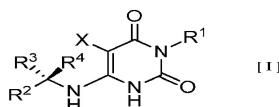


DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD FASE NACIONAL - PCT



1	Título de la Invención (200 caracteres o espacios máximos)		
COMPUESTOS DE PIRIMIDINODIONA CONTRA ESTADOS CARDIACOS			
2	Datos del Solicitante / Titular		
Nombre:	MYOKARDIA, INC.	Dirección Electrónica:	sic@castellanosyco.co
Dirección:	333 Allerton Avenue, South San Francisco, California 94080, ESTADOS UNIDOS DE AMERICA	Domicilio/País de constitución:	ESTADOS UNIDOS DE AMERICA - CALIFORNIA - SOUTH SAN FRANCISCO
Identificación:			
☐ CEDULA DE CIUDADANIA ☒ EMPRESA EXTRANJERA ☐ PASAPORTE		☐ CEDULA DE EXTRANJERIA ☐ NIT	

Número:		1041353-	
3	Solicitantes		
Apellidos - Nombres o Razón Social		Tipo	Identificación
1.	MYOKARDIA, INC.	NN	1041353
4	Datos del Inventor		
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Dirección:		c-o Myokardia, Inc., 333 Allerton Avenue, South San Francisc, Caifornia 94080, ESTADOS UNIDOS DE AMERICA	Domicilio/País de constitución: ESTADOS UNIDOS DE AMERICA - CALIFORNIA - SOUTH SAN FRANCISCO
Identificación:			
☐ CEDULA DE CIUDADANIA ☐ EMPRESA EXTRANJERA ☐ PASAPORTE ☐ CEDULA DE EXTRANJERIA ☐ NIT ☒ No Aplica			
Número:		-	
5	Inventor(es)		
Apellidos - Nombres		Domicilio	
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10.	SONG YONGHONG	ESTADOS UNIDOS DE AMERICA
11.	SRAN ARVINDER	ESTADOS UNIDOS DE AMERICA

6	Datos Inventor(es)
---	--------------------

	País de Residencia	Departamento/Estado	Ciudad	Dirección
1.	ESTADOS UNIDOS DE AMERICA	CALIFORNIA	SOUTH SAN FRANCISCO	c-o Myokardia, Inc., 333 Allerton Avenue, South San Francisc, Caifornia 94080, ESTADOS UNIDOS DE AMERICA
2.	ESTADOS UNIDOS DE AMERICA	CALIFORNIA	SOUTH SAN FRANCISCO	c-o Myokardia, Inc., 333 Allerton Avenue, South San Francisc, Caifornia 94080, ESTADOS UNIDOS DE AMERICA
3.	ESTADOS UNIDOS DE AMERICA	CALIFORNIA	SOUTH SAN FRANCISCO	c-o Myokardia, Inc., 333 Allerton Avenue, South San Francisc, Caifornia 94080, ESTADOS UNIDOS DE AMERICA

4.	ESTADOS UNIDOS DE AMERICA	CALIFORNIA	SOUTH SAN FRANCISCO	c-o Myokardia, Inc., 333 Allerton Avenue, South San Francisc, Caifornia 94080, ESTADOS UNIDOS DE AMERICA
5.	ESTADOS UNIDOS DE AMERICA	CALIFORNIA	SOUTH SAN FRANCISCO	c-o Myokardia, Inc., 333 Allerton Avenue, South San Francisc, Caifornia 94080, ESTADOS UNIDOS DE AMERICA
6.	ESTADOS UNIDOS DE AMERICA	CALIFORNIA	SOUTH SAN FRANCISCO	c-o Myokardia, Inc., 333 Allerton Avenue, South San Francisc, Caifornia 94080, ESTADOS UNIDOS DE AMERICA
7.	ESTADOS UNIDOS DE AMERICA	CALIFORNIA	SOUTH SAN FRANCISCO	c-o Myokardia, Inc., 333 Allerton Avenue, South San Francisc, Caifornia 94080, ESTADOS UNIDOS DE AMERICA
8.	ESTADOS UNIDOS DE AMERICA	CALIFORNIA	SOUTH SAN FRANCISCO	c-o Myokardia, Inc., 333 Allerton Avenue, South San Francisc, Caifornia 94080, ESTADOS UNIDOS DE AMERICA
9.	ESTADOS UNIDOS DE AMERICA	CALIFORNIA	SOUTH SAN FRANCISCO	c-o Myokardia, Inc., 333 Allerton Avenue, South San Francisc, Caifornia 94080, ESTADOS UNIDOS DE AMERICA
10.	ESTADOS UNIDOS DE AMERICA	CALIFORNIA	SOUTH SAN FRANCISCO	c-o Myokardia, Inc., 333 Allerton Avenue, South San Francisc, Caifornia 94080, ESTADOS UNIDOS DE AMERICA
11.	ESTADOS UNIDOS DE AMERICA	CALIFORNIA	SOUTH SAN FRANCISCO	c-o Myokardia, Inc., 333 Allerton Avenue, South San Francisc, Caifornia 94080, ESTADOS UNIDOS DE AMERICA

7	Datos del Representante Legal / Apoderado		
Nombre:		MARGARITA CASTELLANOS ABONDANO	Dirección Electrónica: sic@castellanosyco.co

Dirección:		CALLE 94A 7A 09	Domicilio/País de constitución:	COLOMBIA - BOGOTA D.C. - BOGOTA D.C.
Identificación: ☒ CEDULA DE CIUDADANIA ☐ EMPRESA EXTRANJERA ☐ PASAPORTE ☐ CEDULA DE EXTRANJERIA ☐ NIT Número: 39779654-				
Presentación de Poder				
Año de Radicación				
Número de Radicación				
8	Datos Solicitud: PCT / WO			
Número Solicitud:		PCT/US2014/043192	Fecha Solicitud:	19/06/2014
Número Publicacion:		WO 2014/205223	Fecha Publicacion:	24/12/2014
9	Declaraciones de prioridad		☒ SI ☐ NO	
	(33) País de origen	Codigo del país	(31) No. Solicitud	(32) Fecha
1.	ESTADOS UNIDOS DE AMERICA	US	61/838.088	21/06/2013
2.	ESTADOS UNIDOS DE AMERICA	US	61/939.655	13/02/2014
3.	ESTADOS UNIDOS DE AMERICA	US	61/981.366	18/04/2014
10	Reivindicaciones			
Número reivindicaciones:		22	Pago Reivindicaciones:	Si
11	Reducción de tasas.			
<i>Declaro que carezco de medios económicos para presentar la solicitud de patente.</i> ☐ SI ☒ NO Nota: En caso de ser persona natural y carecer de medios económicos, y por lo tanto, aplique la reducción de tasas a que se refiere la resolución vigente en tarifas, debe firmar la presente solicitud bajo la gravedad de juramento.				
☐ Micro, pequeñas y medianas empresas				

☐ Universidades públicas o privadas

☐ Entidades sin ánimo de lucro

Debe aportar los documentos que se indican en el numeral 17 de anexos

12	Documentos Anexos
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☒ Reivindicaciones

☒ Descripción

☐ Dibujos y/o Figuras

☒ Resumen

☐ Certificado Depósito Material Biológico

☐ Uso de Conocimiento tradicional

☐ Listado de secuencias

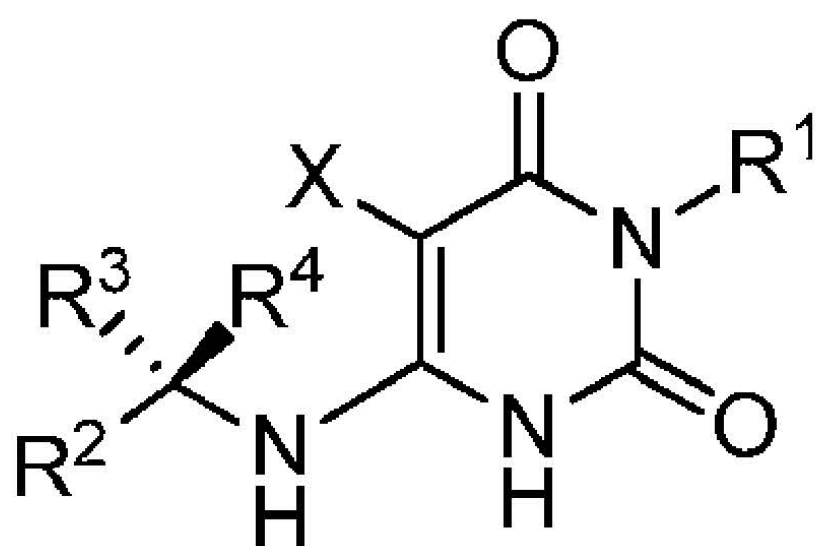
☒ Artes finales 12 x 12 cm

☐ Poderes, si fuere el caso

☐ Copia de la primera solicitud si se reivindica prioridad

☐ Traducción simple de la primera solicitud, si se reivindica prioridad

☒ Otros Anexos



[I]

COMPUESTOS DE PIRIMIDINODIONA CONTRA ESTADOS CARDÍACOS

Referencias cruzadas a solicitudes relacionadas

Esta solicitud es una solicitud que reivindica el beneficio de la normativa 35 U.S.C. § 119(e) de la solicitud provisional de EE.UU. n°. 61/838.088 presentada el 21 de junio de 2013 y la
5 solicitud provisional n° 61/939.655 presentada el 13 de febrero de 2014 y la solicitud
provisión de EE.UU n° 61/981.366 presentada el 18 de abril de 2014, cada una de las cuales
incorpora como referencia a la presente memoria descriptiva en su totalidad.

DECLARACIÓN SOBRE LOS DERECHOS DE INVENCIONES REALIZADAS BAJO INVESTIGACIÓN Y DESARROLLO FEDERALMENTE PATROCINADOS

10 NO APLICABLE

Antecedentes de la invención

La cardiomiopatía hipertrófica genética (hereditaria) (HCM) comprende un grupo de
enfermedades del miocardio dominantes autosomales, monogénicas y altamente
penetrantes. La HCM está provocada por una o más de más de 1.000 mutaciones puntuales
15 conocidas en uno cualquiera de los genes proteicos estructurales que contribuyen a la
unidad funcional del miocardio, el sarcómero. Se encuentra que aproximadamente 1 de cada
500 individuos en la población general tienen una hipertrofia ventricular izquierda no
explicada por otras causas conocidas (por ejemplo, hipertensión o enfermedad valvular) y
muchos de estos se puede observar que tienen HCM, una vez que han sido excluidas otras
20 causas hereditarias (por ejemplo, enfermedades de almacenamiento lisosomal), metabólicas
o infiltrantes.

Las mutaciones de genes del sarcómero que provocan HCM son altamente penetrantes,
pero hay una amplia variabilidad en la gravedad clínica y la trayectoria clínica. Algunos
genotipos están asociados con un trascurso más maligno, pero hay una considerable
25 variabilidad entre e incluso dentro de las familias que portan la misma mutación. Se han
apreciado también diferencias de sexo, siendo generalmente los pacientes masculinos más
gravemente afectados que las pacientes femeninas. Aunque muchos pacientes con HCM
refieren unos síntomas mínimos o nulos durante periodos de tiempo prolongados, la HCM es
una enfermedad progresiva con una carga acumulativa significativa de mortalidad. Los
30 síntomas de intolerancia al esfuerzo predominan y pueden verse exacerbados por el
ejercicio y otras maniobras que aumentan el ritmo cardíaco y/o disminuyen la precarga.
Como con muchos otros trastornos, los síntomas tienden a empeorar con la edad. Con
mucho, la carga clínica más prevalente para pacientes con HCM es una disnea de esfuerzo
que limita sus actividades de la vida diaria y pueden ser debilitantes.

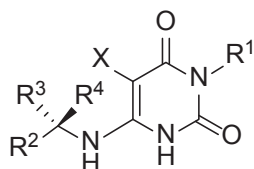
35 Los pacientes con HCM a menudo son sintomáticos en ausencia de anormalidades

hemodinámicas documentadas como obstrucción de la salida del flujo ventricular izquierdo (con o sin regurgitación mitral). Los síntomas del paciente de disnea del esfuerzo pueden empeorar rápidamente con la aparición de fibrilación auricular, una complicación común de la HCM que puede precipitar un edema pulmonar agudo que aumenta el riesgo de enfermedad tromboembólica arterial sistémica, que incluye derrame cerebral. Otros acontecimientos adversos asociados con la HCM incluyen intolerancia hipovolemia o hipervolemia y síncope. La enfermedad coronaria simultánea puede conferir un riesgo superior de síndromes coronarios agudos con respecto a pacientes sin HCM. La muerte cardíaca repentina (SCD) en pacientes con HCM es tanto inusual como difícil de predecir pero es una causa principal de muerte no traumática en adultos jóvenes. Para supervivientes de SCD, la colocación de ICD es una práctica estándar y, en otros pacientes de HCM el riesgo de caracterización, aunque es impreciso, es usado para identificar aquellos para los que la colocación de ICD para una prevención primaria se estima prudente.

La terapia médica para HCM está limitada al tratamiento de los síntomas y no aborda la causa fundamental subyacente de la enfermedad, interrupciones en la función normal del sarcómero. Las terapias actualmente disponibles tienen una eficacia variable para aliviar los síntomas pero normalmente muestran una eficacia disminuida con una duración creciente de la enfermedad. Los pacientes por tanto son empíricamente tratados con bloqueadores beta, bloqueadores de canales de calcio que no son de dihidropiridina y/o disopiramida. Ninguno de estos agentes porta indicaciones marcadas para tratar la HCM, y esencialmente no hay una evidencia de ensayos clínicos rigurosos disponible para dirigir su uso. Esta situación lamentable se ve agravada por el hecho de que no se han identificado terapias médicas nuevas para la HCM durante muchos años. Para pacientes con obstrucción del tracto de salida hemodinámicamente significativo (gradiente restante >300 mm de Hg), en pacientes apropiadamente seleccionados, habitualmente es necesaria una miectomía quirúrgica o ablación del tabique con alcohol para aliviar la obstrucción hemodinámica. Se proporciona nuevos agentes y métodos terapéuticos para remediar la necesidad largamente percibida de un tratamiento mejorado para la HCM y trastornos cardíacos relacionados.

