Seæores
DIVISION DE NUEVAS CREACIONES SUPERINTENDENCIA DE INDUSTRIA Y COFI Bogota, D.C.

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Re.: Código 011-378-444
Expediente No. 06-23.144
Ease nacional de Solicitud
de Patents PCT
CELGENE CORPORATION

En relación con el expediente de la referenda y dando cumplimiento a la Ultima providencia recalda sobre este asunto por medio del presente escrito me permito manifestarles Jo siguiente:

1. Se adjunta un nuevo capitulo reivindicatorio el cual contiene las siguientes precisiones:

Se han modificado ciertas reivindicaciones de tat manera que aparezcan
como dependientes.
Se ha eliminado la referenda a las figuras en las reivindicaciones.
A pesar de que en la descripciOn se ha definido de manera clara el tØrmino "sustancialmente puro" de la Reivindicación 55, Øste se ha eliminado.

Igualmente se han eliminado las reivindicaciones consideradas por el Examinador como no claras y redundantes.

2. Ese Despacho argumenta que el Ejemplo 16 (columnas 17-18) de Dl revela lenalidomida como un sólido blanco. TambiØn dice que 02 enseæa que el estudio de polimorfismo es una tarea de rutina en formulación farmacØutica y que par lo tanto, supuestamente a las reivindicaciones antenores les falta el nivel inventivo. Tat coma se describe abajo, la sociedad solicitante seæalade manera respetuosa, que el Examinador estÆ equivocado acerca de las

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enseæanzas de las referencias citadas, y que demÆs, las reivindicaciones modificadas contienen un paso inventivo sobre DI y D2.

3. DI enseæa la SIntesis del isómero-(S) de Lenalidomida. la cual posee diferentes propiedades de la Lenalidomida RacØmica.

a) El Examinador rechazó las reivindicaciones pendientes sobre la referenda DI citada, una patente de propiedad de Celgene Corporation. En particular,
la argumenta que el Ejemplo 16, columnas 17-18 de DI describe la sIntesis
de lenalidomida. Con todo respeto, ml representada considera que la Division ha malentendido las enseæanzas deDI.

Dl no revela ni sugiere las reivindicaciones pendientes en la solicitud que aqul se tramita. EspecIficamente, la solicitänte observa que las reivindicaciones pendientes se reflere, entre otras, a formas de cnstal que comprenden lenalidomida racemica. Por el contrarlo, Dl en el Ejemplo 16, columnas 17-18, enseæa especIficamente’la sintesis del isOmero-(S) de lenalidomida, no de lenalidomida racØmica. Por ejemplo, en la columna 18, lineas 40-41, el producto del paso sintØtico final se describe como "(S)-3-(1 -Oxo-4-aminoisoindolin-2-il)pipendin-2,6-diona", que es un nombre qulmico para (S)-lenalidomida. Por lo tanto, el Examinador estÆ equivocado al decir que Dl enseæalenalidomida como un sólido blanco. Tal como se explica a continuaciOn, se esperaria que (S)-lenalidomida y lenalidomida racØmica tengan una variedad de propiedades qulmicas, fIsicas y biolOgicas diferentes, y la divulgadiOn de (S)-lenalidomida no puede considerarse equivalente a una divulgaciOn de lenalidomida racØmica.

b.) (S)-lenalidomida y lenalidomida racØmica se difieren en una variedad de aspectos. Desde el punto de vista qulmico, (S)-lenalidomida, segün se describe en el Ejemplo 16 de Dl, posee necesanamente una estereoqulmica diferente en comparaciOn con la lenalidomida racØmica. Desde un punto de vista fIsico, (S)-lenalidomida tiene diferentes propiedades fIsicas en comparaciOn con formas sOlidas que comprenden lenalidomida racØmica. Por ejemplo, Dl en la columna 18 de la lInea 49, divulga que (S)-lenalidomida preparada de acuerdo con el Ejemplo 16, tiene un punto de fusion de 235,5-239°C. Por el contrario, las formas de cristal de

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lenalidomida racØmica que se divulgan en la Publicación tienen diferentes perfiles tØrmicos.

Adicionalmente a las diferencias qulmicas y fisicas, la (S)-lenalidomida que se divulga en DI tambiØn se esperarla que tenga diferencias biológicas en comparaciOn con lenalidomida racØmica. Como evidencia de las diferencias biologicas entre enanciOmeros y los correspondientes racematos de anÆlogos de talidomida sustituidos con amino, los solicitantes envIan para consideraciOn de la Oficina de Patentes, una copia de Muller et al., Bioorganic & Medicinal Chemistry Letters (1999), 9:1625-30 (en adelante "Muller), adjunto como el Anexo A. Muller comparO algunos datos biológicamente relevantes de una serie de anÆlogos sustituidoscon amino, incluido un racemato (compuesto 5a en el Esquema I de la pagina 1626), su (S)-isomero (compuesto (S)-5a en el Esquema 3 de la pÆgina 1627), y su (R)-isómero (compuesto (R) -5a en el Esquema 3 de la pÆgina 1627).

C.) En la Tabla I de la pÆgina 1629, Muller ofrece datos comparativos biolOgicamente relevantes, incluida inhibición porcentual TNF-a a 100 gm, actividad inhibitoria TNF-a en cØlulas sanguineas mononucleares penfØricas humanas (PBMC) estimuladas de lipopolisacÆrido (LIPS), y actividad inhibitoria TNF-a en la sangre entera, para un nümero de anÆlogosde talidomida sustituidos con amina. Los compuestos en la Tabla
I incluyen un racemato (compuesto 5a) y su correspondiente (S)-isOmero (compuesto (S)-5a) y (R)-isómero (compuesto (R)-5a). Muller demuestra que la inhibición de TNF-ct en PBMC Humana Estimulada de LIPS y en la sangre entera varla enormemente entre el racemato, el (S)-isômero, y el (R)-isOmero.

