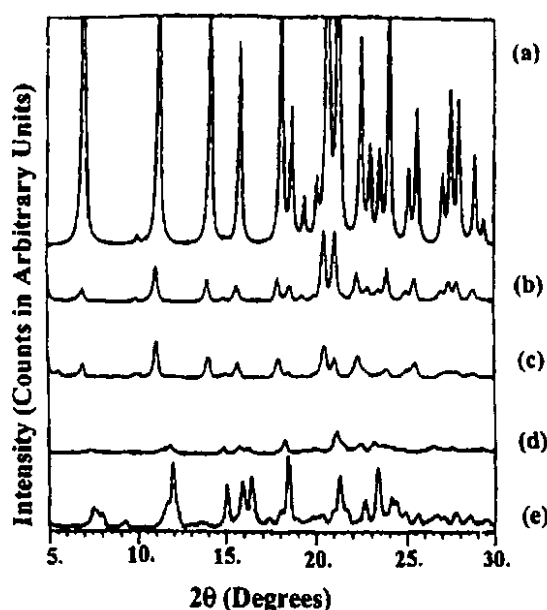


Fig. 13. Powder X-ray diffraction patterns of aspartame hemihydrate: (a) theoretical powder pattern calculated from the crystal structure of aspartame hemihydrate (form I) determined by Hatada et al., (1985) [99], (b) experimental powder pattern of the ball-milled aspartame hemihydrate (form I), (c) experimental powder pattern of aspartame hemihydrate that had been heated for 30 min at 160°C in the presence of steam (form I), (d) experimental powder pattern of aspartame hemihydrate after compression at 250 MPa for 1 min (form II), and (e) aspartame hemihydrate as received (form II) ([82], reproduced with the permission of the American Pharmaceutical Association).

suggested that the trauma to crystals during grinding may lead to a decrease in crystallinity, which should improve the compression capacity and dissolution rate of the drug molecules. This hypothesis was tested by studying the morphology, crystalline state, compression capacity and dissolution properties of native and ground crystals of aspirin and lactose monohydrate [83]. No significant increase in compression capacity was observed when native and ground crystals were compared. Only a slight increase in the dissolution rate was observed for ground aspirin crystals which was attributed to surface defects due to grinding resulting in improved crystal wetting.

The effect of roller compaction on lattice defects and phase change has been examined for aspirin [84]. The water vapor sorption isotherm obtained for aspirin on roller compaction indicated much more

water uptake than had been reported previously for other crystalline samples of aspirin under similar conditions. Various possibilities were suggested for the unusual water uptake of aspirin on roller compaction, such as formation of a polymorphic form of aspirin with a much greater affinity for water, formation of a crystalline hydrate in the aspirin sample, or significant reduction in particle size of the aspirin particles thereby providing an increased specific surface area for water vapor adsorption. It is also possible that roller compaction disrupted the crystalline order of some part of the aspirin crystals forming amorphous regions, which then take up relatively large quantities of water into their bulk structure. This example clearly indicates that processes, such as roller compaction, can introduce considerable disorder in the surface of crystals leading to a marked increase in the tendency to sorb water vapor.

Thermal activation, like mechanical activation during processing, also results in a high-energy state of crystals that may reorganize into a different lattice arrangement resulting in a phase change. The thermal stability of drug substances is important, because formulations are often dried at elevated temperatures after wet granulations so that the tablets may contain small regions of high temperature (hot spots) during compression. Various examples have shown that a change of temperature may influence the stability of drug molecules [16]. The effect of low temperatures, such as during freeze-drying, on the crystalline form of the drug has also been studied. The formation of a new mannitol hydrate during freeze-drying has been reported [85]. The formation of a crystalline hydrate by an excipient during freeze-drying may have several practical consequences, such that the difficulty of removing bound water from the crystal lattice can significantly limit the drying rate, while the residual water that is not removed by freeze-drying may be a potential threat to product stability if it is released during storage. The mannitol hydrate formed during freeze-drying survived the typical drying cycle and converted to the anhydrous polymorph of mannitol upon heating.

Spray drying has also been shown to lead to loss of crystallinity in materials, by a combination of processes involving rapid solidification of dissolved material and solid-state transitions due to milling effects in the atomiser. Spray drying leads to conver-

sion of a crystalline phase to an amorphous state and, because the amorphous state is metastable with respect to the crystalline form, phase transformations are likely to occur within the shelf life of the pharmaceutical product, resulting in loss of quality and potency in the product [86].