Breve resumen de la invención

En un aspecto, se proporciona un compuesto que tiene la fórmula:



o una sal farmacéuticamente aceptable del mismo. En algunas realizaciones, en la fórmula anterior R^1 es un miembro seleccionado entre alquilo C_1-C_8 , cicloalquilo C_3-C_8 , cicloalquil C_3-C_8 -alquilo C_1-C_4 , heterocicloalquilo de 4 a 7 miembros, fenilo, fenil-alquilo C_1-C_4 , heteroarilo de 5 a 6 miembros y heteroarilo de 5 a 6 miembros-alquilo C_1-C_4 , en que cada R^1 está
 5 opcionalmente sustituido con 1-3 R^a ; R^2 es un miembro seleccionado entre fenilo, fenil-alquilo C_1-C_4 , heteroarilo de 5 a 6 miembros y heteroarilo de 5 a 6 miembros-alquilo C_1-C_4 , en que cada R^2 está opcionalmente sustituido con uno 1-5 R^b ; R^3 es un miembro seleccionado entre alquilo C_1-C_4 , cicloalquilo C_3-C_4 y heterocicloalquilo de 4 a 7 miembros en cada R^3 está opcionalmente sustituido con 1-3 R^c ; R^4 es H; X es un miembro
 10 seleccionado entre H y halo y, en algunas realizaciones, C se selecciona entre H y F. Cada R^a , cuando está presente, se selecciona independiente entre halo, CN, hidroxilo, alquilo C_1-C_4 , haloalquilo C_1-C_4 , alcoxi C_1-C_4 , fenilo, fenil-alquilo C_1-C_4 , fenil-alcoxi C_1-C_4 , fenoxi, $-COR^{a1}$, $-CO_2R^{a1}$, $-SO_2R^{a1}$, $-SO_2NR^{a1}R^{a2}$ y $-CONR^{a1}R^{a2}$, en que cada R^{a1} y R^{a2} se selecciona independientemente entre H, alquilo C_1-C_4 y fenilo, u opcionalmente R^{a1} y R^{a2} , cuando están
 15 unidos a un átomo de nitrógeno, se combinan para formar un anillo de 4 a 6 miembros. Análogamente, cada R^b , cuando está presente, se selecciona independientemente entre halo, CN, hidroxilo, alquilo C_1-C_4 , haloalquilo C_1-C_4 , alcoxi C_1-C_4 , fenoxi, fenil-alcoxi C_1-C_4 , metilenodioxi, difluorometilenodioxi, $-COR^{b1}$, $-CO_2R^{b1}$, $-SO_2R^{b1}$, $-SO_2NR^{b1}R^{b2}$, $CONR^{b1}R^{b2}$, $NR^{b1}R^{b2}$, heteroarilo de 5 a 6 miembros y heterociclilo de 5 a 6 miembros opcionalmente
 20 sustituido con oxo, en que cada R^{b1} y R^{b2} se selecciona independientemente entre H y alquilo C_1-C_4 u opcionalmente R^{b1} y R^{b2} , cuando están unidos a un átomo de nitrógeno, se combinan para formar un anillo de 4 a 6 miembros; y cada R^c , cuando está presente, se selecciona independientemente entre halo, hidroxilo y alcoxi C_1-C_2 .

En otro aspecto, se proporciona una composición farmacéutica que contiene un compuesto
 25 o una sal farmacéuticamente aceptable descrita en la presente memoria descriptiva y un excipiente farmacéuticamente aceptable.

En otro aspecto, se proporciona un método para tratar cardiomiopatía hipertrófica (HCM) o un trastorno cardíaco que tiene una o más características patofisiológicas asociadas con la HCM. El método incluye administrar a un sujeto que lo necesita una cantidad eficaz de un
 30 compuesto o una sales farmacéuticamente aceptables descritos en la presente memoria descriptiva.

Breve descripción de los dibujos

La Figura 1 muestra una vía esquemática para la síntesis de los compuesto o sales farmacéuticamente aceptables descritas en la pmd (Figura 1 A) y una vía para la
 35 preparación de aminas quirales (Figura 1 B).

Descripción detallada de la invención

I. General

Una serie de compuestos de pirimidino-diona y sus sales farmacéuticamente aceptables se ha encontrado que reducen el exceso de contractilidad en estados hipercontráctiles y/o favorecen la relajación cardíaca en corazones con disfunción diastólica estabilizando la conformación de miosina cardíaca beta posterior a la hidrólisis de ATP pero antes de unirse fuertemente al filamento de actina y liberar fosfato, reduciendo así la proporción de moléculas de miosina que son capaces de participar en la parte de “amortiguación” del ciclo de contracción muscular. Como tales, los compuestos pueden mejorar la elasticidad cardíaca, reducir la obstrucción del flujo de salida ventricular izquierdo dinámico y/o estático, mejorar la relajación ventricular izquierda diastólica, reducir las presiones diastólicas ventriculares izquierdas (rellenos), reducir la regurgitación mitral funcional y/o reducir las presiones de los enclavamientos capilares auriculares izquierdos y pulmonares en pacientes con HCM, ayudando a superar la disnea de esfuerzo debilitante y/o los síntomas achacables a la obstrucción del flujo de salida ventricular (presíncope o síncope) que acompañan a menudo a la enfermedad. Los compuestos pueden ser usados también para tratar otros trastornos cardíacos.

II. Definiciones

Como se usa en la presente memoria descriptiva, el término “alquilo” se refiere a un radical alifático saturado lineal o ramificado que tiene el número de átomos de carbono indicado. Alquilo puede incluir cualquier número de átomos de carbono, como C₁₋₂, C₁₋₃, C₁₋₄, C₁₋₅, C₁₋₆, C₁₋₇, C₁₋₈, C₂₋₃, C₂₋₄, C₂₋₅, C₂₋₆, C₃₋₄, C₃₋₅, C₃₋₆, C₄₋₅, C₄₋₆ y C₅₋₆. Por ejemplo, alquilo C₁₋₆ incluye, pero sin limitación, metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, terc-butilo, pentilo, isopentilo, hexilo, etc. Alquilo puede referirse a grupos alquilo que tienen hasta 20 átomos de carbono como, pero sin limitación, heptilo, octilo, nonilo, decilo, etc. Salvo que se establezca otra cosa, los grupos alquilo están sin sustituir. Un grupo “alquilo sustituido” puede estar sustituido con uno o más restos seleccionados entre halo, hidroxilo, amino, alquilamino, nitro, ciano y alcoxi.

Como se usa en la presente memoria descriptiva, el término “cicloalquilo” se refiere a un anillo bicíclico condensado o policíclico puenteado, monocíclico, saturado o parcialmente insaturado, que contiene de 3 a 12 átomos en el anillo o el número de átomos indicado. Cicloalquilo puede incluir cualquier número de átomos de carbono como C₃₋₆, C₄₋₆, C₅₋₆, C₃₋₈, C₄₋₈, C₅₋₈, y C₆₋₈. Los anillos cicloalquilo monocíclicos saturados incluyen, por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y ciclooctilo. Los anillos cicloalquilo bicíclicos y policíclicos saturados incluyen, por ejemplo, norbornano [2.2.2]bicyclooctano,

decahidronaftaleno y adamantano. Los grupos cicloalquilo pueden estar también parcialmente insaturados, teniendo uno o más enlaces dobles en el anillo. Los grupos cicloalquilo representativos que son parcialmente insaturados incluyen, pero sin limitación, ciclobuteno, ciclopenteno, ciclohexeno, ciclohexadieno (isómeros 1,3 y 1,4), ciclohepteno, cicloheptadieno, cicloocteno, ciclooctadieno (isómeros 1,3, 1,4 y 1,5) norborneno y norbornadieno. Salvo que se establezca otra cosa, los grupos cicloalquilo están sin sustituir. Un grupo “cicloalquilo sustituido” puede estar sustituido con uno o más restos seleccionados entre halo, hidroxí, amino, alquilamino, nitro, ciano y alcoxi.

Como se usa en la presente memoria descriptiva, el término “heterocicloalquilo” se refiere a un sistema de anillos saturados que tienen de 3 a 12 miembros en el anillo y de 1 a 4 heteroátomos seleccionados entre N, O y S. Pueden estar presentes también heteroátomos adicionales que incluyen, pero sin limitación, B, Al, Si y P en un grupo heterocicloalquilo. Los heteroátomos pueden ser oxidados para formar restos como, pero sin limitación -S(O)- y -S(O)₂-. Los grupos heterocicloalquilo pueden incluir cualquier número de átomos en el anillo como 3 a 6, 4 a 6, 5 a 6 o 4 a 7 miembros del anillo. Puede estar incluido cualquier número adecuado de heteroátomos en los grupos heterocicloalquilo, como 1, 2, 3 o 4 o 1 a 2, 1 a 3, 1 a 4, 2 a 3, 2 a 4 o 3 a 4. Ejemplos de grupos heterocicloalquilo incluyen, pero sin limitación aziridino, acetidino, pirrolidino, piperidino, azepano, azocano, quinuclidino, pirazolidino, imidazolidino, piperazino (isómeros 1,2, 1,3 y 1,4), oxirano, oxetano, tetrahidrofurano, oxano (tetrahidropirano), oxepano, tiirano, tietano, tiolano (tetrahidrotiofeno), tiano (tetrahidrotiopirano), oxazolidino, isoxazolidino, tiazolidino, isotiazolidino, dioxolano, ditiolano, morfolino, tiomorfolino, dioxano o ditiano. Los grupos heterocicloalquilo están sin sustituir, pero pueden ser descritos, en algunas realizaciones, como sustituidos. Los grupos “heterocicloalquilo sustituido” pueden estar sustituidos con uno o más restos seleccionados entre halo, hidroxí, amino, alquilamino, nitro, ciano y alcoxi.

Como se usa en la presente memoria descriptiva, el término “heteroarilo” se refiere a un anillo aromático monocíclico o bicíclico condensado o tricíclico que contiene de 5 a 16 átomos del anillo, en que 1 a 5 de los átomos del anillo son heteroátomos como N, O o S. Pueden estar presentes también heteroátomos adicionales que incluyen, pero sin limitación, B, Al, Si y P en un grupo heteroarilo. Los heteroátomos pueden ser oxidados para formar restos como, pero sin limitación, -S(O)- y -S(O)₂-. Los grupos heteroarilo pueden incluir cualquier número de átomos del anillo, como 5 a 6, 5 a 8, 6 a 8, 5 a 9, 5 a 10, 5 a 11 o 5 a 12 miembros del anillo. Puede estar incluido cualquier número adecuado de heteroátomos en los grupos heteroarilo como 1, 2, 3, 4 ó 5 ó 1 a 2, 1 a 3, 1 a 4, 1 a 5, 2 a 3, 2 a 4, 2 a 5, 3 a 4 ó 3 a 5. Los grupos heteroarilo pueden tener de 5 a 8 miembros del anillo y de 1 a 4

heteroátomos, o de 5 a 8 miembros del anillo y de 1 a 3 heteroátomos, o de 5 a 6 miembros del anillo y de 1 a 4 heteroátomos, o de 5 a 6 miembros del anillo y de 1 a 3 heteroátomos. Ejemplos de grupos heteroarilo incluyen, pero sin limitación, pirrol, piridino, imidazol, pirazol, triazol, tetrazol, pirazino, pirimidino, piridazino, triazino (isómeros 1,2,3, 1,2,4 y 1,3,5), tiofeno, furano, tiazol, isotiazol, oxazol e isoxazol. Los grupos heteroarilo pueden estar sin sustituir, pero pueden ser descritos en algunas realizaciones como sustituidos. Los grupos “heteroarilo sustituido” pueden estar sustituidos con uno o más restos seleccionados entre halo, hidroxí, amino, alquilamino, nitro, ciano y alcoxi.

Como se usa en la presente memoria descriptiva, el término “alcoxi” se refiere a un grupo alquilo que tiene un átomo de oxígeno que conecta el grupo alquilo al punto de unión, es decir, alquil-O-. En cuanto a la parte alquílica, los grupos alcoxi pueden tener cualquier número adecuado de átomos de carbono como SSS o C₁-C₄. Los grupos alcoxi incluyen, por ejemplo, metoxi, etoxi, propoxi, isopropoxi, butoxi, 2-butoxi, isobutoxi, sec-butoxi, terc-butoxi, pentoxi, hexoxi, etc. Los grupos alcoxi están sin sustituir, pero pueden ser descritos en algunas realizaciones como sustituidos. Los grupos “alcoxi sustituido” pueden estar sustituidos con uno o más restos seleccionados entre halo, hidroxí, amino, alquilamino, nitro, ciano y alcoxi.

Como se usan en la presente memoria descriptiva, los términos “halo” y “halógeno” se refieren a flúor, cloro, bromo y yodo.

Como se usa en la presente memoria descriptiva, la expresión “farmacéuticamente aceptable” se refiere a una sustancia que es compatible con un compuesto o sal como se describe en la presente memoria descriptiva, así como cualesquiera otros ingredientes con los que se formule el compuesto. Además, una sustancia farmacéuticamente aceptable no es perjudicial para el receptor de la sustancia.