Por lo tanto, esa Division caracterizO incorrectamente las enseæanzasdel Ejemplo 16 de Dl, que se refiere a la sintesis de (S)-lenalidomida y n6. a lenalidomida racØmica. De hecho, (S)-lenalidomida y lenalidomida racØmica son compuestos qulmica, fIsica y Jbiol6gicamente distintos. AdemÆs, los solicitantes observan que las presentes reivindicaciones se refleren a fomias de cristal nuevas e inventivas que comprenden lenalidomida racØmica, las cuales no se enseæan ni sugieren en Dl. Tal como se describe en la especificaciOn tat coma fue presentada de la

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Publicaciôn 192, las formas de cristal de las reivindicaciones pendientes \ poseen, por ejemplo, propiedades de estabilidad tØrmica, propiedades de porciOnldeserción de humedad, propiedades de tasa de solubilidad y disolución y propiedades de estabilidad mecÆnica ütiles para la preparación, fabricaciôn y formulaciôn de un producto farmacØutico. Dl, el cual enseæa
la sintesis de (1-lenalidomida, no enseæa ni sugiere formas de cristal de lenalidomida racØmica ni sus propiedades ütiles, segün se divulga y reclama en la presente solicitud. Por 10 tanto, las reivindicaciones pendientes poseen novedad y paso inventivo sobre la referenda de Dl citada.

4. La DivulQaciOn de una fOrmula pulmica no niega el carÆcter inventivode una nueva forma de cristal pue comprende esa fOrmula gulmica.

a.) Mi representada afirma que el conocimiento de la fOrmula qulmica de lenalidomida racØmica previo a la fecha de la presente solicitud no afectaria
el carÆcter inventivo de las presentes reivindicaciones, las cuales se refleren a nuevas formas de cristal que comprenden lenalidomida racØmica.
Tal como se explicO amba, Dl no enseæani sugiere las formas de cristal que se reclaman. AdemÆs, ladescnpciOn del Examinador del experimento de cristalización como "rutina" es incorrecta - como se explica abajo, el expenmento de la cnstalizaciOn puede ser notoramente difIcil e impredecible. La Oficina de Patentes estÆ equivocadacuando dice que el estudlo de polimorfismo no puede implicar un paso inventivo.

b.) Basados Unicamente en el conocimiento de la fOrmula qulmica de una molØcula farmaceutica, generalmente es impredecible si la molØcula formarÆ, porejemplo, un aceite, un sôlido amorfo, un sólido cnstalino o una mezcla de Ia anterior. AdemÆs, aün si una molØcula farmacØutica forma un sôlido cnstalino, generalmente es impredecible Si el compuesto formarÆ mÆs de un sôlido cristalino. Por ejemplo, un articulo de 2006 en Materials Research Bulletin explica que "generalmente no es posible predecir de manera computacional el nümero de polimorfos observables de aün las molØculas mÆs simples". Ver Jones, W. et al., Mater. Res. Bull. (2006), 31:875-79 en la pig 875 (adjunto aquI como el Anexo B).

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La imprevisibilidad asociada con la formación de cualquier forma de una molØcula farmacØutica resulta de numerosos factores. Por ejemplo, diferentes formas polimórlicas pueden tener energias dentro de un rango muy angosto; ademÆs, los cÆlculos teOncos no refiejan con precisiOn condiciones expenmentales de laboratono. Adicionalmente, vanos factores que afectan la nucleaciOn y el crecimiento de los cristales, incluida la funciOn del solvente durante la cristalizaciOn quedan por entenderse claramente. Como resultado del alto grado de imprevisibilidad en este campo, los investigadores deben realizar experimentaciones detalladas con el fin de avenguar y entender la formaciOn de cualquier forma sôlida que comprenda un compuesto farmacØutico en particular.

c.) Entender la(s) forma(s) sOlida(s) de un compuesto farmaceutico se complica aün mÆs por la posibilidad de formaciOn solvato. Sin una experimentación detallada, un investigador ordinano no puede predecir si un compuesto farmacØutico se cristalizarÆcon o sin la incorporaciOn de solvente (por ej: agua) en el enrejado del cristal. Esta imprevisibilidad se enfatizó en el capItulo de un libro relacionado con qulmica de materiales en estado sôlido, el cual describiO recientes avances en el campo de sOlidos moleculares. Este capItulo decia: "La ocurrencia de solvatos y polimorfos, particularmente relevantes en la industna farmacØutica es todavIa un aspecto de la quimica de cnstal que se entiende poco". Andrew D. Bond & William Jones, Controlling Crystal Architecture in Molecular Solids: The Supramolecular Approach, in Supramolecular Organization and Materials Design, 391, 436 (W. Jones & C.N.R. Rao, ed. 2001) (adjunto aqul como el Anexo C). Entender si un compuesto farmacØutico se cristalizarÆcomo un solvato (tal como por ej: On hidrato) requiere bastante expenmentaciOn y no puede predecirse solo con base en la formula molecular del compuesto.

En la fecha de presentaciOn de la pnondad de la presente solicitud, "la predicciOn de la estructura para molØculas orgÆnicas en general segula siendo una meta lejana". Ver Bond & Jones en 435. Limitaciones significativas a los esfuerzos en la predicciOn de estructura incluyen el nümero y la complejidad de la(s) molØcula(s) en la unidad asimØtrica cristalografica. Por ejemplo, un artIculo reciente reconoció que "la predicciOn de estructuras de cnstal con mÆsde una molØcula en la unidad asimØtrica...representa un desafIo mayor en el campo de la predicciOn de

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estructuras de cristal". Ver Cruz Cabeza, AJ. et al., J. Am. Chem. Soc. (2006), 128:14466-67, en 14466 (adjunto aqul como el Anexo D). En la prÆctica, esto significa que la formación y relación estoiquiomØtrica de cualquier solvato farmacØutico, tat como hidrato, continua siendo impredecible por lo general. La complejidad molecular, incluida flexibilidad molecular y los grupos funcionales que unen hidrógeno tambiØn limita la capacidad de predecir cualquier forma sólida de una molØcula. Ver Day, G.M. et al., Cryst. Growth Des. (2004), 4(6):1327-40 (adjunto aqul como el Anexo E).

d.) Por lo tanto, la potencial formaciOn de cualquier forma sôlida que comprenda un compuesto farmacØutico en particular, debe determinarse experimentalmente empleando una variedad de tØcnicas analiticas y de investigacion. Los resultados de este tipo de experimentaciôn son empIricos y bastante impredecibles, y cualquier forma sOlida que se avengue en el curso de esta expenmentación representa un avance importante para entender la qulmica de estado sólido de ese compuesto. Por 10 tanto, la aclaraciOn de una nueva forma sOlida de un compuesto farmacØutico - aün
si se ha revelado la formula quimica del compuesto, representa un paso novedoso e inventivo.