In view of the significant effects that the state of disorder in crystalline solids caused by pharmaceutical processing can have on the properties of pharmaceutical solids, it is important to be able to assess the extent of disorder in a solid quantitatively down to very low levels. Various methods have been used to measure the percent disorder, such as using predetermined mixtures, measurements of X-ray powder diffraction, density and heats of crystallization which revealed limits of detectability down to about 10%. Using water vapor sorption measurements under very carefully controlled conditions, it was possible to detect disorder as low as 1% in milled samples of sucrose [87]. A comparison of the four methods mentioned above for estimating the percent disorder of milled samples of sucrose gave very consistent results, once the underlying factors that make these techniques sensitive to the concentration of amorphous content were recognized and taken into account.

4.3. Degree of crystallinity

The previous section has emphasized that many pharmaceutical processes lead to a decrease in crystallinity of drug phases. Various studies have concluded that the formation of amorphous material during processing is highly undesirable. The amorphous material, being in a thermodynamically metastable state, is susceptible to reconversion to the crystalline state, affecting many physico-chemical characteristics of the drug. A later chapter provides detailed coverage of amorphous materials. An estimation of the degree of crystallinity of a sample before and after processing poses one of the larger challenges facing the pharmaceutical field. Powder X-ray diffractometry is still the commonly used method for determining the degree of crystallinity, though this method suffers from some limitations due to peak broadening, amorphous halo, and preferred orientation which make interpretation and quantitation difficult. DSC may not be a sensitive method for measuring crystallinity due to crystalliza-

tion of the amorphous content at elevated temperatures and the effects of differences in heat capacity. Solution calorimetry has been proposed as an accurate method for analysis of percent crystallinity [11,88,89]. A decrease in the endothermic enthalpy of solution indicates a decrease in the crystallinity of the sample. However, differences in surface area produced by grinding or by other processing techniques can also result in changes in the heat of wetting of a sample. Judicious choice of solvent can be employed to reduce such surface effects, which themselves contribute to the observed crystallinity of the sample.

Near infrared (NIR) spectroscopy is another technique being used to measure the degree of crystallinity, and has also proved useful in studies of the polymorphism and water content of sugars. The NIR spectrum of a sample contains both physical and chemical information. Being noninvasive, nondestructive and operable at room temperature, the method is a valuable tool with which to assess changes in the amorphous and crystalline state of lactose [90]. NIR has been used to follow the changes in the amorphous state, the onset of crystallization, and the changes between α - and β -lactose, which accompany the onset of crystallization. In another study, the nucleation and crystallization kinetics of amorphous lactose was investigated by gravimetry in an automated vacuum moisture balance. The combination of isothermal and nonisothermal activation energies allowed the investigation of both crystal growth and nucleation mechanisms and led to the separation of activation energies for nucleation and growth [91].

4.4. Characterization of mixtures of polymorphs

Another common problem encountered during drug development is quantitative control of the proportion of polymorphic forms present in a mixture. According to the US FDA regulations, the method of analysis for the proportion of forms must be validated, and also the proportion of forms must remain within stated limits through the retest date of the drug substance and potentially throughout the shelf life of the product. This is a very onerous requirement, especially if the forms have a tendency to interconvert. Bym et al. [11] suggested that the best way to deal with this problem is probably by

developing methods to prepare only one crystal form and maintaining this form throughout processing. Powder X-ray diffractometry is often a useful method to determine the percentages of polymorphs in a mixture. However, the detection limit is variable from case to case, and is sometimes as high as 15%. It is therefore important to develop sensitive analytical methods with a lower limit of detection.

Attenuated total reflectance (ATR) FTIR spectroscopy has been shown to be valuable for the quantitative analysis of the polymorphic content of bulk pharmaceutical materials. The feasibility of using ATR-FTIR for the qualitative and quantitative analysis of mixtures of pharmaceutical polymorphs has been studied using three known polymorphs of ganciclovir as a model compound [92]. Definitive identification and quantitation of all three polymorphs could be achieved using ATR-FTIR spectroscopy in conjunction with partial least-squares modeling. This technique has many advantages, such as speed, nondestructiveness, relative ease of use, and most important, no sample pretreatment before measurement.