Como se usa en la presente memoria descriptiva, el término “sal” se refiere a una sal ácida o básica de un compuesto descrito en la presente memoria descriptiva. Las sales farmacéuticamente aceptables pueden derivar, por ejemplo, de ácidos minerales (ácido clorhídrico, ácido bromhídrico, ácido fosfórico y similares), ácidos orgánicos (ácido acético, ácido propiónico, ácido glutámico, ácido cítrico y similares) e iones de amonio cuaternario.

Debe entenderse que las sales farmacéuticamente aceptables son no tóxicas. Se puede encontrar información adicional sobre sales farmacéuticamente aceptables en la publicación Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, que se incorpora como referencia a la presente memoria descriptiva. La forma neutra de un compuesto puede ser regenerada poniendo en contacto la sal con una base o ácido y aislando el compuesto parental de una manera convencional.

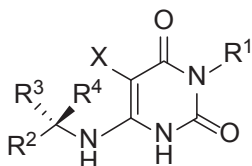
Como se usa en la presente memoria descriptiva, la expresión “composición farmacéutica” se refiere a un producto que comprende un compuesto o sales farmacéuticamente aceptables descrito en la presente memoria descriptiva, un excipiente como se define en la presente memoria descriptiva y otros ingredientes opcionales en cantidades especificadas, así como cualquier producto que resulte directa o indirectamente de la combinación de los ingredientes especificados en las cantidades especificadas.

Como se usa en la presente memoria descriptiva, el término “excipiente” se refiere a una sustancia que ayuda a la administración de un agente activo a un sujeto. Los excipientes farmacéuticos incluyen, pero sin limitación, aglutinantes, materiales de carga, disgregantes, lubricantes, revestimientos, edulcorantes, sabores y colores. Un experto en la técnica reconocerá que pueden ser útiles otros excipientes.

Como se usa en la presente memoria descriptiva, los términos “tratar”, “tratando” y “tratamiento” se refieren a cualesquiera indicios de éxito en el tratamiento o mejora de una patología, lesión, estado o síntoma relacionado con la cardiomiopatía hipertrófica, que incluyen cualquier parámetro objetivo o subjetivo como mitigación; remisión; disminución de síntomas; haciendo que la patología, lesión, estado o síntomas sea más tolerable para el paciente; disminución de la frecuencia o duración de la patología, lesión, estado o síntoma; o, en algunas situaciones, prevenir la aparición de la patología, lesión, estado o síntoma. El tratamiento o mejora puede estar basado en cualquier parámetro objetivo o subjetivo que incluyen, por ejemplo, el resultado de un examen físico.

III. Compuestos y sus sales farmacéuticamente aceptables

En un aspecto, se proporciona un compuesto que tiene la fórmula:



o una sales farmacéuticamente aceptables del mismo.

En la fórmula anterior, R¹ es un miembro seleccionado entre alquilo C₁-C₈, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo C₁-C₄, heterocicloalquilo de 4 a 7 miembros, fenilo, fenil-alquilo C₁-C₄, heteroarilo de 5 a 6 miembros y heteroarilo de 5 a 6 miembros-alquilo C₁-C₄, en que cada R¹ está opcionalmente sustituido con 1-3 R^a; R² es un miembro seleccionado entre fenilo, fenil-alquilo C₁-C₄, heteroarilo de 5 a 6 miembros y heteroarilo de 5 a 6 miembros-alquilo C₁-C₄, en que cada R² está opcionalmente sustituido con 1-5R^b; R³ es un miembro seleccionado entre alquilo C₁-C₄, ciclo alquilo C₃-C₄ y heterocicloalquilo de 4 a 7 miembros en que cada R³ está opcionalmente sustituido con 1-3 R^c; R⁴ es H, X es un miembro

seleccionado entre H y halo, y en realizaciones seleccionadas se selecciona entre H y F. Cada R^a , cuando está presente, se selecciona independientemente entre halo, CN, hidroxilo, alquilo C_1-C_4 , haloalquilo C_1-C_4 , alcoxi C_1-C_4 , fenilo, fenil-alquilo C_1-C_4 , fenil-alcoxi C_1-C_4 , fenoxi, $-COR^{a1}$, $-CO_2R^{a1}$, $-SO_2R^{a1}$, $-SO_2NR^{a1}R^{a2}$ y $-CONR^{a1}R^{a2}$ en cada R^{a1} y R^{a2} se selecciona independientemente entre H, alquilo C_1-C_4 y fenilo u opcionalmente R^{a1} y R^{a2} , cuando están unidos a un átomo de nitrógeno, se combinan para formar un anillo de 4 a 6 miembros. Análogamente, cada R^b , cuando está presente, se selecciona independientemente entre halo, CN, hidroxilo, alquilo C_1-C_4 , haloalquilo C_1-C_4 , alcoxi C_1-C_4 , fenoxi, fenil-alcoxi C_1-C_4 , metilenodioxi, difluorometilenodioxi, $-COR^{b1}$, $-CO_2R^{b1}$, $-SO_2R^{b1}$, $-SO_2NR^{b1}R^{b2}$, $-CONR^{b1}R^{b2}$, $-NR^{b1}R^{b2}$, heteroarilo de 5 a 6 miembros y heterociclilo de 5 a 6 miembros opcionalmente sustituido con oxo, en que cada R^{b1} y R^{b2} se selecciona independientemente entre H y alquilo C_1-C_4 u opcionalmente R^{b1} y R^{b2} , cuando están unidos a un átomo de nitrógeno, se combinan para formar un anillo de 4 a 6 miembros; y cada R^c , cuando está presente, se selecciona independientemente entre halo, hidroxilo y alcoxi C_1-C_2 .

En algunas realizaciones, R^1 se selecciona entre alquilo C_1-C_8 , cicloalquilo C_3-C_8 , heterocicloalquilo de 4 a 7 miembros, fenilo o heteroarilo de 5 a 6 miembros, en que cada R^1 está opcionalmente sustituido con 1-3 R^a . R^2 es fenilo, que está opcionalmente sustituido con 1-5 R^b . R^3 se selecciona entre alquilo C_1-C_4 , cicloalquilo C_3-C_4 o heterocicloalquilo de 4 a 7 miembros, en que cada R^3 está opcionalmente sustituido con 1-2 R^c . R^4 es H y X es H o F.

En algunas realizaciones, cada R^a , cuando está presente, es independientemente halo, CN, alquilo C_1-C_4 , alcoxi C_1-C_4 , $-COR^{a1}$, $-CO_2R^{a1}$, $-SO_2R^{a1}$, $-SO_2NR^{a1}R^{a2}$ o $-CONR^{a1}R^{a2}$, en cada R^{a1} y R^{a2} es independientemente H o alquilo C_1-C_4 . Alternativamente R^{a1} y R^{a2} , cuando están unidos a un átomo de nitrógeno se combinan opcionalmente para formar un anillo de 4 a 6 miembros. Cada R^b , cuando está presente, es independientemente halo, CN, alquilo C_1-C_4 , alcoxi C_1-C_4 , $-COR^{b1}$, $-CO_2R^{b1}$, $-SO_2R^{b1}$, $-SO_2NR^{b1}R^{b2}$, $-CONR^{b1}R^{b2}$, $-NR^{b1}R^{b2}$, heteroarilo de 5 a 6 miembros o heterociclilo de 5 a 6 miembros opcionalmente sustituido con oxo, en que cada R^{b1} y R^{b2} es independientemente H o alquilo C_1-C_4 . Alternativamente, R^{b1} y R^{b2} , cuando están unidos a un átomo de nitrógeno, están opcionalmente combinados para formar un anillo de 4 a 6 miembros. Cada R^c , cuando está presente, es independientemente halo o alcoxi C_1-C_2 .

En algunas realizaciones, X es H.

En algunas realizaciones, R^1 es alquilo C_3-C_4 , cicloalquilo C_3-C_5 o heterocicloalquilo de 4 a 6 miembros, en que cada R^1 está opcionalmente sustituido con 1-3 R^a .

En algunas realizaciones, R^1 es fenilo o heteroarilo de 5 a 6 miembros, en que cada R^1 está opcionalmente sustituido con 1-3 R^a .

En algunas realizaciones, R^1 es alquilo C_3-C_4 , ciclo alquilo C_3-C_5 o heterocicloalquilo de 4 a 6 miembros.

En algunas realizaciones, R^1 es heterocicloalquilo de 4 a 6 miembros, opcionalmente sustituido con 1-2 R^a seleccionado entre alquilo C_1-C_4 , alcoxi C_1-C_4 , $-COR^{a1}$, $-CO_2R^{a1}$, $-SO_2R^{a1}$, $-SO_2NR^{a1}R^{a2}$ y $-CONR^{a1}R^{a2}$, en que cada R^{a1} y R^{a2} es independientemente H o alquilo C_1-C_4 .

En algunas realizaciones, R^1 es ciclobutilo, isopropilo, isobutilo, 1-metoxipropan-2-ilo, ciclopentilo, ciclohexilo, 4-tetrahidropiraniilo, 1-(metilsulfonil)piperidin-4-ilo, 1-(metoxycarbonil)piperidin-4-ilo, 4,4-difluorociclohexilo, fenilo, 2-piridilo, 3-piridilo, 3-isoxazolilo, 5-isoxazolilo, o 1-metil-3-pirazolilo..

En algunas realizaciones, R^2 está opcionalmente sustituido con 1-2 R^b .

En algunas realizaciones, R^2 es fenilo, 3-metilfenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2,5-difluorofenilo, 3,5-difluorofenilo, 3-clorofenilo, 3-metoxifenilo, 3-(3-oxazolidin-2-onil)fenilo, 3-(2-metil-1-imidazil)fenilo, 3-(1-pirazolil)fenilo o 3-(1,2,4-triazol-1-il)fenilo..

En algunas realizaciones, R^3 es alquilo C_1-C_4 , alcoxi C_1-C_4 -alquilo o cicloalquilo C_3-C_4 .

En algunas realizaciones, R^3 es metilo, etilo, propilo, ciclopropilo, ciclobutilo o 2-metoximetilo.

En algunas realizaciones, R^3 es metilo.

Los compuestos o sales farmacéuticamente aceptables descritos en la presente memoria descriptiva pueden tener cualquier combinación de los grupos R^1 , R^2 , R^3 , R^4 , R^a , R^{a1} , R^{a2} , R^b , R^{b1} , R^{b2} , R^c y X anteriormente citados. Las realizaciones seleccionadas para R^2 , por ejemplo, pueden estar combinadas con cualquiera de las realizaciones seleccionadas citadas para R^1 que, a su vez, pueden estar combinadas con cualquiera de las realizaciones seleccionadas citadas para R^3 .

En algunas realizaciones, por ejemplo, R^1 es alquilo C_3-C_8 ; R^3 es cicloalquilo C_3-C_4 o heterocicloalquilo de 4 a 7 miembros; y R^2 es fenilo. En otras realizaciones, R^1 es heterocicloalquilo de 4 a 7 miembros o heteroarilo de 5 a 6 miembros que está opcionalmente sustituido con alquilo C_1-C_4 , $-CO_2R^{a1}$, $-SO_2NR^{a1}R^{a2}$ o $-SO_2R^{a1}$; R^3 es cicloalquilo C_3-C_4 o heterocicloalquilo de 4 a 7 miembros y R^2 es fenilo. Todavía en otras realizaciones, R^1 es cicloalquilo C_3-C_8 o fenilo, R^3 es cicloalquilo C_3-C_4 o heterocicloalquilo de 4 a 7 miembros y R^2 es fenilo.

En otras realizaciones, R^1 es alquilo C_3-C_8 ; R^3 es alquilo C_1-C_4 ; y R^2 es fenilo. Todavía en otras realizaciones, R^1 es heterocicloalquilo de 4 a 7 miembros o heteroarilo de 5 a 6 miembros que está opcionalmente sustituido con alquilo C_1-C_4 , $-CO_2R^{a1}$ o $-SO_2R^{a1}$; R^3 es alquilo C_1-C_4 ; y R^2 es fenilo. Todavía en otras realizaciones, R^1 es cicloalquilo C_3-C_8 o fenilo;

R^3 es alquilo C_1-C_4 y R^2 es fenilo.

En algunas realizaciones, R^1 es alquilo C_3-C_8 ; R^3 es cicloalquilo C_3-C_4 o heterocicloalquilo de 4 a 7 miembros y R^2 es fenilo sustituido con 1-2alcoxi C_1-C_4 o halo. Todavía en otras realizaciones, R^1 es heterocicloalquilo de 4 a 7 miembros o heteroarilo de 5 a 6 miembros que está opcionalmente sustituido con alquilo C_1-C_4 , $-CO_2R^{a1}$ o $-SO_2R^{a1}$; R^3 es cicloalquilo C_3-C_4 o heterocicloalquilo de 4 a 7 miembros; y R^2 es fenilo sustituido con 1-2alcoxi C_1-C_4 o halo. Todavía en otras realizaciones, R^1 es cicloalquilo C_3-C_8 o fenilo; R^3 es cicloalquilo C_3-C_4 o heterocicloalquilo de 4 a 7 miembros y R^2 es fenilo sustituido con 1-2alcoxi C_1-C_4 o halo. En algunas realizaciones, R^1 es alquilo C_3-C_8 ; R^3 es alquilo C_1-C_4 y R^2 es fenilo sustituido con 1-2alcoxi C_1-C_4 o halo. En otras realizaciones, R^1 es heterocicloalquilo de 4 a 7 miembros o heteroarilo de 5 a 6 miembros que está opcionalmente sustituido con alquilo C_1-C_4 , $-CO_2R^{a1}$ o $-SO_2R^{a1}$; R^3 es alquilo C_1-C_4 y R^2 es fenilo sustituido con 1-2alcoxi C_1-C_4 o halo. En otras realizaciones, R^1 es cicloalquilo C_3-C_8 o fenilo; R^3 es alquilo C_1-C_4 y R^2 es fenilo sustituido con 1-2alcoxi C_1-C_4 o halo.