5. Las reivindicaciones iendientes tienen nivel inventivo

La referencia Dl que cita la DivisiOn menciona la sIntesis de (S)-lenalidomida, que se esperarIa posee numerosas diferencias en las propiedades qulmicas, fIsicas y biolOgicas en comparaciOn con la lenalidomida racØmica. AdemÆs,las reivindicaciones pendientes que se refieren entre otras cosas, a formas de cristal que comprenden lenalidomida racØmica, no se enseæanni sugieren en la tecnica anterior, incluida la referenda Dl. La cristalizaciOn requiere creatividad
y experimentación inventiva, y las formas de cristal que se divulgan y reivindican en la presente solicitud no se enseæan 0 sugieren en la tØcnica
anterior.

6. Teniendo en cuenta Ia dispuesto por el Consejo de Estado en sentencia profenda dentro del Expediente No. 7684 el 22 dØ Octubre de 2004 y acogida

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Reivindicaciones

[Forma A]

3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-iI)-piperidin-2,6-diona cristalina quo
tiene un patrOn de ddracciOn de polvo de rayos X quo comprende picos a apro)imadamente 8, 14,5 y 16 grados 20.

2 La 3-(4-amino-1-oxo-1,3 dihidro-isoindol-2-ii)-piperidin-2,6-diona cristalina
de la reMndicaciOn 1, on donde el patrOn comprende picos a 7,9, 14,4 y 15,8 grados 20.

3 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-ii)-piperidin-2,6-diona cristalina
de la reivindicaciOn 1, on donde el patron comprende ademÆs picos a aproximadamente 17,5, 20,5, 24y 26 grados 20.

4 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-iI)-piperidin-2,6-diona cristalina
de la reivindicaciOn 3, on donde el patrOn comprende picas a aproximadamente 17,6, 20,6, 24,1 y 26,0 grados 20,

5 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-ii)-piperidin-2,6-diona cristalina
de cualquiera de las reivindicaciones 1-4, quo tiene un termograma de calonmetria de exploraciOn diferencial quo comprende un endodermo con una maxima de cerca de 270°C.

6 La 3-(4-amino-1-oxo-1 73 dihidro-isoindol-2-ii)-piperidin-2,6-diona aistalina
de cualquiera de las reivindicaciones 1-5, quo no es solvatada.

[Forma B]

7 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-iI)-pipetidin-2,6-diona cnstalina quo
tiene un patrOn de dtfracciOn de polvo de rayos X qua comprende picas a apro)imadamente 16,22 y27 grados 20

8 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-ii)-piperidin-2,6-diona cristalina
de la reivindicaciOn 7, on donde el patrOn comprende picas a 15,8, 22,2 y 26,7 grados 20.

9 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-ii)-pipendin-2,6-diona cristalina
de la reivindicaciOn 7, on donde el patrOn comprende ademÆs un picaa cerca de 18 grados 20.

10 La 3-(4-amino-1-oxo-1,3 dihidro-isoindol-2-ii)-piperidin-2,6-diona cnstalina
de la reivindicación 9, en donde el patron comprende un pico a 18,2 grados 20.

11 La 3-(4-amino -1 -oxo-1,3 dihidro-isoindol-2-ii)-pipendin-2,6-diona cristalina
de la reivindicaciOn 7, que tiene un termograma de calonmetria de exploraciOn diferencial que comprende endotermos con maximas de entre 146°C y 268°C.

12 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-ii)-pipendin-2,6-diona cristalina
de la reivindicaciOn 7, que pierde cerca de 3,1% de volÆtiles en una basede peso cuando se calienta a cerca de 175°C.

13 La 3-(4-amino-1-oxo-1 13 dihidro-isoindol-2-iI)-piperidin-2,6-diona cristalina
de la reivindicaciOn 7, que tiene cerca de 0,46 moles de agua por mol de 3-(4-amino-1-oxo-1,3 dihidro-isoindol-2-ii)-pipendin-2,6-diona.

14 La 3-(4-amino-1-oxo-1,3 dihidro-isoindol-2-ii)-pipendin-2,6-diona cristalina
de cualquiera de las reivindicaciones 78-13, que es hemihidratada.

[Forma C]

15 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-iI)-piperidin-2,6-diona cristalina que
tiene un patron de difracciOn de polvo de rayos X que comprende picos a aproximadamente 8, 15,5 y 25 grados 20.

16 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-iI)-piperidin-2,6-diona cristalina
de la reivindicaciOn 15, en donde el patrOn comprende picos a 7,9, 15,8 y 24,9 grados 20.

17 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-ii)-pipeiidin-2,6-diona cristalina
de la reivindicaciOn 150 16 que tiene un termograma de calonmetrIa de exploraciOn diferencial que comprende endodermos con mÆximasde entre 150°C y 269°C.

18 La 3-(4-amino-1-oxo-1 13 dihidro-isoindol-2-iI)-pipeiidin-2,6-diona cristalina
de cualquiera de las reivindicaciones 15-17 que es solvatada.

[Forma DJ

19 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-ii)-pipendin-2,6-diona cnstalina que
tiene un patrOn de difracciOn de polvo de rayos X que comprende picos a aproximadamente 12,27 y28 grados 20.

20 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-iI)-pipendin-2,6-diona cristalina
de la reivindicaciOn 19, en donde el patrOn comprende picos a 11,9, 26,5 y 27,8 grados 20.