Raman spectroscopy is another technique that is being widely used to quantitatively estimate the percentage of one polymorph in a mixture of polymorphs. FT-Raman spectrometry offers many advantages, the most prominent being, minimal sample preparation, sensitivity to polymorphism, and noninterference from water. Two polymorphs of fluconazole were characterized using FT-Raman spectroscopy and principal components regression using cross validation provided quantitative analysis of the percentage of one polymorphic form in the mixture of other forms [93]. A novel sample holder was developed whereby the sample is held in an NMR tube which is rotated around its axis and at the same time moved up and down. This method of sample presentation leads to a large increase in the volume studied and is important for inhomogeneous samples for which sub-sampling is a problem. Possible degradation of the sample through heating by the laser can also be avoided [94].

X-Ray powder diffractometry is still the common method for the quantitative estimation of polymorphs in a mixture of polymorphs. This method requires that at least one high-intensity peak unique to each form is available for intensity measurements and that

the plot of the peak intensity ratio as a function of the weight ratio of the components should result in a straight line. Modern computer controlled X-ray powder diffractometers now permit quantitative analysis of multicomponent mixtures using the complete powder diffraction profile rather than a limited amount of low-angle integrated intensity data. Artificial neural networks (ANNs) in quantitative X-ray powder diffractometry were used successfully to identify and quantify the two known modifications of ranitidine hydrochloride even when the weight fraction of one polymorph in the mixture was as low as 0.01 [95]. ANNs have been used mostly in problems of pattern recognition and modeling, and is therefore useful in deciphering the pattern in diffraction data from polymorphic mixtures. The ANNs model predicted concentration precisely, accurately, and with minimal bias through a wide range of ratios of the two known ranitidine hydrochloride polymorphic forms in a mixture (Fig. 14). This method minimizes the problems associated with preferred orientation and overlapping X-ray lines. The same group of researchers has shown the potential of ANNs in combination with DRIFT spectroscopy to analyze the polymorphic purity of crystalline ranitidine hydrochloride as a bulk drug and as an active ingredient of

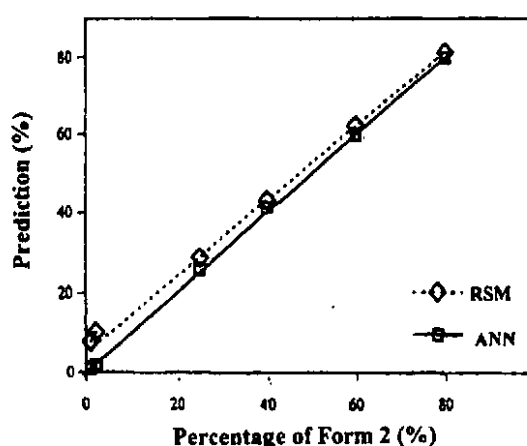


Fig. 14. Predicted concentrations of the two polymorphic forms (form 1 and 2) of ranitidine hydrochloride by the response surface methodology (RSM), a statistical modeling method, and by the artificial neural networks (ANNs) method, plotted against measured percentage of form 2 ([95], reproduced with the permission of Elsevier Science).

a tablet formulation. Simultaneous identification and quantification of all the ingredients in the tablet formulation was possible. This study has shown that the complex problem of quantifying a drug in mixtures containing two or more components with overlapping spectra can be solved by the DRIFT-ANNs technique [96].

Another technique, which is gaining popularity in the quantitative analysis of mixtures of polymorphs, is solid-state ^{13}C -CP-MAS NMR spectroscopy. This method was preferred for quantitative analysis of polymorphic mixtures of the herbicide, pendimethalin, which exists as two polymorphs with different colors and crystal habits [27]. ^{13}C -NMR provided the most sensitive and definitive evidence of the transition from the yellow to the orange form. This method enabled as little as 2% of orange pendimethalin to be determined in a sample consisting mostly of the yellow polymorph. It is the least invasive of the instrumental methods and can be used to detect the ratio of the two polymorphs in solid formulations.

A related challenge faced by the pharmaceutical industry is the determination of the polymorphic nature of the drug in the presence of excipients in a dosage form especially when the active drug is present as a low percentage of the overall formulation [97]. This problem can be addressed by developing sensitive techniques with lower limits of detection or by using a combination of techniques.