En algunas realizaciones, R^1 es alquilo C_3-C_8 ; R^3 es cicloalquilo C_3-C_4 o heterocicloalquilo de 4 a 7 miembros y R^2 es fenilo sustituido con heteroarilo de 5 a 6 miembros o heterociclilo de 5 a 6 miembros, opcionalmente sustituido con oxo. En otras realizaciones, R^1 es heterocicloalquilo de 4 a 7 miembros o heteroarilo de 5 a 6 miembros que está opcionalmente sustituido con alquilo C_1-C_4 , $-CO_2R^{a1}$ o $-SO_2R^{a1}$; R^3 es cicloalquilo C_3-C_4 o heterocicloalquilo de 4 a 7 miembros; y R^2 es fenilo sustituido con heteroarilo de 5 a 6 miembros o heterociclilo de 5 a 6 miembros, opcionalmente sustituido con oxo. En otras realizaciones, R^1 es cicloalquilo C_3-C_8 o fenilo; R^3 es cicloalquilo C_3-C_4 o heterocicloalquilo de 4 a 7 miembros y R^2 es fenilo sustituido con heteroarilo de 5 a 6 miembros o heterociclilo de 5 a 6 miembros opcionalmente sustituido con oxo.

En algunas realizaciones, R^1 es alquilo C_3-C_8 ; R^3 es alquilo C_1-C_4 y R^2 es fenilo sustituido con heteroarilo de 5 a 6 miembros o heterociclilo de 5 a 6 miembros opcionalmente sustituido con oxo. En otras realizaciones, R^1 es heterocicloalquilo de 4 a 7 miembros o heteroarilo de 5 a 6 miembros que está opcionalmente sustituido con alquilo C_1-C_4 , $-CO_2R^{a1}$ o $-SO_2R^{a1}$; R^3 es alquilo C_1-C_4 y R^2 es fenilo sustituido con heteroarilo de 5 a 6 miembros o heterociclilo de 5 a 6 miembros opcionalmente sustituido con oxo. En otras realizaciones, R^1 es cicloalquilo C_3-C_8 o fenilo; R^3 es alquilo C_1-C_4 y R^2 es fenilo sustituido con heteroarilo de 5 a 6 miembros o heterociclilo de 5 a 6 miembros opcionalmente sustituido con oxo.

En algunas realizaciones, R^1 es alquilo C_3-C_8 ; R^3 es cicloalquilo C_3-C_4 o heterocicloalquilo de 4 a 7 miembros y R^2 es fenilo sustituido con CN, alquilo C_1-C_4 , $-COR^{b1}$, $-CO_2R^{b1}$, $-SO_2R^{b1}$, $-CO_2NR^{b1}R^{b2}$, $-CONR^{b1}R^{b2}$ o $-NR^{b1}R^{b2}$. En otras realizaciones, R^1 es heterocicloalquilo de 4 a

7 miembros o heteroarilo de 5 a 6 miembros que está opcionalmente sustituido con alquilo C₁-C₄, -CO₂R^{a1} o -SO₂R^{a1}; R³ es cicloalquilo C₃-C₄ o heterocicloalquilo de 4 a 7 miembros y R² es fenilo sustituido con CN, alquilo C₁-C₄, -COR^{b1}, -CO₂R^{b1}, -SO₂R^{b1}, -CONR^{b1}R^{b2} o NR^{b1}R^{b2}. En otras realizaciones, R¹ es cicloalquilo C₃-C₈ o fenilo; R³ es cicloalquilo C₃-C₄ o heterocicloalquilo de 4 a 7 miembros y R² es fenilo sustituido con CN, alquilo C₁-C₄, -COR^{b1}, -CO₂R^{b1}, -SO₂R^{b1}, -CO₂NR^{b1}R^{b2} o -NR^{b1}R^{b2}.

En algunas realizaciones, R¹ es alquilo C₃-C₈; R³ es alquilo C₁-C₄ y R² es fenilo sustituido con CN, alquilo C₁-C₄, -COR^{b1}, -CO₂R^{b1}, -SO₂R^{b1}, -CONR^{b1}R^{b2} o -NR^{b1}R^{b2}. En otras realizaciones, R¹ es heterocicloalquilo de 4 a 7 miembros o heteroarilo de 5 a 6 miembros que está opcionalmente sustituido con alquilo C₁-C₄, -CO₂R^{a1} o -SO₂R^{a1}; R³ es alquilo C₁-C₄ y R² es fenilo sustituido con CN, alquilo C₁-C₄, -COR^{b1}, -CO₂R^{b1}, -SO₂R^{b1}, -CONR^{b1}R^{b2} o NR^{b1}R^{b2}. En otras realizaciones, R¹ es cicloalquilo C₃-C₈ o fenilo; R³ es alquilo C₁-C₄ y R² es fenilo sustituido con CN, alquilo C₁-C₄, -COR^{b1}, -CO₂R^{b1}, -SO₂R^{b1}, -CO₂NR^{b1}R^{b2}, -NR^{b1}R^{b2} o -CONR^{a1}R^{a2}.

En algunas realizaciones R¹ es isopropilo; R² está opcionalmente sustituido con 1-2 R^b; y R³ es metilo.

En algunas realizaciones, R¹ es un heterocicloalquilo de 4 a 6 miembros, opcionalmente sustituido con 1-2 R^a seleccionado entre alquilo C₁-C₄, alcoxi C₁-C₄, -COR^{a1}, -CO₂R^{a1}, -SO₂R^{a1}, -SO₂NR^{a1}R^{a2}, y -CONR^{a1}R^{a2}, en que cada uno de R^{a1} y R^{a2} puede ser independientemente H o alquilo C₁-C₄; R² está opcionalmente sustituido con 1-2 R^b; y R³ es metilo.

En algunas realizaciones, R¹ es fenilo o heteroarilo de 5 a 6 miembros, en que cada R¹ está opcionalmente sustituido con 1-3 R^a; R² está opcionalmente sustituido con 1-2 R^b y R³ es metilo.

X puede ser H en cualquiera de las realizaciones anteriormente expuestas. En otras realizaciones, X puede ser F en cualquiera de las realizaciones anteriormente expuestas. Todavía adicionalmente, los compuestos proporcionados en la presente memoria descriptiva con una estereoquímica identificada (indicada como R o S, o con representaciones de enlaces discontinuos u ondulados) se entenderá por el experto en la técnica que están sustancialmente exentos de otros isómeros (por ejemplo, al menos 80%, 90%, 95% hasta 100% exento de otro isómero).

En algunas realizaciones, el compuesto se selecciona entre:

(S)-3-isopropil-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;

(S)-5-fluoro-3-isopropil-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;

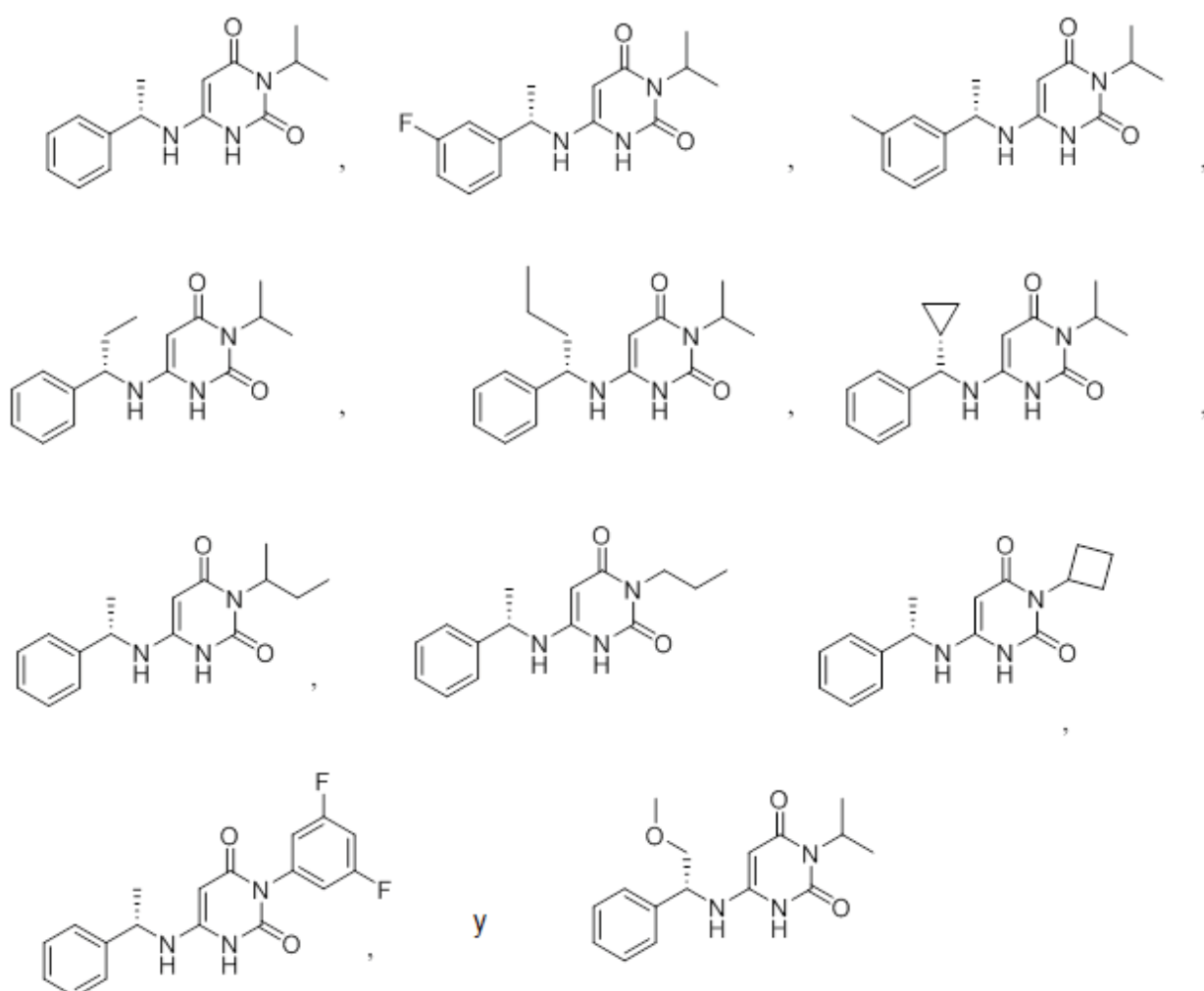
(S)-5-bromo-3-isopropil-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;

- (S)-6-((1-(3-clorofenil)etil)amino)-5-fluoro-3-isopropilpirimidino-2,4(1H,3H)-diona;
- (S)-6-((1-(3,5-difluorofenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
- (S)-6-((ciclopropil(fenil)metil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
- (S)-6-((ciclopropil(3-metoxifenil)metil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
- 5 (S)-6-((ciclobutil(fenil)metil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
- (S)-6-((1-(3-fluorofenil)etil)amino)-3-(tetrahidro-2H-piran-4-il)pirimidino-2,4(1H,3H)-diona;
- (S)-6-((1-(3-metoxifenil)etil)amino)-3-(tetrahidro-2H-piran-4-il)pirimidino-2,4(1H,3H)-diona;
- 6-(((S)-1-feniletil)amino)-3-(tetrahidrofuran-3-il)pirimidino-2,4(1H,3H)-diona;
- (S)-3-(1-(metilsulfonil)piperidin-4-il)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
- 10 metil (S)-4-(2,6-dioxo-4-((1-feniletil)amino)-3,6-dihidropirimidin-1(2H)-il)piperidino-1-carboxilato;
- 3-((R)-sec-butil)-6-(((S)-1-(3-metoxifenil)etil)amino)pirimidino-2,4(1H,3H)-diona;
- (S)-6-((1-feniletil)amino)-3-(piridin-3-il)pirimidino-2,4(1H,3H)-diona;
- (S)-3-(isoxazol-3-il)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
- 15 (S)-6-((1-(3-(1H-pirazol-1-il)fenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
- (S)-3-isopropil-6-((1-(3-metoxifenil)etil)amino)pirimidino-2,4(1H,3H)-diona;
- (S)-3-isopropil-6-((1-(2-metoxifenil)etil)amino)pirimidino-2,4(1H,3H)-diona;
- (S)-3-isopropil-6-((1-fenilpropil)amino)pirimidino-2,4(1H,3H)-diona;
- (S)-3-isopropil-5-metil-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
- 20 (S)-6-((1-(2-fluorofenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
- (S)-6-((1-(3-fluorofenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
- (S)-6-((1-(3-clorofenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
- (S)-6-((1-(4-fluorofenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
- (S)-5-fluoro-3-isopropil-6-((1-fenilpropil)amino)pirimidino-2,4(1H,3H)-diona;
- 25 (S)-5-fluoro-6-((1-(3-fluorofenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
- (S)-5-fluoro-3-isopropil-6-((1-(3-metoxifenil)etil)amino)pirimidino-2,4(1H,3H)-diona;
- (S)-6-((1-(2,5-difluorofenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
- (S)-6-((1-(3-bromofenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
- (S)-3-etil-6-((1-fenilpropil)amino)pirimidino-2,4(1H,3H)-diona;
- 30 (S)-3-ciclopropil-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
- (S)-6-((1-feniletil)amino)-3-(piridin-2-il)pirimidino-2,4(1H,3H)-diona;
- (S)-3-(1-metil-1H-pirazol-3-il)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
- (S)-3-(isoxazol-5-il)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
- (S)-6-((1-(3-(1H-1,2,4-triazol-1-il)fenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
- 35 (S)-3-isopropil-6-((1-(3-(2-metil-1H-imidazol-1-il)fenil)etil)amino)pirimidino-2,4(1H,3H)-diona;