21 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-iI)-piperidin-2,6-diona cristalina
de la reivindicaciOn 19620, quo tiene un termograma de calonmetria de exploraciOn diferencial quo comprende endodermos con maximas de entre 122°C y 270°C.

22 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-iI)-piperidin-2,6-diona cristalina
de cualquiera de las reivindicaciones 19-21, quo es solvatada.

[Forma EJ

23 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-ii)-pipendin-2,6-diona cristalina quo
tiene un patrOn de difracciOn de polvo de rayos X quo comprende picos a aproximadamente 20, 24,5 y29 grados 20.

24 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-ii)-piperidin-2,6-diona cristalina
de la reivindicaciOn 23, on donde el patron comprende picos a 20,0, 24,7 y 28,6 grados 20.

25 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-ii)-piperidin-2,6-diona cnstalina
de la reivindicaciOn 23024 quo tiene un termograma de calorlimetrIa de exploraciOn diferencial quo comprende endodermos con mÆximas de entre 99°C y 269°C.

26 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-ii)-piperidin-2,6-diona cristalina
de cualquiera de las reMndicaciones 23-25, quo es dihidratada.

[Forma 9

27 3-(4-amino-1-oxo-1,3 dihidro-isoindol-2-iI)-pipendin-2,6-diona cristalina quo
tiene un patrOn de difracciOn de polvo de rayos X quo comprende picos a aproximadamente 19, 19,5 y25 grados 20.

28 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-ii)-pipendin-2,6-diona cristalina
de la reivindicaciOn 27, on donde el patron comprende picos a 18,9, 19,7 y 24,9 grados

20.

29 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-il)-piperidin-2,6-diona cristalina
de la reivindicaciOn 27028 quo tiene un termograma de calonmetrIa de exploraciOn diferencial quo comprende un endodermo con una maxima de cerca de 269°C.

30 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-ii)-piperidin-2,6-diona cristalina
de cualquiera de las reivindicaciones 27-29, quo no es solvatada.

[Forma 0]

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31 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-ii)-piperidin-2,6-diona cristalina que
tiene un patrOn de difracciOn de polvo de rayos X qua comprende picos a aproximadamente 21,23 y 24,5 grados 20.

32 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-ii)-piperidin-2,6-diona cristalina
de la reivindicaciOn 31, on donde el patrOn comprende picos a 21,3, 22,5 y 24,3 grados

20.

33 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-il)-piperidin-2,6-diona cristalina
de la reivindicaciOn 31 032, que bone un termograma de calorimetrIa de exploraciOn diferencial que comprende un endodermo de cerca de 248°C.

34 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-ii)-pipendin-2,6-diona cristalina
de cualquiera de las reivindicaciones 31-33, que no es solvatada.

[Forma H]

35 3-(4-amino-1-oxo-1,3 dihidro-isoindol-2-ii)-pipendin-2,6-diona cnstalina que
tiene un patron de difracdOn de polvo de rayos X que comprende picas a aproximadamente 15, 26y31 grados 20.

36 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-iI)-pipendin-2,6-diona cristalina
de la reivindicaciOn 35, en donde el patrOn comprende picas a 15,2, 25,6 y 30,7 grados
20.

37 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-ii)-pipendin-2,6-diona cristalina
de la reivindicaciOn 35036 que tiene un termograma de calonmetrIa de exploraciOn diferencial que comprende un endodermo de entre 50°C y 125°C y un endodermo con una maxima de cerca de 269°C.

38 La 3-(4-amino-1-oxo-1,3 dihidro-isoindol-2-ii)-pipendin-2,6-diona cristalina
de cualquiera de las reivindicaciones 35-37, que as hidratada.

39 La 3-(4-amino-1-oxo-1 13 dihidro-isoindol-2-ii)-piperidin-2,6-diona cristalina
de cualquiera de las reivindicaciones 1-38, que as mÆs que cercade 80% pura.

40 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-il)-piperidin-2,6-diona cristalina
de cualquiera de las reivindicaciones 1-38, qua as mÆs que cercade 90% pura.

41 La 3-(4-amino-1 -oxo-1,3 dihidro-isoindol-2-ii)-piperidin-2,6-diona cristalina
de cualquiera de las reivindicaciones 1-38, que as mÆsque cerca de 95% pura.

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42 La 3-(4-amino-1-oxo-1,3 dihidro-isoindol-2-ii)-pipendin-2,6-diana cristalina
de cualquiera de las reivindicaciones 1-38, que es mÆsque cerca de 97% pura

43 Una mezcla de la 3-(4-amino-1-oxo-1,3 dihidro-isoindol-2-il)-piperidin-2,6-
diana cristalina de cualquiera de las reivindicaciones 7-14, y la 3-(4-amino-1-oxo-1,3 dihidro-isoindol-2-il)-piperidin-2,6-diona cristalina de cualquiera de las reivindicaciones 23-

26.

44 Una composiciôn farmacØutica que comprende 3-(4-amino-1-oxo-1,3
dihidro-isoindol-2-iI)-piperidin-2,6-diona amorfa y la 3-(4-amino-1-oxo-1 13 dihidro-isoindol-2-iI)-piperidin-2,6-diona cristalina de cualquiera de las reivindicaciones 1-38.

45 La composiciôn farmacØutica de la reivindicación 44, que comprende mÆs
que cerca de 50% de 3-(4-amino-1-oxo-1,3 dihidro-isoindol-2-ii)-piperidin-26-diona cristalina.

46 Una composición farmaceutica que comprende la 3-(4-amino-1-oxo-1,3
dihidro-isoindol-2-ii)-pipendin-2,6-diona cristalina de cualquiera de las reivindicaciones 1-42, y un excipiente farmaceuticamente aceptable.