5. Conclusions

In order to save time and cost it is very important to choose the most suitable form of the crystalline drug in the initial stages of drug development. In recent years a good deal of research has been directed towards achieving this goal. Systematic isolation and early characterization of the largest number of possible forms of a drug reduces the chances of surprises at the late production stage due to identification of a new crystalline form or phase change. With the development of more sophisticated computational tools, the main focus of many investigators is to be able to predict all the possible forms of a drug from its molecular structure. Understanding the origins of the multiple solid forms of a drug

molecule, either due to differences in packing arrangement or conformation of the molecules, becomes the first step in prediction. Single crystal X-ray diffractometry and solid-state NMR spectroscopy are two techniques that are gaining increased application in determining the various crystal structures and the origins of polymorphism and pseudo-polymorphism of a particular drug. When crystal structures can be calculated with certainty, it will be possible to predict the various polymorphs of a compound and this information could be used to guide experimental studies. This goal may be difficult to achieve owing to the complex molecular structures of new organic molecules and the presence of several molecules in each asymmetric unit, but the future development of improved force fields and increased computational speeds, may make it achievable.

Improved experimental methods leading to more accurate and detailed phase diagrams are also finding increased use in determining the stability of various polymorphs. It is important to make every effort to prepare and to identify the most stable polymorph in order to guide the selection of the optimal form for development. The emergence of sensitive methods and the use of combination techniques, facilitate the identification and the more accurate characterization of the various polymorphs of a drug molecule. One of the main analytical challenges faced by the pharmaceutical analyst is the development of better quantitative methods for identifying a single polymorph in a mixture of polymorphs and for determining the percentages of amorphous or crystalline content of the drug. More and more sensitive methods are being developed to address this problem.

An increased understanding of the phenomenon of polymorphism should enable pharmaceutical scientists to gain control over the crystallization process in order to selectively obtain the desired polymorph or suppress the growth of an undesired one. Phase changes during processing and scale-up are a problem, which may be avoided by carefully designed initial small-scale studies. The availability of detailed structural data, combined with strategic design of substrates and additives, has led to significant advances in the control over the polymorphs obtained in a particular crystallization [98]. With all the information available from these initial studies, it

should be possible to design and to select processing conditions which would give a desired polymorph and maintain the desired form throughout the various stages of drug processing and manufacture.

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the crystal free to grow at the opposite pole. Since it is bound at the slow growing NH_4^+ end of the polar axis, it does not interfere with the fast growing CO_3^{2-} end.

J. Grinding

Polymorphic transformations have been observed to occur on grinding of certain materials, such as sulfathiazole, barbital, phenylbutazone, cephalixin, chloramphenicol palmitate, indomethacin, and chlorpropamide. Byrn [46] has stated that polymorphic transformations in the solid state require the three steps of (a) molecular loosening (nucleation by separation from the lattice), (b) solid solution formation, and (c) separation of the product (crystallization of the new phase). Depending on the material and the conditions employed, grinding can result in conversion to an amorphous substance. With the exercise of care, different polymorphic forms can be obtained. Otsuka et al. [57] showed that metastable Forms B and C of chloramphenicol palmitate were transformed into stable Form A upon grinding at room temperature. Indomethacin was transformed into a noncrystalline solid during grinding at 4°C , and into metastable Form A by grinding at 30°C . Caffeine Form II is converted into Form I with grinding, and a 95% phase conversion was obtained following 60 hours of grinding time [38].

II. METHODS EMPLOYED TO OBTAIN HYDRATE FORMS

Pharmaceutical solids may come into contact with water during processing steps, such as crystallization, lyophilization, wet granulation, aqueous film-coating, or spray-drying. Moreover, they may be exposed to water during storage in an atmosphere containing water vapor, or in a dosage form consisting of materials that contain water (e.g., excipients) and are capable of transferring it to other ingredients. Water may be adsorbed onto the solid surface and/or may be absorbed in the bulk solid structure. When water is incorporated into the crystal lattice of the compound in stoichiometric proportions, the molecular adduct or adducts formed are referred to as hydrates [58]. More than 90 hydrates

are described in various USP monographs. Hydrates can be prepared by recrystallization from water or from mixed aqueous solvents. They can also result, in some instances, from exposure of crystal solvates (such as methanولات or ethanولات) to an atmosphere containing water vapor.