- (S)-3-isopropil-6-((1-(3-(2-oxooxazolidin-3-il)fenil)etil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-3-ciclohexil-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-3-fenil-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-3-etil-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 5 (S)-3-metil-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-6-((1-feniletil)amino)-3-propilpirimidino-2,4(1H,3H)-diona;
 (S)-3-(3,5-difluorofenil)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-3-isopropil-6-((1-(m-tolil)etil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-6-((1-(4-fluorofenil)propan-2-il)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
 10 (R)-3-isopropil-6-((2,2,2-trifluoro-1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 3-((R)-1-(benciloxi)propan-2-il)-6-(((S)-1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 3-((R)-1-idroxiopropan-2-il)-6-(((S)-1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-3-isopropil-6-((1-(3-(trifluorometil)fenil)etil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-2-(1-((1-isopropil-2,6-dioxi-1,2,3,6-tetrahidropirimidin-4-il)amino)etil)benzonitrile
 15 (S)-3-bencil-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-3-(2,6-difluorofenil)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-6-((1-(2,6-difluorofenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
 (S)-3-isopropil-6-((1-(piridin-4-il)propan-2-il)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-6-((1-(4-(benciloxi)fenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
 20 (S)-6-((1-(4-idroxiifenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
 (R)-6-((2-(benciloxi)-1-feniletil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
 (S)-3-(6-metilpiridin-2-il)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-3-(2,2-difluoroetil)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-6-((1-(benzo[d][1,3]dioxol-5-il)etil)amino)-3-(2,2,2-trifluoroetil)pirimidino-2,4(1H,3H)-diona;
 25 (S)-3-isopropil-6-((1-(o-tolil)etil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-3-ciclobutil-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-3-isopropil-6-((1-(2-(trifluorometil)fenil)etil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-3-(1-metilciclopropil)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-6-((1-(3-(1H-imidazol-1-il)fenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
 30 (S)-6-((1-feniletil)amino)-3-(piridazin-4-il)pirimidino-2,4(1H,3H)-diona;
 (S)-4-((1-feniletil)amino)-2H-[1,5'-bipirimidino]-2,6(3H)-diona;
 (S)-6-((1-feniletil)amino)-3-(pirazin-2-il)pirimidino-2,4(1H,3H)-diona;
 (S)-3-isopropil-6-((1-(piridin-3-il)etil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-3-(1-metil-1H-pirazol-4-il)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 35 (S)-3-isopropil-6-((1-fenilbutil)amino)pirimidino-2,4(1H,3H)-diona;

- 6-(((S)-1-feniletil)amino)-3-((R)-tetraidro-2H-piran-3-il)pirimidino-2,4(1H,3H)-diona;
 (S)-3-ciclopentil-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-3-isopropil-6-((2-metil-1-fenilpropil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-3-(4,4-difluorociclohexil)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 5 (S)-3-(pentan-3-il)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-3-(1-benzoilpiperidin-4-il)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-3-isopropil-6-((4-fenilbutan-2-il)amino)pirimidino-2,4(1H,3H)-diona;
 metil (S)-2-(2,6-dioxo-4-((1-feniletil)amino)-3,6-dihidropirimidin-1(2H)-il)acetato
 (S)-3-isopropil-6-((1-fenilpropan-2-il)amino)pirimidino-2,4(1H,3H)-diona;
 10 3-(((S)-1-(benciloxi)propan-2-il)-6-(((S)-1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 3-(((S)-1-idroxiopropan-2-il)-6-(((S)-1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 (R)-6-((2-idroxi-1-feniletil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
 6-(((S)-1-feniletil)amino)-3-((R)-1,1,1-trifluoropropan-2-il)pirimidino-2,4(1H,3H)-diona;
 6-(((S)-1-feniletil)amino)-3-((S)-1,1,1-trifluoropropan-2-il)pirimidino-2,4(1H,3H)-diona;
 15 6-(((S)-1-feniletil)amino)-3-(4,4,4-trifluorobutan-2-il)pirimidino-2,4(1H,3H)-diona;
 (S)-6-((1-feniletil)amino)-3-(2,2,2-trifluoroetil)pirimidino-2,4(1H,3H)-diona;
 (S)-3-(terc-butil)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-3-(2-metoxietil)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 6-(((S)-1-fenilpropil)amino)-3-((S)-1,1,1-trifluoropropan-2-il)pirimidino-2,4(1H,3H)-diona;
 20 3-((R)-1-ciclopropiletil)-6-(((S)-1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 3-((S)-1-ciclopropiletil)-6-(((S)-1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-6-((ciclobutil(fenil)metil)amino)-3-etilpirimidino-2,4(1H,3H)-diona;
 (S)-6-((1-(benzo[d][1,3]dioxol-5-il)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
 (S)-6-((1-(benzo[d][1,3]dioxol-5-il)etil)amino)-3-etilpirimidino-2,4(1H,3H)-diona;
 25 (S)-6-((1-fenilpropil)amino)-3-(2,2,2-trifluoroetil)pirimidino-2,4(1H,3H)-diona;
 (S)-3-(ciclopropilmetil)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 (S)-6-((ciclopropil(fenil)metil)amino)-3-(2,2,2-trifluoroetil)pirimidino-2,4(1H,3H)-diona;
 (S)-6-((ciclobutil(fenil)metil)amino)-3-(2,2,2-trifluoroetil)pirimidino-2,4(1H,3H)-diona;
 (S)-3-(1,3-dihidroxiopropan-2-il)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona;
 30 6-(((S)-1-(4-fluorofenil)propan-2-il)amino)-3-((S)-1,1,1-trifluoropropan-2-il)pirimidino-
 2,4(1H,3H)-diona;
 (S)-6-((1-(3-idroxifenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
 6-((1-(2-idroxifenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
 (S)-6-((1-feniletil)amino)-3-(1-(trifluorometil)ciclopropil)pirimidino-2,4(1H,3H)-diona;
 35 (S)-3-(3,5-difluorofenil)-6-((1-(4-fluorofenil)propan-2-il)amino)pirimidino-2,4(1H,3H)-diona;

- (S)-6-((1-(2,2-difluorobenzo[d][1,3]dioxol-5-il)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
- (S)-6-((1-(2-clorofenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
- (S)-3-isopropil-6-((1-(4-metoxifenil)etil)amino)pirimidino-2,4(1H,3H)-diona;
- 5 (S)-6-((ciclopropil(fenil)metil)amino)-3-etilpirimidino-2,4(1H,3H)-diona;
- (S)-6-((1-(3-clorofenil)etil)amino)-3-etilpirimidino-2,4(1H,3H)-diona;
- (S)-3-etil-6-((1-(3-(trifluorometil)fenil)etil)amino)pirimidino-2,4(1H,3H)-diona;
- (S)-3-(ciclopropilmetil)-6-((1-(3-fluorofenil)etil)amino)pirimidino-2,4(1H,3H)-diona;
- (S)-3-(ciclopropilmetil)-6-((1-(3-(trifluorometil)fenil)etil)amino)pirimidino-2,4(1H,3H)-diona;
- 10 (S)-6-((1-(3-clorofenil)etil)amino)-3-(ciclopropilmetil)pirimidino-2,4(1H,3H)-diona;
- (S)-5-cloro-6-((1-(2,2-difluorobenzo[d][1,3]dioxol-5-il)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
- (S)-6-((1-(3-fluorofenil)etil)amino)-3-propilpirimidino-2,4(1H,3H)-diona;
- (S)-6-((1-(3-clorofenil)etil)amino)-3-propilpirimidino-2,4(1H,3H)-diona;
- 15 (S)-3-propil-6-((1-(3-(trifluorometil)fenil)etil)amino)pirimidino-2,4(1H,3H)-diona;
- (S)-3-ciclobutil-6-((1-(4-fluorofenil)etil)amino)pirimidino-2,4(1H,3H)-diona;
- (S)-6-((1-(2-hidroxifenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona;
- (S)-6-((1-(3,4-difluorofenil)etil)amino)-3-etilpirimidino-2,4(1H,3H)-diona;
- 3-((S)-sec-butil)-6-(((S)-1-(4-fluorofenil)etil)amino)pirimidino-2,4(1H,3H)-diona;
- 20 (S)-6-((1-(4-fluorofenil)etil)amino)-3-propilpirimidino-2,4(1H,3H)-diona; y
- (S)-3-(6-fluoropiridin-2-il)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona, o una sales farmacéuticamente aceptables del cualquiera de los anteriores.
- En algunas realizaciones, el compuesto se selecciona entre



o una sales farmacéuticamente aceptables de los mismos.

El compuesto o sales farmacéuticamente aceptables descritos en la presente memoria descriptiva (I) pueden ser preparados mediante cualquier método adecuado. Los compuestos pueden ser preparados, por ejemplo, mediante la vía indicada en la Figura 1. Como se muestra en la Figura 1A, una pirimidino-triona (v) puede ser sintetizada a través de la condensación de una urea (iii) con un malonato (iv). La urea (iii) puede ser preparada a través de reacción de una amina (i) con un cianato apropiado (ii). La pirimidino-triona (v) se hace derivar con un grupo lábil adecuado (Lg) para proporcionar el intermedio (vi). El grupo lábil puede ser, pero no está limitado a ello, un halógeno como un cloruro o yoduro. Un intermedio halogenado (vi) puede ser preparado a partir de pirimidino-trionas mediante métodos como los descritos por Brown (*The Chemistry of Heterocyclic Compounds, The Pyrimidinas*, John Wiley & Sons, 2009). Los intermedios (vi) pueden ser convertidos en compuestos de fórmula (I) a través de reacción con aminas (vii). Algunas aminas quirales pueden ser preparadas a partir de una cetona o aldehído (ix) como se muestra en la Figura

1B; una sulfinil-imina (xii) derivada de la cetona o aldehído se puede hacer reaccionar con un reactivo de Grignard (xiii) para proporcionar una amina quiral (vii). Un experto en la técnica apreciará que los compuestos descritos en la presente memoria descriptiva pueden ser preparados a través de otros métodos, como los descritos por LaRock (*Comprehensive*
5 *Organic Transformations: A Guide to Functional Group Preparations*, Wiley, 1999).

IV. Composiciones

También se proporciona una composición farmacéutica que contiene un compuesto o sales farmacéuticamente aceptables descritas en la presente memoria descriptiva y un excipiente farmacéuticamente aceptable. Las composiciones pueden ser útiles para tratar
10 cardiomiopatía hipertrófica en seres humanos y otros sujetos.

Las composiciones farmacéuticas para la administración de los compuestos o sales farmacéuticamente aceptables descritos en la presente memoria descriptiva pueden ser presentadas convenientemente en formas de dosificación unitaria y pueden ser preparadas mediante cualquiera de los métodos conocidos en farmacia y suministro de fármacos. Todos
15 los métodos incluyen la etapa de poner el ingrediente activo en asociación con un vehículo que contenga uno o más ingredientes accesorios. En general, las composiciones farmacéuticas se preparan poniendo de forma uniforme e íntima el ingrediente activo en asociación con un vehículo líquido o vehículo sólido finamente dividido o ambos y, seguidamente, si es necesario, conformar el producto en forma de la formulación deseada.
20 En la composición farmacéutica, el ingrediente activo es generalmente incluido en una cantidad suficiente para producir el efecto deseado tras una contractilidad del miocardio (es decir, para disminuir la contractilidad sistólica a menudo supranormal en la HCM) y mejorar la relajación ventricular izquierda en la diástole. Esta relajación mejorada puede aliviar los síntomas en una cardiomiopatía hipertrófica y otras etiologías de disfunción diastólica.
25 Puede mejorar también los efectos de la disfunción diastólica provocando un impedimento del flujo sanguíneo coronario, mejorando este último como agente adjunto en la angina de pecho y cardiopatía isquémica. También puede conferir beneficios sobre la remodelación ventricular izquierda sanitaria en HCM y otras causas de hipertrofia ventricular izquierda debido al volumen crónico o sobrecarga de presión, por ejemplo cardiopatía valvular o
30 hipertensión sistémica.

Las composiciones farmacéutica que contienen el ingrediente activo pueden estar en una forma adecuada para un uso oral, por ejemplo, en forma de comprimidos, píldoras, pastillas, suspensiones acuosas o aceitosas, polvos o gránulos dispersables, emulsiones, cápsulas duras o blandas, jarabes, elixires, soluciones, parches bucales, geles orales, gomas de
35 mascar, comprimidos masticables, polvo efervescente y comprimidos efervescentes. Las

composiciones destinadas para un uso oral pueden ser preparada mediante cualquier método conocido en la técnica para la fabricación de composiciones farmacéutica y estas composiciones pueden contener uno o más agentes seleccionados entre el grupo que consiste en agentes edulcorantes, agentes para dar sabor, agentes colorantes, antioxidantes y agentes conservantes con el fin de proporcionar preparaciones farmacéuticamente decorosas y de sabor agradable. Los comprimidos contienen el ingrediente activo mezclado con excipientes no tóxicos farmacéuticamente aceptables que sean adecuados para la fabricación de comprimidos. Estos excipientes pueden ser, por ejemplo, diluyentes inertes como celulosa, dióxido de silicio, óxido de aluminio, carbonato de calcio, carbonato de sodio, glucosa, manitol, sorbitol, lactosa, fosfato de calcio o fosfato de sodio; agentes de granulación y disgregantes, por ejemplo, almidón de maíz o ácido algínico; agentes aglutinantes, por ejemplo, PVP, celulosa, PEG, almidón, gelatina o goma arábica y agentes lubricantes, por ejemplo, estearato de magnesio, ácido esteárico o talco. Los comprimidos pueden estar sin revestir o pueden ser revestidos, de forma entérica o de otra manera, mediante técnicas conocidas para retrasar la disgregación y absorción en el tracto gastrointestinal y proporcionar así una acción sostenida a lo largo de un periodo más prolongado. Por ejemplo, puede ser empleado un material de retraso en el tiempo como monoestearato de glicerilo o diestearato de glicerilo. Pueden estar revestidos también para formar comprimidos terapéuticos osmóticos para una liberación controlada.