47 La composiciôn farmacØutica de la reivindicación 46, on donde la
composiciôn es una sola forma de dosis unitana.

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MEDICINALCHEMISTRY I.Emsts

AMINO-SUBSTITUTED THALIDOMIDE ANALOGS; POTENT INHIBITORS OF TNF-a PRODUCTION

George W. Roger Chen,6 Shaei-Yun Huang, Laura 0. ComiI,a Lu Min Wong,’ Rebecca T. Patterson, Ywd Chen," Gilla Kaplan," and David I. Stirling.0

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Abstracti Thalidomide, (1), is a known inhibitor of TNF-a release in LPS stimulated human PBMC. Herein we describe the NF-a inhibitory activity of amino substituted analogs of thalidomide (1) and its isoindolin-l-one analog, EM-12 (2). The 4-amino substituted analogs were found to be potent inhibitors ofTNF-a release in LPS stimulated human PBMC. @ 1999 Elsevier Science Lid. All rights reserved

Introduction: Thalidomide (2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione), (1) was developed as a sedative without the side effects of barbiturates in the 1950’s by Chemie Grunenthal.’ Thalidomide quickly became a popular sedative in Europe and Australia and was subsequently used for the treatment of morning sickness in pregnant women. However, thalidomide was removed from the marketplace when its use was linked to birth defects. Thalidomide’s teratogØnic properties made the drug infamous and catalyzed the development of the current drug approval regulations. A serendipitous discovery in 1965 by Sheskin while treating erythema nodosum leprosum (ENL), an acute inflammatory condition associated with lepromatous leprosy led to the discovery that thalidomide possesses immunomodulatory properties.2 Since this initial discovery, thalidomide has been found to afford clinical benefit in a variety of autoimmune and inflammatory disease states.

Thaildomfile (1) ’ EM-12 (2)

In 1991 it was reported that thalidomide Aa selective inhibitor of tumor necrosis factor-tx (TNF.tx) over production in Stimulated human monocytes.4 TNF-a is a key cytokune in the Inflammatory cascade and elevated TNF-a levels are associated with inflammatory diseases.5 Recent successful clinical trials in rheumatoid arthritis and inflammatory bowel disease with ThF-a antibodies and soluble TNF-a receptors have validated the inhibition ofTNF-a as a clinical treatment.6

The clinical activity ofthalidomide and the importance of TNF-ix inhibifiori led us to initiate a program.
to improve the TNF-a inhibitory activity of thalidomide by structural modification. We have previously

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’ reported a series ofthalidomide analogs derived from -amino-j-aryIpropanoic acid derivatives that are potent inhibitors (if TNF-a.1 Further studies revealed these compounds to be potent inhibitors of phosphodiesterase
type 4 (PDE4).8 The PDE4 inhibitory potency for most of these compounds has correlated with their TNF-a inhibitory activity. PDE4 is the major PDE isoenzyme present in monocytes and macrophages, key producers of
TNF-u. PDE enzymes control the levels of cyclic adenosine monophosphate (cAMP) by hydrolysis of cAMP to 5’-AMP. Inhibition of PDE4 in stimulated monocytes has been demonstrated to elevate levels of cAMP and inhibit ofTNF-a production.9
In further studies to improve the TNF-a inhibitory activity of thalidomide, we prepared a series of amino-phthaloyl substituted analogs of thalidomide (1) and its isoindoline-1-one analog, EM-12 (2). Some amino substituted thalidomide analogs have previously been reported but were not assayed for their TNF-a inhibitory activity.’0 EM-12 (2) has been reported to be a more potent teratogen than thalidomide in rabbits, rats, and monkeys." When 2 was evaluated for TNF-a inhibitory activity in LPS stimulated human PBMC it was found to have similar activity to thalidomide. The isoindolinone replacement ofthe phthaloyl ring increases the stability of the molecule and may lead to increased bioavailability. Herein, we report the structure-activity relationships of amino substitution ofthe phthaloyl ring ofthalidomide and isoindolinone ring ofEM-12 on the TNF-a inhibitory activity in LPS stimulated human PBMC.
Scheme 1

_____ O4J

Cbz-L-glutamine a.b

c

3

O’NQqO C, d N_(?=O

4a X = 4-NO2 So = 4-NH2

4b X m 5-NO2 Sb X = 5-NH.,
Reagents (a) CDI, THF, reflux (b) H2. 10% Pd/C, EtOAc/4N HCI (C) 3, AcQH, reflux (d) 10% Pd/C, acetone.

Chemistry. The amino substituted analogs of thalidomide were prepared as illustrated in Scheme 1.12 The amino thalidomide analogs were prepared via the condensation of 3-aminopiperidine-2,6-dione hydrochloride. (3). Compound 3 was prepared in two steps from commercially available Cbz-L-glutamine. Treatment ofCbz-L-glutamine with carbonyl diimidazole (CDI) in refluxing THF afforded Cbz-aminoglutarimide. The Cbz Protecting group was readily removed by hydrogenolysis under 50-60 psi of hydrogen in the presence of 10% Pd/C in a mixture of ethyl acetate and 4 N HCL The hydrochloride (3) was used directly in the anhydride

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condensation reaction without purification. Treatment of 3 with 3- or 4-nitrophthalic anhydrides in refluxing acetic acid afforded the 4- and 5-nitro substituted thalidomide analogs 4a and 4b, respectively, in good yields. The nitro groups of4a and 4b were reduced by hydrogenation in a Parr shaker under 50-60 psi of hydrogen in the present of 10% PdIC to afford the desired 4- and 5-amino substituted thalidomide analog Sa and 5b, respectively.13 The amino substituted Isoindolinone analogs were prepared as illustrated Scheme 2.12 Treatment of3 with the appropriately substituted nitro substituted methyl 2-(bromomethy!)benzoates, 6a-d yielded the four isomeric nitro EM-12 analogs 7a-d. The nitro groups were hydrogenated to the desired amino compound as described above to afford $a-d. The four isomeric nitro substituted methyl 24bromomethyl)benzoates (6a-d) were prepared by benzylic bromination ofthe corresponding commercially available nitro substituted methyl 2-methylbenzoates.
Scheme 2