Crystalline substances often form with water molecules located at specific sites in the crystal lattice, which are held in coordination complexes around lattice cations. This type of water is denoted as water of crystallization and is common for inorganic compounds. For example, nickel sulfate forms a well-defined hexahydrate, where the waters of hydration are bound directly to the Ni(II) ion. Extraneous inclusion of water molecules can occur if a coprecipitated cation carries solvation molecules with it. Water also can be incorporated into random pockets as a result of physical entrapment of the mother liquor. Well-defined multiple hydrate species can also form with organic molecules. For example, raffinose forms a pentahydrate.

Although most hydrates exhibit a whole-number-ratio stoichiometry, an unusual case is the metastable hydrate of caffeine, which contains only 0.8 moles of water per mole of caffeine. Only in a saturated water vapor atmosphere will additional amounts of water be adsorbed at the surface of the 4/5-hydrate to yield a 5/6 hydrate [59].

In some instances, a compound of a given hydration state may crystallize in more than one form, so that the hydrates themselves exhibit polymorphism. One such example is nitrofurantoin, which forms two monohydrates that have distinctly different temperatures and enthalpies of dehydration. The monohydrates have quite different packing arrangements, with Form I possessing a layer structure and Form II exhibiting a herringbone motif. The included water molecules play a major role in stabilizing the crystal structures. Whereas water molecules are contained in isolated cavities in Form II, in Form I they are located in continuous channels, and this apparently facilitates the escape of water when these crystals are heated [60].

Another example of hydrate polymorphism is amiloride hydrochloride [61], which can be obtained in two polymorphic dihydrate forms. These forms are indistinguishable by techniques other than x-ray diffraction.

It is noted that scopolamine hydrobromide has been reported

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to exist as the anhydrous form, a "hemihydrate," a sesquihydrate, and a trihydrate [62], while the unit cell parameters and the molecular geometry of these are all the same as those of the hemihydrate. This finding suggests that the "hemihydrate" is actually a partially desolvated sesquihydrate.

Ouabaine is another example of a compound that exhibits many different hydration levels, the most hydrated form being stable at the lowest temperature. Thus the nonahydrate phase of ouabaine is obtained from water at 0–15°C, the octahydrate phase at 15–28°C, and the dihydrate phase at 28–90°C. In addition, ouabaine phases corresponding to 4.5 H₂O, 4 H₂O, and 3 H₂O may be obtained from mixtures of water with other solvents. The anhydrous phase of ouabaine anhydrate is crystallized from ethanol at high temperatures [63].

Typically, hydrates are obtained by recrystallization from water. For example, trazodone hydrochloride tetrahydrate was prepared by dissolving the anhydrate in hot distilled water, allowing the solution to remain at room temperature overnight, and storing the collected crystals at 75% relative humidity and 25°C until they reached constant weight [64].

Hydrates can sometimes be obtained by simply suspending the anhydrous material in water, whereupon a form of Ostwald ripening occurs. For instance, aqueous suspensions of anhydrous metronidazole benzoate are metastable, and storage at temperatures lower than 38°C leads to monohydrate formation accompanied by crystal growth [65]. Sorbitol provides another example of this behavior, where slow cooling of a saturated aqueous solution yields long thin needles of sorbitol hydrate [66]. When suspended in water, anhydrous carbamazepine is transformed to carbamazepine dihydrate [67]. In other instances, hydrates can be obtained from mixed solvent systems. Acemetacin monohydrate can be obtained by slow evaporation from a mixture of acetone and water at room temperature [68].

Simply exposing an anhydrous powder to high relative humidity can often lead to formation of a hydrate. On exposure to a relative humidity of 100%, dexmedetomidine hydrochloride is converted to a monohydrate [69]. Droloxifene citrate is an example of a compound that is not very hygroscopic and yet forms a hydrate. Only after storage of the anhydrous form at 85% relative humidity does some sorption of

water occur. The monohydrate phase can be formed by exposing the anhydrous form to 98% relative humidity for ten days at 24°C [70].

III. METHODS EMPLOYED TO OBTAIN SOLVATE FORMS

Often, when solvents are employed in the purification of new drug substances by recrystallization, it is observed that the isolated crystals include solvent molecules, either entrapped within empty spaces in the lattice or interacting via hydrogen bonding or van der Waals force with molecules constituting the crystal lattice. Solvent molecules also can be found in close association with metal ions, completing the coordination sphere of the metal atom. Coordinated solvent molecules are considered as part of the crystallized molecule. A crystal with large empty channels or cavities is not stable because of packing demands. The size and chemical environment of the cavity or channel determine what kind of solvent molecule can be included in the structure and what kind of interaction occurs between solvent and structure.