Las formulaciones para un uso oral pueden ser presentadas también en forma de cápsulas de gelatina dura en las que el ingrediente activo está mezclado con un diluyente sólido inerte, por ejemplo, carbonato de calcio, fosfato de calcio o caolín, o cápsulas de gelatina blanda en las que el ingrediente activo es mezclado con agua o un medio de aceite, por ejemplo, aceite de cacahuete, parafina líquida o aceite de oliva. Adicionalmente, las emulsiones pueden ser preparadas con un ingrediente no miscible con agua como aceites y estabilizada con tensioactivos como mono-diglicéridos, ésteres de PEG y similares.

Las suspensiones acuosas contienen los materiales activos mezclados con excipientes adecuados para la fabricación de suspensiones acuosas. Estos excipientes son agentes suspensores, por ejemplo, carboximetilcelulosa de sodio, metilcelulosa, hidroxipropilmetilcelulosa, alginato de sodio, polivinilpirrolidona, goma de tragacanto y goma arábica; agentes dispersantes o humectantes que pueden ser un fosfátido que se produce de forma natural, por ejemplo, lecitina o productos de condensación de un óxido de alquilino con ácidos grasos, por ejemplo, poli(estearato de etileno) o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo, heptadecaetilenoxicetanol o productos de condensación de óxido de etileno con ésteres

parciales derivados de ácidos grasos y un hexitol como poli(monooleato de oxietileno-sorbitol) o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo, poli(monooleato de etileno-sorbitan). Las suspensiones acuosas pueden contener también uno o más conservantes, por ejemplo, p-hidroxibenzoato de etilo o n-propilo, uno o más agentes colorantes, uno o más agentes para dar sabor y uno o más agentes edulcorantes, como sacarosa o sacarina.

Las suspensiones en aceite pueden ser formuladas poniendo en suspensión el ingrediente activo en un aceite vegetal, por ejemplo, aceite de cacahuete, aceite de oliva, aceite de sésamo o aceite de coco o en un aceite mineral como parafina líquida. Las suspensiones aceitosas pueden contener un agente espesante, por ejemplo, cera de abejas, parafina dura o alcohol cetílico. Pueden ser añadidos agentes edulcorantes como los anteriormente expuestos y agentes para dar sabor, para proporcionar una preparación oral de sabor agradable. Estas composiciones pueden ser conservadas mediante la adición de un antioxidante como ácido ascórbico.

Los polvos y gránulos dispersables adecuados para la preparación de una suspensión acuosa mediante la adición de agua proporcionan el ingrediente activo mezclado con un agente dispersante o humectante, agente suspensor y uno o más conservantes. Los agentes dispersantes o humectantes adecuados están ilustrados por los ya mencionados con anterioridad. Pueden estar presentes también excipientes adicionales, por ejemplo, agentes edulcorantes, para dar sabor y colorantes.

Las composiciones farmacéutica descritas en la presente memoria descriptiva pueden estar también en la forma de emulsiones de aceite en agua. La fase aceitosa puede ser un aceite vegetal, por ejemplo, aceite de oliva o aceite de cacahuete o un aceite mineral, por ejemplo, parafina líquida o mezclas de estos. Los agentes emulsionantes adecuados pueden ser gomas que se producen de forma natural, por ejemplo, goma arábica o goma de tragacanto, fosfátidos que se producen de forma natural, por ejemplo, soja, lecitina y ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo, monooleato de sorbitán y productos de condensación de dichos ésteres parciales con óxido de etileno, por ejemplo, poli(monooleato de oxietileno-sorbitán). Las emulsiones pueden contener también agentes edulcorantes y para sabor.

Los jarabes y elixires pueden ser formulados con agentes edulcorantes, por ejemplo glicerol, propilenglicol, sorbitol o sacarosa. Estas formulaciones pueden contener también un emoliente, un conservante y agentes para dar sabor y colorantes. Pueden ser preparadas soluciones orales en combinación, por ejemplo, con ciclodextrina, PEG y tensioactivos.

Las composiciones farmacéuticas pueden estar en la forma de una suspensión estéril

acuosa inyectable u oleaginosa. Esta suspensión puede ser formulada según la técnica conocida usando los agentes dispersantes o humectantes adecuados y agentes suspensores que se han mencionado con anterioridad. La preparación inyectable esterilizada puede ser también una solución o suspensión inyectable esterilizada en un diluyente o disolvente no tóxico farmacéuticamente aceptable, por ejemplo, como una solución de 1,3-butanodiol. Entre los vehículos y disolventes aceptables que pueden ser empleados están agua, solución de Ringer y solución isotónica de cloruro de sodio. Además, los aceites fijos esterilizados son convencionalmente empleados como un medio disolvente o suspensor. Para estos fines puede ser empleado cualquier aceite fijo suave que incluye mono- o di-glicéridos sintéticos. Además, pueden ser usados ácidos grasos como ácido oleico en la preparación de productos inyectables.

Los compuestos o sales farmacéuticamente aceptables descritos en la presente memoria descriptiva pueden ser administrados también en la forma de supositorios para la administración rectal del fármaco. Estas composiciones pueden ser preparadas mezclando el fármaco con un excipiente no irritante adecuado que sea sólido a temperaturas ordinarias pero líquido a la temperatura rectal y que, por lo tanto, se fundirán en el recto para liberar el fármaco. Estos materiales incluyen manteca de cacao y polietilenglicoles. Adicionalmente, los compuestos o sales farmacéuticamente aceptables pueden ser administrados a través de un suministro ocular por medio de soluciones o ungüentos. Todavía adicionalmente, el suministro transdermal de los compuestos o sales farmacéuticamente aceptables objeto de la invención se puede realizar por medio de parches ióntoforéticos y similares. Para un uso tópico, se emplean cremas, ungüentos, gelatinas, soluciones o suspensiones, etc. que contienen los compuestos o sales farmacéuticamente aceptables descritos en la presente memoria descriptiva. Como se usa en la presente memoria descriptiva, una aplicación tópica está previsto que incluya el uso de líquidos de lavado bucal y para hacer gárgaras.

Los compuestos o sales farmacéuticamente aceptables descritos en la presente memoria descriptiva pueden estar acoplados también a un vehículo que es un polímero adecuado para vehículos para fármacos dirigibles a diana. Estos polímeros incluyen polivinilpirrolidona, copolímero de pirano, polihidroxi-propil-metacrilamida-fenol, polihidroxietil-aspartamido-fenol o poli(óxido de etileno)-polilisina sustituido con residuos de palmitol. Además, los compuestos o sales farmacéuticamente aceptables descritos en la presente memoria descriptiva pueden estar acoplados a un vehículo que es un polímero biodegradable útil para conseguir una liberación controlada de un fármaco como poli(ácido acético), poli(ácido glicólico), copolímeros de poli(ácido láctico y glicólico), poliepsilon-caprolactona, poli(ácido hidroxibutílico), poliortoésteres, poliacetales, polihidropiranos, policianoacrilatos y

copolímeros de bloques reticulados o anfipáticos de hidrogeles. Los polímeros y matrices polímeras semiimpermeables pueden ser formados como artículos conformados como válvulas, pinzas, tubos, prótesis y similares.

V. Métodos para tratar trastornos cardíacos

5 Las mutaciones que conducen a HCM provocan una perturbación significativa en los mecanismos de miosina. Estas mutaciones ejercen sus efectos a través de distintos mecanismos dependiendo de sus ubicaciones en el gen de miosina. Las mutaciones de HCM bien estudiadas, R403Q y R453C, están ubicadas en secciones diferentes del dominio motor y provocan distintas perturbaciones mecánicas que conducen al resultado común
10 de una producción aumentada de fuerza. Aunque no se desean vinculaciones teóricas particulares, se cree que los compuestos farmacéuticamente aceptables descritos en la presente memoria descriptiva se pueden unir directamente a las proteínas sarcómeras mutantes y corregir su función aberrante, tanto en cis (afectando a la misma función específica) como trans (alterando una función complementaria). Como tal, pueden
15 proporcionar un beneficio terapéutico para pacientes de HCM contrarrestando la relajación hipercontráctil y/o impedida asociada a esta enfermedad.

También se proporciona un método para tratar cardiomiopatía hipertrófica (HCM) o un trastorno cardíaco que tiene una o más características patofisiológicas asociadas con la HCM. El método incluye administrar a un sujeto que lo necesita una cantidad eficaz de un
20 compuesto o sales farmacéuticamente aceptables descrito en la presente memoria descriptiva.

Los compuestos de la invención y sus sales farmacéuticamente aceptables pueden alterar el historial natural de la HCM y otras enfermedades en lugar de meramente paliar los síntomas. Los mecanismos que confieren un beneficio clínico a pacientes de HCM se pueden extender
25 a pacientes con otras formas de enfermedad cardíaca que comparten una patofisiología similar, con o sin una influencia genética demostrable. Por ejemplo, un tratamiento eficaz para HCM, mejorando la relajación ventricular durante la diástole, puede ser eficaz también en una población más amplia caracterizada por una disfunción diastólica. Los compuestos de la invención y sus sales farmacéuticamente aceptables pueden dirigir a diana
30 específicamente las causas de raíz de los estados o actuar tras otras trayectorias en dirección descendente. Consecuentemente, los compuestos de la invención o sus sales farmacéuticamente aceptables pueden conferir también una ventaja a pacientes que sufren un fallo cardíaco diastólico con una fracción de eyección conservada, enfermedad cardíaca isquémica, angina de pecho o cardiomiopatía restrictiva. Los compuestos de la invención o
35 sus sales farmacéuticamente aceptables pueden favorecer también la remodelación

ventricular conveniente de una hipertrofia ventricular izquierda debida a sobrecarga de volumen o presión; por ejemplo, regurgitación mitral crónica, estenosis aórtica crónica o hipertensión sistémica crónica; conjuntamente con terapias dirigidas a corregir o aliviar la causa primaria de la sobrecarga de volumen o presión (reparación/sustitución de válvulas, terapia antihipertensora eficaz). Reduciendo las presiones de relleno ventriculares izquierdas, los compuestos podrían reducir el riesgo de edema pulmonar y fallo respiratorio. Al reducir o eliminar la regurgitación mitral funcional y/o rebajar las presiones auriculares izquierdas, se puede reducir el riesgo de fibrilación auricular paroxismal o permanente y reducir con esto el riesgo que conllevan las complicaciones tromboembólicas arteriales que incluyen, pero sin limitación, el derrame cerebral embólico arterial. Al reducir o eliminar la obstrucción del flujo de salida dinámico y/o ventricular izquierdo estático, se puede reducir la probabilidad de necesitar una terapia de reducción del tabique atrial, ya sea quirúrgica o percutánea, con sus riesgos acompañados de complicaciones a corto y largo plazo. Los compuestos o sus sales farmacéuticamente aceptables pueden reducir la gravedad del estado isquémico crónico asociado con la HCM y reducir así el riesgo de la muerte cardíaca repentina (SDC) o su equivalente en pacientes con cardioversores-desfibriladores implantables (descargas ICD frecuentes y/o repetidas) y/o la necesidad de medicaciones antiarrítmicas potencialmente tóxicas. Los compuestos o sales farmacéuticamente aceptables podrían ser útiles para reducir o eliminar la necesidad de medicaciones simultáneas con sus toxicidades potenciales acompañadas, interacciones entre fármacos y/o efectos secundarios. Los compuestos o sales farmacéuticamente aceptables pueden reducir la fibrosis de miocardio intersticial y/o ralentizar el progreso, detener o invertir la hipertrofia ventricular izquierda.

Dependiendo de la enfermedad que va a ser tratada y del estado del sujeto, los compuestos o sales farmacéuticamente aceptables descritos en la presente memoria descriptiva pueden ser administrados por vía oral, parenteral (por ejemplo, intramuscular, intraperitoneal, intravenosa, ICV, inyección o infusión intracisternal, inyección subcutánea o implante), mediante implantación (por ejemplo, cuando el compuesto o sales farmacéuticamente aceptables está acoplado a un dispositivo de endoprótesis), mediante pulverización para inhalación o vías de administración nasal, vaginal, rectal, sublingual o tópica y pueden ser formulados solos o conjuntamente, en formulaciones unitarias de dosificación adecuadas que contienen vehículos no tóxicos farmacéuticamente aceptables, adyuvantes y vehículos apropiados para cada vía de administración.

En el tratamiento o prevención de estados que requieren una relajación ventricular mejorada durante la diástole, un nivel de dosificación apropiado será generalmente de

aproximadamente 0,001 a 100 mg por kg de peso corporal del paciente por día, que puede ser administrado en dosis únicas o múltiples. En algunas realizaciones, el nivel de dosificación será de aproximadamente 0,01 a aproximadamente 25 mg/kg por día; en algunas realizaciones, de aproximadamente 0,05 a aproximadamente 10 mg/kg por día. Un nivel de dosificación adecuado puede ser de aproximadamente 0,01 a 25 mg/kg por día, aproximadamente 0,05 a 10 mg/kg por día, o aproximadamente 0,1 a 5 mg/kg por día. Dentro de este intervalo la dosificación puede ser de 0,005 a 0,05, 0,05 a 0,5 o 0,5 a 5,0 mg/kg por día. En algunas realizaciones, para una administración oral, las composiciones se proporcionan en la forma de comprimidos que contienen 1,0 a 1.000 miligramos del ingrediente activo, particularmente 1,0, 5,0, 10,0, 15,0, 20,0, 25,0, 50,0, 75,0, 100,0, 150,0, 200,0, 250,0, 300,0, 400,0, 500,0, 600,0, 750,0, 800,0, 900,0, y 1.000,0 miligramos del ingrediente activo para el ajuste sintomático de la dosificación al paciente que va a ser tratado. Los compuestos o sales farmacéuticamente aceptables pueden ser administrados en un régimen de 1 a 4 veces por día, en algunas realizaciones, una o dos veces al día.