03

a 0’ b. C
:NIi=o
02N Or X 4
Ga 3-NO2 7a X = 4-NO2 Ba X= 4-NH2
Sb 4-NO2 Tb X c 5-NO2 8b X= 5-NH2
Sc 5-NO2 Tc X = 6-NO2 Sc X= 6-NH2
Gd 6-NO2 7d X = 7-NO2 Gd X= 7-NH3
Reagents: (a) light, NBS. Cd4. reflux (b) 3, Et3N. DMF, 80 °C, (d) H21 10% Pd/C, MGOH The R and S isomers of Sn were prepared starting from the S- and R-isomers of glutamine t-butyl ester (Scheme 3). The aura substituted Nefa reagent analog, 10 was prepared by treatment of 3-nitrophthalimide with ethyl chloroformate.’4 Net’s reagent is a reagent commonly used in the preparation of chiral N-phthaloyl protected ammo acids. Treatment of 10 with the single isomers of t-butyl glutamine afforded the phthaloyl glutamine derivatives, (5)- and (R)- 11. The t-butyl group was removed using standard acidic conditions to afford (S)- and (R)- 12. To avoid racemization, the ring closure was accomplished using the method reported by Casini and Feiappi’5 for the synthesis ofthe single isomers ofthalidomide to afford (R)- and (5)- of 4a,13 The nitro groups were reduced as described earlier in acetone to afford the single isomers of 5a.
Scheme 3

tfNco2Et a,b VN-_I,--Pd - 5N---???o

10 (S)- and (R)-11 Rt-Butyl (S)- and (R)- 4a X = NO2
(S)- and (R)- 12 R = H (S)- and (R)-5XNH,
Reagents: (a) EL3N, (R) or (S) t-butyi glutamine HCI; (b) HCI, CH2CJ2; (C) SOC6 pyr/Et3N; (d) H2, 10% Pd/C. acetone.

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The 4-amino-c -methyl analog (14) of thalidomide was prepared from u-methylglutamic acid (Scheme
4). By standard chemistry a-methylglutamic acid was converted to Cbz-a-rnethylglutamic acid anhydride (15). Treatment ofthe anhydride with ammenia afforded a mixture of z- and y-amidcs, 16. This mixture was cyclized with CDI to the Cbz-protected amlnoglutarimide 17. The Cbz-group was removed by hydrogenation under acidic conditions to afford aminoglutarimide hydrochloride 18. Condensation with 3.nitrophthalic anhydride followed by reduction ofthe nitro group afforded 14.
Scheme 4

ZHN)J)o a, b, C X-j>=O d, e Q NZ)=O

18 17X=Z-NH x 0

I8X=CIH3N 19XN02
14X= NH2

Reagents (a) NH3, CH2CI (b) CDI. THF; (c) H2, 10% Pd/C, EtOH!4N HCI;
(d) 3-NO27phthallc anydride, ACOH. reflux (a) H2. Pd/C, acetone.

Biological Assays. ThF-a inhibitory activity was measured in lipopolysechazidc (LPS) stimulated PBMC as previously reported! The human whole blood TNF-a inhibition assay was run in a similar fashion to the PBMC assay except heparinized fresh human whole blood was plated directly into niicrotiter plates. The assay was then continued as previously reported for the PBMC assay. The assay for PDE4 enzyme inhibition was run as previously described.’
Results and Discussion. Thalidomide has been reported to be a selective inhibitor ofTNF-a in U’S stimulated human monocytes4 Thalidomide has a ThF-ix ICso of ’-200 pM in 125 stimulated PBMC.’ Previous research with thalidomide analogs suggested that phthaloyl substitution could lead to increases in activity! Although the amino substitution had been previously described, these analogs had not been tested for their ability to inhibit TNF-u production (Table 1). The 5-amino analog, Sb, was found to have a TNF-a IC50 of 100 pM. No inhibitory activity was observed at the lower concentrations tested (less than or equal to 10 pM). The 4-amino analog. Sn, was significantly more potent with an IC50 of 13 tiM. Thus, this compound was 15,000 times more potent than thalidomide as a TNF-a inhibitor in vitro. The novel isomeric amino-substituted EM-12 analogs were then prepared and tested. Unlike thalidomide where there are only two regio isomers, there are four possible regio isomers, Sa-d. Only the 4-amino analog 8a potently inhibited TNF-ł. production (ICs9 less than 100 pM). Compound Ba was found to have an IC50of 1)nM (Table I). This substitution correlates with the amino substitution on Sn and demonstrated that the amino group needed to be opposite to the carbonyl ofthe isoindolinone for optimal activity. The 5- and R-isomers of5a were prepared and evaluated. The S-isomer of So was found to be the more active isomer with a ThF-a ICo of 3.9 tiM. The R-isomer was 20-fold less active with a TNF 1050 of 94 nM. Although (R)-Sa’s optical purity was greater than 95% cc, some activity was probably due to residual (5)-isomer in the sample.

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The u-methyl analog ofthalidomide, 13, has also been reported to demonstrate similar TNF-a inhibitory activity to thalidomide.’6 This compound does not contain the racemizable chiral center found in thalidomide. The 4-amino analog 14 was a potent inhibitor ofTNF-u with an IC50 of 44 nM. Work is in progress to prepare the single isomers of 14 and will be reported on in the future.
Compounds Sn, Sn, and 14 were evaluated for PDE4 inhibitory activity using PDE4 enzyme isolated
from U937 cells.8 All three compounds were inactive (<5001* inhibition) at 100 iiM, the highest concentration assayed. These results strongly suggested that these compounds do not act by PDE4 inhibition. The three active analogs, 5*, 8*, and 14 were evaluated for their ability to inhibit NF-a levels LPS stimulated human whole blood to mimic their activity in vivo. The compounds had only modest declines in activity in this assay. (Table I).
Table 1 NF-a Inhibition in U’S Stimulated Human PBMC and Whole Blood
Compd TNF-a Inhibit. TNF-a Whole Blood
At 100 pM 1050 TNF-a 105
5* 95% 13 nM 25 nM
Sb 55% 100,000 nM NI)
Sa 740/a 100 nM 490 nM
Sb 15% ND ND
Sc 12% ND NI)
Sd 18% NI) ND
14 980/0 44 nM 216 nM
(3)-5a 990/0 3.9 nM 14 nM
(R)-5a 85% 93 nM 73 nM
In summary, we have discovered three high potency inhibitors of TNF-a by 4-amino substitution of thalidomide, EM-12, and a-methylthalidomide. The (S).4-amino substituted analog of 5* was found to be  50,000 times more potent than thalidomide at inhibiting NP-a levels in LPS stimulated human PBMC. None the three compounds showed significant activity as a PDE4 inhibitor. A recent publication reported 14 to enhance NP-a production in 12-0-tefradecanoyl-phorbol 13-acetate stimulated human leukemia HL-60 cells. These discordant results are possibly related to our usc of primary human cells stimulated with LPS in contrast to the other investigators use ofthe HL-60 cell line fimulated with TPA. Further, we have demonstrated that these compounds retain high activity in the milieu of whole human blood. We are presently investigating the structure-activity relationships of other substituted phthaloyl and isoindolinone analogs ofthalidomide and EM-12 and will be publishing on the biological profiles of5*, 8*, and 14.18