Depending on the nature of molecular packing arrangements, it may happen that the inclusion of solvent is necessary to build a stable crystal structure. van Geerestein et al. [71] found during numerous crystallization attempts of 11β-[4-(dimethylamino)phenyl]-17β-hydroxy-17α-(1-propynyl) estradiol-4,9-diene-3-one that crystals were only obtainable in the presence of *n*-butyl acetate or *n*-propyl acetate. The crystal structure of the compound crystallized from *n*-butyl acetate/methylcyclohexane was solved, and one solvent molecule was found in the crystal structure that showed no strong interactions with the rest of the structure. Apparently, this solvent molecule was necessary to fill empty space resulting after the molecular packing. Solvates in which the solvent fills empty space are generally nonstoichiometric, such as the nonstoichiometric solvates formed by droloxifene citrate with acetonitrile, 2-propanol, ethanol, 1-propanol, and 1-butanol. Typically such solvates exhibit the same x-ray diffraction pattern as does the unsolvated compound.

When solvent molecules increase the strength of the crystal lattice, they can affect the stability of the compound to solid-state decom-

position. It has been observed that the four solvated and one nonsolvated structures of prenisolone *tert*-butyl acetate affect the flexibility of the steroid nucleus and the structure-dependent degradation of the compound when exposed to air and light [72].

van der Sluis and Kroon found 1,247 different compounds with cocrystallized solvents in the Cambridge Crystallographic Database [73]. Out of 46,460 total structures, they found 9,464 solvate structures, and 95% of these contained one of the 15 solvents given in Table 2.

The most commonly encountered solvates among pharmaceuticals are those of 1:1 stoichiometry, but occasionally mixed solvate species are encountered. For structures containing more than one solvent type, one generally finds nonpolar solvents crystallizing together on the one hand and polar solvents on the other. For example, the most common solvents found cocrystallizing with water are (in order of im-

portance) ethanol, methanol, and acetone. An interesting example of a structure containing a polar and a nonpolar solvent is the sodium salt of the antibiotic K-41, *p*-bromobenzoate monohydrate *n*-hexane solvate [74], which is crystallized from *n*-hexane saturated with water. Perhaps the best known mixed solvate is doxycycline hyclate: (doxycycline · HCl)₂ · C₂H₆O · H₂O. Triamterene also forms a mixed solvate, containing one *N,N*-dimethylformamide molecule and one water molecule within the crystal lattice [75].

The techniques used to obtain solvates are generally similar to the solvent methods used to obtain polymorphs, i.e. crystallization from a single solvent, from mixed solvents, or by vapor diffusion. Sometimes, it is possible to exchange one solvent within the crystal structure for another. When one recrystallizes a hydrate from dry methanol, in most cases one is left with either a methanol solvate or an anhydrous, unsolvated form of the compound.

A large number of solvates have been reported, especially for steroids and antibiotics. It has been observed that cortisone acetate and dexamethasone acetate can be crystallized as 10 different solvates. Dirithromycin, a semisynthetic macrolide antibiotic, crystallizes in two anhydrous polymorphic forms and in at least nine stoichiometric solvate forms. Six of the known solvates are isomorphic, having nearly identical x-ray powder diffraction patterns [76]. In addition to the anhydrate and dihydrate, erythromycin also forms solvates with acetone, chloroform, ethanol, *n*-butanol, and *i*-propanol [77].

It may be instructive to consider some examples of solvate formation. The compound 5-methoxysulphadiazine forms 1:1 host-guest solvates with dioxane, chloroform, and tetrahydrofuran [78]. These were prepared by heating to boiling a solution of the sulfonamide in the appropriate solvent, followed by slow cooling to obtain large crystals. Spironolactone forms 1:1 solvates with methanol, ethanol, ethyl acetate, and benzene. It also forms a 2:1 spironolactone-acetonitrile solvate [79,80]. The spironolactone solvates were prepared by crystallization in a refrigerator from solutions that were nearly saturated at room temperature.