Sin embargo, se entenderá que el nivel de dosis específico y la frecuencia de dosificación para cualquier paciente particular se puede variar y dependerá de una diversidad de factores que incluyen la actividad del compuesto específico o sales farmacéuticamente aceptables empleado, la estabilidad metabólica y la duración de la acción de ese compuesto o sales farmacéuticamente aceptables, la edad, peso corporal, características hereditarias, salud general, sexo y dieta del sujeto, así como el modo y tiempo de administración, ritmo de excreción, combinación de fármacos y la gravedad del estado particular para el sujeto que experimenta la terapia.

Los compuestos y composiciones proporcionados en la presente memoria descriptiva pueden ser usados en combinación con otros fármacos y son usados en el tratamiento, prevención, supresión o mejora de enfermedades o estados para los que son útiles los compuestos y composiciones proporcionados en la presente memoria descriptiva. Estos otros fármacos pueden ser administrados, mediante una vía y en una cantidad comúnmente usados para los mismos, de forma simultánea o secuencial con un compuesto o composición proporcionado en la presente memoria descriptiva. Cuando un compuesto o composición proporcionado en la presente memoria descriptiva es usado de forma simultánea con uno o más de otros fármacos, se prefiere una composición farmacéutica que contenga estos otros fármacos además del compuesto o composición proporcionado en la presente memoria descriptiva. Consecuentemente, las composiciones farmacéuticas proporcionadas en la presente memoria descriptiva incluyen las que contienen también uno o más ingredientes activos o agentes terapéuticos, además de un compuesto o composición

proporcionado en la presente memoria descriptiva. Los agentes activos adicionales adecuados incluyen, por ejemplo: terapias que retardan el progreso de un fallo cardíaco o infra-regulan la estimulación neurohormonal del corazón e intentan prevenir la remodelación cardíaca (por ejemplo, inhibidores de ACE, bloqueadores de receptores de angiotensina (ARB), bloqueadores β , antagonistas de receptores de aldosterona o inhibidores endopeptidasa neural); terapias que mejoran la función cardíaca estimulando la contractilidad cardíaca (por ejemplo, agentes inotrópicos positivos como el agonista β -adrenérgico dobutamina o el inhibidor de fosfodiesterasa milrinona); y terapias que reducen la precarga cardíaca (por ejemplo, diuréticos como furosemida), o la carga posterior (vaso dilata-
10 dores de cualquier clase que incluyen, pero sin limitación, bloqueadores de canales de calcio, inhibidores de fosfodiesterasa, antagonistas de receptores de endotelina, inhibidores de renina o moduladores de miosina de músculos lisos). La relación en peso del compuesto proporcionado en la presente memoria descriptiva respecto al segundo ingrediente activo se puede hacer variar y dependerá de la dosis eficaz de cada ingrediente. Generalmente, se
15 usará una dosis eficaz de cada uno.

VI. Ejemplos

Abreviaturas:

ac: acuoso

BBr₃: tribromuro de boro

20 CH₂Cl₂: diclorometano

CH₃CN: acetonitrilo

CH₃OH: metanol

DIAD: azodicarboxilato de diisopropilo

DIEA: diisopropil-etilamina

25 DMF: dimetilformamida

DMSO: dimetil-sufóxido

equiv.: equivalentes

Et₃N: trietilamina

Et₂O: dietil-éter

30 EtOH: etanol

FeSO₄: sulfato ferroso

h: hora(s)

HCl: cloruro de hidrógeno

H₂O: agua

35 K₂CO₃: carbonato de potasio

KHSO₄: bisulfato de potasio

KNCO: isocianato de potasio

LiBr: bromuro de litio

MgSO₄: sulfato de magnesio

5 ml: mililitro

MW: microondas (reacción hecha en un reactor de microondas)

NaCl: cloruro de sodio

NaH: hidruro de sodio

NaHCO₃: bicarbonato de sodio

10 NaOEt: etóxido de sodio

NaOH: hidróxido de sodio

NaOMe: metóxido de sodio

Na₂SO₄: sulfato de sodio

NH₄Cl: cloruro de amonio

15 NMP: n-metil-pirrolidinona

pH: -log [H⁺]

POCl₃: tricloruro de fósforo

PPTS: p-toluenosulfonato de piridinio

RP-HPLC: cromatografía líquida a presión elevada de fase inversa

20 TA: temperatura ambiente

SEMCl: cloruro de 2-(trimetilsilil)etoximetilo

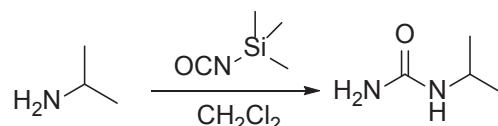
TEBAC: cloruro de trietilbencilamonio

TFA: ácido trifluoroacético

THF: tetrahidrofurano

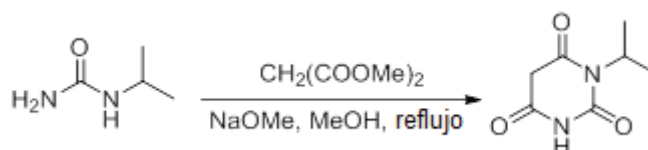
25 TLC: cromatografía de capa fina

Ejemplo 1. Preparación de (S)-3-Isopropil-6-((1-feniletil) amino)pirimidino-2,4(1H,3H)-diona.

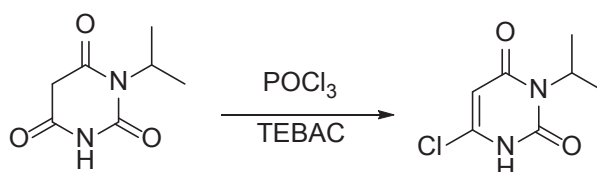


30 Compuesto 1.1. Isopropilurea. A una solución agitada de isopropilamina (15,3 g, 0,258 moles, 1,0 equiv.) en CH₂Cl₂ (200 ml) bajo argón a 200 °C se añadió gota a gota isocianato de trimetilsililo (30 g, 0,26 moles, 1,0 equiv.). La mezcla resultante se dejó alcanzar temperatura ambiente y se agitó durante una noche. Después de enfriar a 0 °C, se añadió gota a gota CH₃OH (100 ml). La solución resultante se agitó durante 2 horas (h) a temperatura ambiente y seguidamente se concentró bajo presión reducida. El residuo en

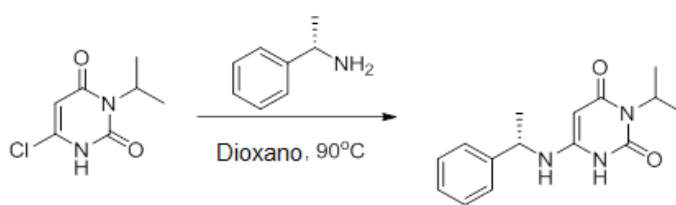
bruto se cristalizó en CH₃OH:Et₂O (1:20) para proporcionar 15,4 g (58%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES+) 103 (M+H)⁺.



Compuesto 1.2. Ácido 1-isopropil-barbitúrico. A una solución agitada de 1.1 (14,4 g, 0,14 moles, 1,00 equiv.) en CH₃OH (500 ml) se añadieron malonato de dimetilo (19,55 g, 1,148 moles, 1,05 equiv.) y metóxido de sodio (18,9 g, 0,35 moles, 2,50 equiv.). La mezcla resultante se agitó durante una noche a 65 °C. Después de enfriar a temperatura ambiente y seguidamente a 0 °C, el pH se ajustó cuidadosamente a 3 usando HCl concentrado acuoso. La mezcla resultante se concentró bajo presión reducida. El residuo se recogió en EtOH (200 ml) y se filtró. El filtrado se concentró bajo presión reducida y el residuo se purificó por cromatografía de columna de gel de sílice usando CH₂Cl₂/CH₃OH (20:1) como eluyente para producir 16,8 g (50 %) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES+) 171 (M+H)⁺.¹ ¹H-RMN (300 MHz, d₆-DMSO): δ 11,19 (s, 1H), 4,83 (m, 1H), 3,58 (s, 2H), 1,32 (d, J = 6. 0 Hz, 6H).

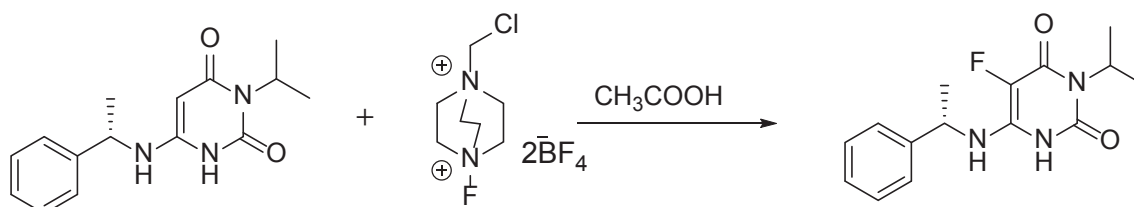


Compuesto 1.3. 6-cloro-3-isopropilpirimidino-2,4(1H,3H)-diona. A un matraz de fondo redondo de 100 ml que contenía compuesto 1.2 (114 g, 66,99 mmoles, 1,00 equiv.) bajo argón se añadieron cloruro de trietilbencilamonio (21,3 g, 93,51 mmoles, 1,40 equiv.) y POCl₃ (30 ml). La mezcla resultante se agitó durante una noche a 50 °C. Después de enfriar a temperatura ambiente, la mezcla se concentró bajo presión reducida. El residuo se disolvió en CH₂Cl₂ (150 ml) seguido de adición lenta de H₂O (100 ml). Las fases se separaron y la capa orgánica se lavó con H₂O (100 ml), se secó con Na₂SO₄ anhidro y se concentró bajo presión reducida. El residuo en bruto se purificó por cromatografía de columna de gel de sílice usando EtOAc/éter de petróleo (1:1) como eluyente para producir 5,12 g (40%) del compuesto del título en forma de un sólido amarillo claro. ¹H-RMN (300 MHz, d₆-DMSO): δ 12,22 (s, 1H), 5,88 (s, 1H), 4,95 (m, 1H), 1,34 (d, J = 6. 0 Hz, 6H).



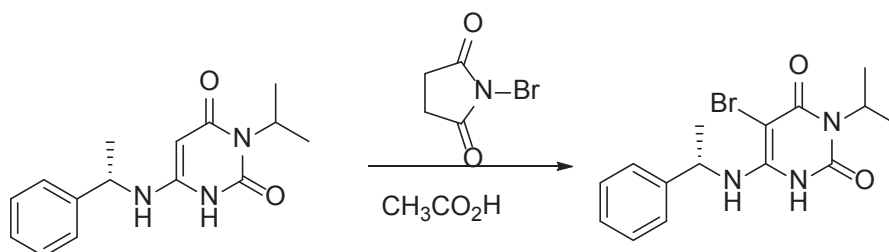
Compuesto 1. (S)-3-Isopropil-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona. A una solución de 6-cloro-3-isopropilpirimidino-2,4(1H,3H)-diona (1.3, 1,0 g, 5,31 mmol) en 1,4-dioxano (20 ml) se añadió (S)- α -metilbencilamina (Sigma-Aldrich, 1,43 g, 11,7 mmoles, 2,2 equiv). La mezcla de reacción se agitó a 80 °C durante 24 h. Después de enfriar a temperatura ambiente, la mezcla se concentró bajo presión reducida. El residuo se recogió en EtOAc (70 ml) y se lavó con HCl acuoso 1N (2x50 ml) y salmuera (40 ml). La capa orgánica se secó Na_2SO_4 anhidro y seguidamente se concentró bajo presión reducida hasta la mitad del volumen original para producir un precipitado. Se añadió hexano (20 ml) y la mezcla se agitó a temperatura ambiente. El sólido resultante se recogió por filtración, se lavó con hexano (20 ml) y se secó para producir 1,0 g (69%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES+) 274 (M+H)⁺. ¹H-RMN (400 MHz, d_6 -DMSO): δ 9,77 (s, 1H), 7,32 (m, 4H), 7,24 (m, 1H), 6. 50 (d, J = 6. 8 Hz, 1H), 4,87 (m, 1H), 4,52 (m, 1H), 4,31 (d, J=6. 8 Hz, 1H), 1,37 (m, 3H), 1,24 (m, 6H). ¹H RMN (400 MHz, CD_3OD) δ ppm 7,39-7,20 (m, 5H), 5,01 (m, 1H), 4,48 (m, 1H), 1,49 (d, J = 6. 7 Hz, 3H), 1,36 (m, 6H).

Ejemplo 2. Preparación de (S)-5-Fluoro-3-isopropil-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona (2).