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Pharmaceutical

Cocrystals.m An Emerging. Approach to Physical Property Enhancement
William Jones, W.D. Samuel Motherwell, and Andrew V. Trask

Abstract
Pharmaceutical cocrystals are crystalline molecular complexes containing
therapeutic molecules They represent an emerging class of pharmaceutical materials offenng the prospect of optimized physical properties This article highlights important opportunities and challenges associated with the design and synthesis of pharmaceutical cocrystals. CocrystatiIzatlon is first placed into context with the more established approaches to physical property optimization of poiymorph hydrate and salt selection A directed Intermolecular-Interaction-based approach to cocrystal design is described. The enhancement of specific physical properties, such as dissolution rate and physical stability, is illustrated by summarizing several recent reports Synthetic approaches to cocrystailizatlon are considered in particular, the selectivity and screening related opportunities afforded by solid-state grinding and solvent-drop grinding methods are discussed Finally, an outlook on future developments summarizes the growth potential in this field, especially with regard to targeted, informaticsdriven cocrystal screening approaches

Keywords biomedical, crystal growth, crystalline.

Introduction
On average, about a decade of research
and development is expended in the dis-
covery and commercialization of a new pharmaceutical product. Initial R&D ef-forts center on the identification of a suit-able molecular structure, physical form, and formulation. Whereas the molecular structure of the active pharmaceutical in-

gredient (API) of a drug substance is se- lected to optimize therapeutic properties,
selecting the physical form of an API rep-resents a strategic opportunity for opti-mizing such physical properties as solubility, dissolution rate, hygroscopicity, physical stability, and chemical stability.’ MostAPIs are dosed as solids, and most
solid APIs exist in the crystalline form.

Frequently, however, the API does not crystallize on its own or it crystallizes into one or more crystal forms that possess un-desirable physical properties. In either case, an alternative crystal form is typically sought. Various options include single-
component inglecomponentand multiple-component mod-ifications of an API, including polymorphs, salts,solvates, and hydrates. In addition to these established crystalline API modifica-tions, pharmaceutical cocrystals, or crys-

talline molecular complexes involving an API, have recently attracted interest as an alternative approach.

This article outlines how pharmaceuti-
cal cocrystals offer an alternative ap-proach to physical property optimization

during crystal form selection. Important design strategies for making cocrystals are described, along with some recent examples of using cocrystals to enhance specific physical properties. Cocrystal screening and synthesis are also covered, particu-larly using solid-state grinding and solvent-drop selective cocrystal synthesis.

Solid-State Modifications ofAPIs

Polymorphs Apolymorph is "a solid crystalline phase
of a given compound resulting from the possibility of at least two different arrange-ments of the molecules of that compound in the solid state."2 Different polymorphs of a given compound each possess a unique set of physicochemical properties, and many, if notmost, compounds exhibit polymorphism to some extent14 Some compounds exist in more than ten crystal form modifications.5 At present, it is not generally possible to computationally pre-dict the number of observable polymorphs of even the simplest molecules,6 and as a result, the use of high-throughput screen-ing methods to search for new polymor-phic forms has become an important tool in form screening.5

Hydrates and Solvates
Frequently during crystallization, sol-
vent may be taken up and incorporated as part ofthe crystalstructure. Mostsolvents, however, are biologically toxic; as a re-sult, most solvate-containing crystals aresult, avoided in the development of the solid form of an API.

An important exception is the subclass
of API hydrates, which are well known in pharmaceutical products.’,’ It has been es-timated that one-third of pharmaceutical molecules are capable of forming hy-drates.9’1° As a result of process-induced stresses, such as changes in temperature, pressure, or relative humidity, hydrates often convert into anhydrous crystal forms. This conversion from hydrate to anhydrate can result in significant changes in physical properties and can present major issues, for example, during storage, where hydrate conversion can compromise dosage form appearance and integrity.

Phamiaceutical Salts
Salt formation is a common approach to
modifying the properties of an API.11-13 Salt formation is an addbase reaction be-tween the API and an acidic or basic

substance. It is an attractive strategy, be- cause most pharmaceutical compounds
possess either acidic or basic functionality,
and the widespread use of salt formation
is evidenced by the large number of mar-
keted crystalline salts of APIS.14

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Pharmaceutical Cocrystals An Emerging Approach to Physical Property Enhancement