Another steroid that forms solvates is stanozolol [81]. Solvates having 1:1 stoichiometry were prepared by recrystallization from methanol, ethanol, and 2-propanol, by heating the compound in the

Table 2 Distribution of the 15 Most Abundant Solvents in the Cambridge Crystallographic Database, as the Percentage of Solvate Structures

Solvent	Occurrence (%)
Water	61.4
Methylene dichloride	5.9
Benzene	4.7
Methanol	4.1
Acetone	2.8
Chloroform	2.8
Ethanol	2.6
Tetrahydrofuran	2.3
Toluene	2.2
Acetonitrile	1.9
<i>N,N</i> -dimethylformamide	0.9
Diethyl ether	0.9
Pyridine	0.7
Dimethyl sulfoxide	0.5
Dioxane	0.5

Source: From Ref. 73. Reproduced with permission of the copyright owner.

appropriate solvent to 60–70°C and then cooling to 0°C in an ice bath to induce crystallization. The compound also forms a monohydrate and two polymorphs. The polymorphs were prepared by heating the solvates to either 130°C (Form II) or 205°C (Form I).

Mefloquine hydrochloride is an interesting case of a compound that forms stoichiometric 1:1 solvates on cooling hot (50°C) saturated acetone solutions (Form B, acetone solvate 1:1), hot (50°C) saturated isopropanol (Form I, isopropanol solvate 1:1), and a nonstoichiometric ethanol solvate (2.12% ethanol) from hot (50°C) saturated ethanol, Form E, whose x-ray powder pattern does not change following heating to 80°C, in spite of a decrease in the ethanol level to 0.12%. Mefloquine hydrochloride can also be obtained in a nonsolvated form from hot (70°C) saturated acetonitrile (Form A) and as two hemihydrates from water (Forms D and C) prepared at room temperature and at 30°C [82].

IV. METHODS EMPLOYED TO OBTAIN AMORPHOUS MATERIALS

Solids can exist in crystalline or amorphous form. Crystalline materials have defined structures, stoichiometric compositions, and melting points and are characterized by their chemical, thermal, electrical, optical, and mechanical properties [83]. By contrast, amorphous materials have no clearly defined molecular structure and no long-range order, so their structure can be viewed as being similar to that of a frozen liquid but without the thermal fluctuations observed in the liquid phase. As a result, amorphous materials exhibit the classical diffuse "halo" x-ray powder diffraction pattern rather than the sharp peaks observed in the pattern of a crystalline substance. When the halo is broad, it is often difficult to distinguish between a material that is truly amorphous (e.g., a true glass) and one that is merely microcrystalline. This situation exists because when microcrystallites have diameters less than about 50 Å in diameter, a similar "halo" effect is observed.

While crystalline solids offer the advantages of chemical and thermodynamic stability, amorphous solids are occasionally preferred because they undergo dissolution at a faster rate. Rapid dissolution is desirable in the case of solids, which must be dissolved prior to paren-

teral administration. Faster dissolution is also important for poorly soluble compounds administered orally, since there is often a correlation between dissolution rate and bioavailability. In fact, there are instances in which only the amorphous form has adequate bioavailability.

Amorphous solids can be precipitated from solution or obtained from melts of compounds by carrying out the solidification in such a way as to avoid the thermodynamically preferred crystallization process. They also can be prepared by disrupting an existing crystal structure. Excess free energy and entropy are incorporated into solids as they are converted into the amorphous state, since solidification occurs without permitting the molecules to reach their lowest energy states.

A. Solidification of the Melt

Amorphous solids are often created by rapidly cooling a liquid so that crystallization nuclei can neither be created nor grow sufficiently, whereupon the liquid then remains in the fluid state well below the normal freezing point. In principle, a liquid should freeze (crystallize) when cooled to a temperature below its freezing point. However, if the rate of cooling is high relative to the rate of crystallization, then the liquid state can persist well below the normal freezing point. As cooling continues there is a rise in the rate of increase of the viscosity of the supercooled liquid per unit drop in temperature. The initially mobile fluid turns into a syrup, then into a viscoelastic state, and finally into a brittle glass. A glass is, therefore, a supercooled liquid, and is characterized by an extremely high viscosity (typically of the order of 10¹⁴ Pa · s). Mechanically, if not structurally, glasses can be regarded as solids.

The characteristic temperature below which melted solids must be cooled to form a glass is the glass transition temperature T_g . The glass transition is a dynamic event that occurs at a temperature below which coordinated molecular motion becomes so slow that a liquid can be considered to take on the properties of a solid. While the exact value of this transition temperature depends on the heating rate, the glass transition temperature is generally found to be about two-thirds that of the melting temperature T_m . Glass transition temperatures reported for pharmaceuticals also follow this general rule, as can be seen in the