Pharmaceutical Cocrjstals
A more recent approach to pharmaceu-
tical physical property optimization is
pharmaceutical cocrystal formation. A
cocrystal may be thought of as a crys-
talline complex of two or more neutral molecular constituents bound together in the crystal lattice through noncovalent interactions, often including hydrogen bonding.
The application of cocrystallization to
the pharmaceutical industry provides in-herent benefits as compared with salt for-mation in at least two ways. The first is that, at least in theory, all types of mole-cules can form cocrystals, including weakly ionizable and non-ionizable APIs, which are traditionally considered to present a higher risk in terms of physical property optimization because they have either limited or no capacity for salt formation. A second benefit is that, whereas for
toxicological reasons only 12 orso acidic or basic counterions are explored in a typical API salt screen,1215 there are many poten-tial counter-molecules thatmay be used in cocrystal synthesis. (A counter-molecule maybe defined as the species cocrystallized with theAPI.) The U.S. Food andDrugAd-ministration manages several lists of sub-stances that have precedence as food in-gredients (e.g., the FDA’s GRAS list, a list

of substances "generally recognized as safe"), with the total amount ofsubstances
numbering in the thousands. Although the increased scope of cocrystals is a benefit in that it suggests a greater likelihood of achieving a desirable physical property profile for an API physical form, it also presents a challenge in terms of screen-ing efforts, even with high-throughput screening.
To maximize efficiency in screening for
cocrystals, therefore, improved rational cocrystal design and more efficient cocrys-tal screening protocols are needed.

Synthon Approach to Cocrystal
Design
The formation of cocrystals has been
studied for some time in academic re-

search, and various important studiessearch,

aimed at understanding cocrystal design have been published.
In early studies, Etter and co-workers
proposed several "hydrogen-bond rules," including the observations that (1) all good proton donors and acceptors are used in hydrogen bonding, and (2) the best donor

typically pairs with the best acceptor in a given crystal structure.16 The combined use of the hydrogen-bond rules with a geometric analysis (known

as graph-set

analysis17) assisted Etter and co-workers in implementing rational cocrystal design

in the synthesis ofmany new supramolec-ular structures.
Allenet aL demonstrated a quantification
of the "robustness" of a certain class of intermolecular arrangements (commonly called motifs, orsynthons) involving strong hydrogen-bonded bimolecularringmotifs. Their analysis involved examining trends within theCambridge Structural Database (CSD), a searchable repository containing more than 300,000 small-molecule crystal sttures.18 They assessed the robustness of a motif in terms of its "formation prob-ability," that is, the observed frequency of motif formation among all structures con-taining the necessary functional group components. Ahigher formation probabil-ity suggested a greater utility in a cocrys-tal design scheme.
By relying on robust intermolecular in-
teractions with demonstrated solid-state

reproducibility, synthon-based cocrystal design has become increasingly important to the synthesis of new cocrystal materials. In the future, automated searches for for-mation probabilities pertaining to the mo-lecular structure of an API of interest will be an important step toward rational pharmaceutical cocrystal design.

Pharmaceutical Cocryst.als and
Physical Property Enhancement
During the past few years, the focus on
pharmaceutical cocrystals has increased significantly." In 2002, Oswald et al. demon-strated cocrystallization of the analgesic drug paracetamol (acetaniinophen) with six different counter-molecules, each of which was capable of acting as a hydrogen-bond acceptor.20 Shortly thereafter, Zaworotko and co-workersreported cocrys-tals ofthe APIsIbuprofen, flurbipmfen, and

aspirin with several hydrogen-bond ac- ceptors.21 These examples served as early proof that a series of cocrystals with com- mon hydrogen-bonding features may be
obtained with APIs. Aside from melting point data, however, these reports focused essentially on structural features without addressing the functional properties that these cocrystals might offer. Additionally,

from an industrial standpoint, these were only model systems, in that the non-API components were, in most cases,

not known to be safe for human ingestion.
In a subsequent paper, Zaworotko and
co-workers reported on a series of cocrys-tals oftheAPI carbamazepine, a drug used in the treatment of epilepsy,with a variety of different counter-molecules, including several that are biologically nontoxic, in-cluding acetic add, nicotinamide (vitamin

B3), and the well-known sweetener sac- charin.12The report brought to light the

’1?
variety of possible counter-molecules that may form cocrystals with a single APL
Despite the increase in reports contain-
ing new pharmaceutical cocrystal struc-tures, however, only a limited number of studies have directly addressed the real-ization of physical property modification. One report of a pharmaceutical cocrystal with enhanced dissolution properties in-volved cocrystals of several nontoxic C4 (four-carbon) 1,4-dicarboxylic acids with itraconazole, an antifungal drug withvery low aqueous solubility in its crystalline free base form.11 The cocrystals reportedly resulted from a high-throughput crystal form screen of itraconazole, and the acids in the study were known to be biologically nontoxic atcommon pharmaceutical dosage levels.15 Single-crystal data were reported for one ofthe cocrystals, a 2:1 itraconazole:
succinic acid cocrystal (Figure 1), where it was observed that the diacid spanned two itraconazole molecules via 0H...N hydrogen bonds. All of the cocrystals demonstrated an enhanced dissolution

profile as compared with itraconazole free base, and in some cases the dissolution profiles of the cocrystals approached that of amorphous itraconazole, which itself had been developed for the specific aim of enhancing the dissolution rate of the API. The same study also emphasized the
value of performing high-throughput cocrystal screening in addition to imple-menting rational design methodology. In the itraconazole:sucdnic acid cocrystal, the diacid formed a hydrogen bond with the five-membered triazole ring rather than with the most basic site on the drug molecule, the nitrogen of the six-membered piperazine (PKa = 3.7). This example appeared to violate the best-donorbest-acceptor hydrogen-bond rule in preference for what may have been a geometric consideration: attempts to cocrystallize itraconazole with dicar-boxylic acid chain lengths other than C4, including malonic (C3), glutaric (C5), and

adipic (C6) acids, were reportedly unsuc- cessful. Until it becomes possible to confi-

dently predict which counter-molecules

will formcocrystals with a givenAPL high- throughput screening will continue to be

of tremendous value to this research field.
A second demonstration of dissolution
rate enhancement via cocrystallization involved three pharmaceutical cocrystals of the API fluoxetine, the active ingredient

in the antidepressant drug Proza0 This case was of particular interest from the
standpoint of cocrystal design: the re-searchers formed cocrystals by combiningesearchers a c?rboxylic acid with the hydrochloric acid (HC1) salt of fluoxetine, generating three novel cocrystals ofsalts. For example,

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