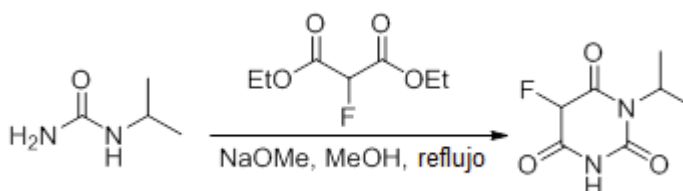
A una solución de 1 (80 mg, 0,293 mmol) en ácido acético (2,0 ml) se añadió selectflúor (104 mg, 0,293 mmoles, 1,0 equiv.). La mezcla se agitó a temperatura ambiente durante 2 h. Seguidamente se concentró bajo presión reducida. El residuo se purificó por cromatografía de columna de gel de sílice, se eluyó con 0-50% de EtOAc en hexanos para proporcionar 6 mg (7%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES+) 292 (M+H)⁺. ¹H RMN (400 MHz, CD_3OD): δ ppm 7,36-7,24 (m, 5H), 5,04-4,97 (m, 1H), 4,94-4,88 (m, 1H), 1,54 (d, J = 8,0 Hz, 3H), 1,39 (m, 6H).

Ejemplo 3. Preparación de (S)-5-Bromo-3-isopropil-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona (3).

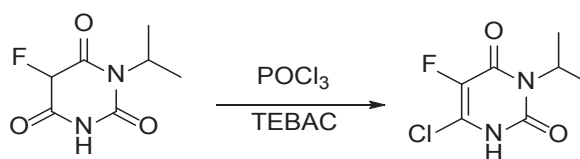


A una solución de **1** (55 mg, 0,201 mmol) en ácido acético (1,0 ml) se añadió N-bromosuccinamida (35 mg, 0,196 mmol). La mezcla se agitó a temperatura ambiente durante 1 hora. Seguidamente se concentró bajo presión reducida. El residuo se purificó por cromatografía de gel de sílice, eluyendo con 0-40% de EtOAc en hexanos para proporcionar 52 mg (74%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES+) 352. 354 (M+H, modelo de bromo)⁺. ¹H-RMN (400 MHz, CDCl₃) δ ppm 8,96 (s ancho, 1H), 7,43-7,28 (m, 5H), 5,28 (d, J = 7,4 Hz, 1H), 5,14 (m, 1H), 4,87 (m, 1H), 1,62 (d, J = 6.7 Hz, 3H), 1,45-1,39 (m, 6H).

Ejemplo 4. Preparación de (S)-6-((1-(3-Clorofenil)etil)amino)-5-fluoro-3-isopropilpirimidino-2,4(1H,3H)-diona.



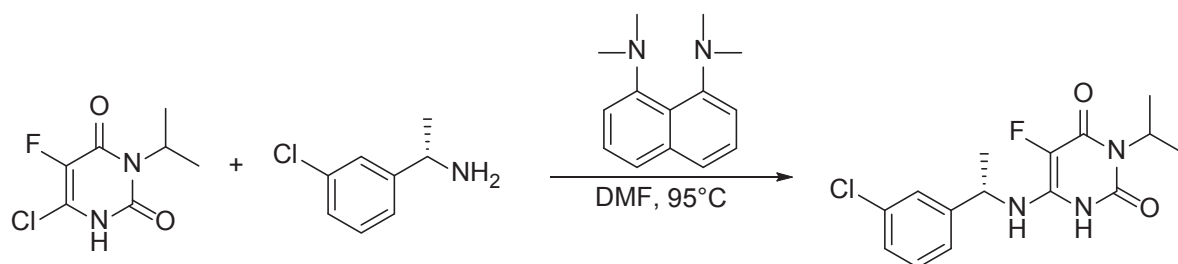
Compuesto 4.1. 5-Fluoro-1-isopropilpirimidino-2,4,6(1H,3H,5H)-triona. A un matraz de fondo redondo de 100 ml que contenía una solución de **1.1** (1,31 g, 0,013 moles, 1,00 equiv.) en CH₃OH (15 ml) se añadieron fluoromalonato de dietilo (2,41 g, 0,014 moles, 1,05 equiv.) y metóxido de sodio (1,74 g, 0,032 moles, 2,50 equiv.). El matraz de la reacción se equipó con un condensador de reflujo y se agitó durante 4 h en un baño de aceite calentado a 85 °C. La reacción se enfrió a 0 °C y se inactivó con una adición cuidadosa de HCl concentrado, ajustando a pH= 2 con la adición de HCl concentrado en exceso. La mezcla de reacción se concentró bajo presión reducida y el residuo resultante se secó durante 18 h bajo alto vacío para proporcionar 2,65 g del compuesto del título (98%). ¹H-RMN (400 MHz, CDCl₃): δ ppm 5,53 (d, J = 24,0 Hz, 1H), 4,91 (m, 2H), 1,46 (m, 6H).



Compuesto 4.2. 6-Cloro-5-fluoro-3-isopropilpirimidino-2,4(1H,3H)-diona. A un matraz de

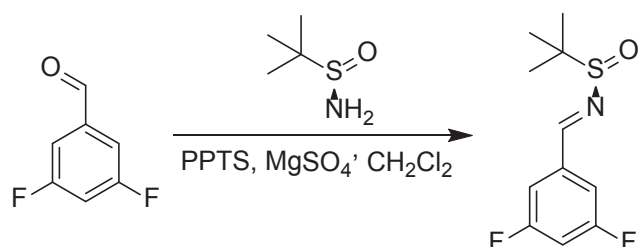
fondo redondo de 100 ml equipado con condensador a reflujo que contenía 4.1 (2,65 g, 0,014 mmoles, 1,00 equiv.) se añadieron cloruro de trietilbencilamonio (4,50 g, 0,019 mmoles, 1,40 equiv) y POCl₃ (25 ml). La mezcla de reacción se agitó durante 4 h a 50 °C y seguidamente se concentró a temperatura ambiente. La mezcla se concentró bajo presión reducida y el residuo resultante se disolvió en CH₂Cl₂ (50 ml). Se añadió agua (50 ml) lentamente y las capas se separaron. La capa orgánica se lavó una segunda vez con H₂O (100 ml), se secó sobre MgSO₄ anhidro y se concentró bajo presión reducida. El residuo resultante se purificó mediante cromatografía rápida (gel de sílice, 30% de EtOAc en hexanos) para producir 2,67 g (93%) del compuesto del título en forma de un sólido blanco.

¹H-RMN (400 MHz, CDCl₃): δ ppm 5,19-5,05 (m, 2H), 1,48 (d, J=7,04 Hz, 6H).

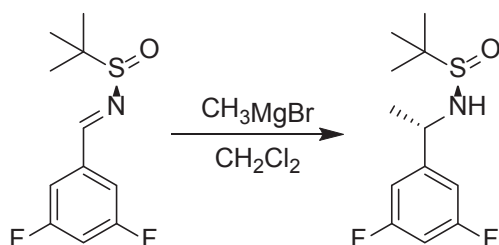


Compuesto 4. (S)-6-((1-(3-Clorofenil)etil)amino)-5-fluoro-3-isopropilpirimidino-2,4(1H,3H)-diona. A una solución de 4.2 (150 mg, 0,70 mmoles, 1 equiv) en DMF (2 ml) contenida en un recipiente a presión de paredes pesadas se añadió (S)-3-cloro-α-metilbencilamina (150 mg, 0,70 mmoles, 1,0 equiv) y una esponja de protones (190 mg, 0,90 moles, 1,25 equiv). El recipiente a presión se cerró herméticamente y la mezcla de reacción se calentó a 95 °C durante 3 h por detrás de un protector de explosiones. La mezcla de reacción se enfrió a temperatura ambiente y se concentró bajo presión reducida. El residuo resultante se purificó mediante RP-HPLC preparativa utilizando un dispositivo Shimadzu, Prominence LC-20AP sistema equipado con una columna Phenomenex Gemini-NX C18 (eluyendo con 10-90% de CH₃CN/H₂O en 30 minutos, 20 ml/min (que contenían ambos 0,1% de TFA)). Las fracciones que contenían compuesto puro se combinaron y se liofilizaron para proporcionar 30 mg (13%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES⁺) 326 (M+H)⁺. ¹H-RMN (400 MHz, CDCl₃) δ ppm 9,47 (s ancho, 1H), 7,35-7,27 (m, 3H), 7,22-7,16 (m, 1H), 5,12 (m, 1H), 4,89 (m, 1H), 4,69 (d, J = 5,9 Hz, 1H), 1,59 (d, J = 6. 7 Hz, 3H), 1,43 (m, 6H).

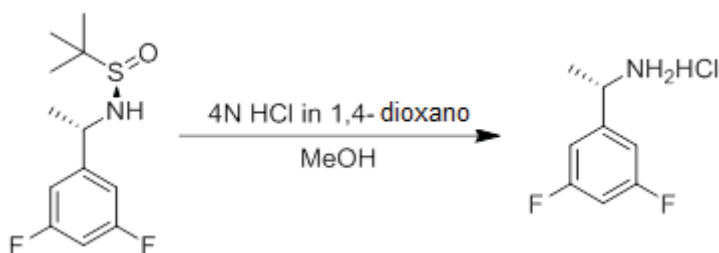
Ejemplo 5. Preparación de (S)-6-((1-(3,5-Difluorofenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona



Compuesto 5.1. ((*R,E*)-*N*-(3,5-difluorobenzilidene)-2-metilpropano-2-sulfonamida. A una solución de 3,5-difluorobenzaldehído (1,00 g, 7,04 mmoles, 1,00 equiv) en CH₂Cl₂ (20 ml) se añadió p-toluenosulfonato de piridinio (0,089 g, 0,35 mmoles, 0,05 equiv), (*R*)-(+)-2-metilpropano-2-sulfonamida (0,852 g, 7,03 mmoles, 1,00 equiv) y MgSO₄ (4,2 g, 35,00 mmoles, 5,00 equiv). La mezcla resultante se agitó durante 1 noche a temperatura ambiente. La mezcla de reacción se filtró y se concentró bajo presión reducida. El residuo resultante se purificó mediante cromatografía rápida (gel de sílice, 20% de EtOAc en éter de petróleo) para proporcionar 500 mg (29%) del compuesto del título en forma de un aceite amarillo.

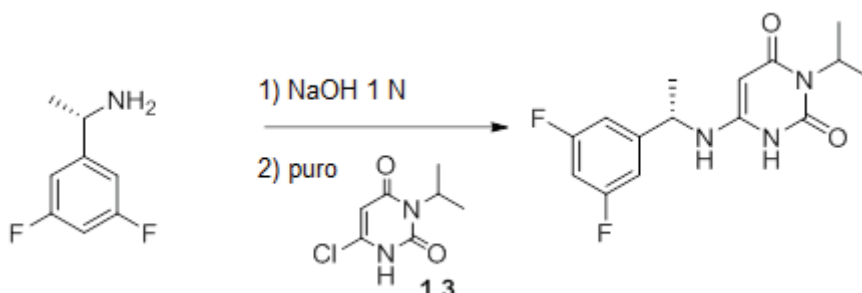


Compuesto 5.2. (*R*)-*N*-((*S*)-1-(3,5-difluorofenil)etil)-2-metilpropano-2-sulfonamida. Se añadió gota a gota bromuro de metil-magnesio (5,17 ml, 3M, 2,00 equiv) a una solución de 5.1 (1,9 g, 7,75 mmoles, 1,00 equiv) en CH₂Cl₂ (50 ml) a -48 °C. La mezcla de reacción se calentó a temperatura ambiente y se agitó durante 1 noche. La reacción se inactivó cuidadosamente con una solución acuosa saturada de NH₄Cl (20 ml). Las capas se separaron y la capa acuosa se extrajo adicionalmente con CH₂Cl₂ (3x50 ml). Las capas orgánicas combinadas se secaron sobre MgSO₄ anhidro y se concentraron bajo presión reducida para proporcionar 1,3 g (64%) del compuesto del título en forma de un aceite amarillo. ¹H RMN (300 MHz, CDCl₃): δ ppm 6.92-6.81 (m, 2H), 6.75-6.65 (m, 1H), 4.65-4.55. (m, 1H), 3.46-3.42 (m, 1H), 1.53-1.44 (m, 3H), 1.26-1.22 (m, 9H).



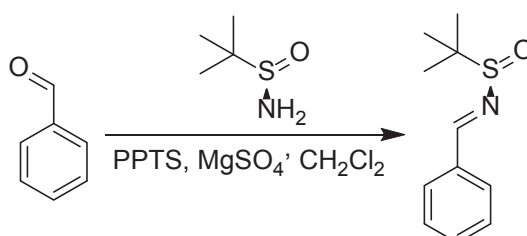
Compuesto 5.3. Hidrocloruro de (*S*)-1-(3,5-Difluorofenil)etan-1-amina. A una solución de 5.2

(1,3 g, 4,97 mmoles, 1,00 equiv) en CH₃OH (10 ml) se añadió HCl 4N en 1,4-dioxano (2,67 ml, 2,00 equiv). La mezcla de reacción se agitó durante 0,5 h a temperatura ambiente y seguidamente se concentró bajo presión reducida. El residuo resultante se disolvió en CH₃OH (3 ml) y se añadió Et₂O (300 ml). El precipitado resultante se aisló por filtración para proporcionar 0,80 g (83%) del compuesto del título. ¹H RMN (300 MHz, D₂O): δ ppm 6. 98-6. 83 (m, 3H), 4,45-4,38 (m, 1H), 1,51-1,48 (d, J = 6. 9 Hz, 3H).



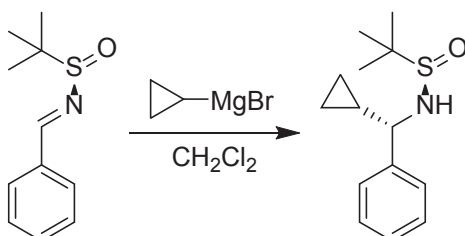
Compuesto 5. (S)-6-((1-(3,5-Difluorofenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona. Se disolvió compuesto 5.3 (50 mg, 0,32 mmoles, 1,00 equiv) en NaOH 1N (100 ml) y la mezcla resultante se agitó a 25 °C. Después de 1 h, la mezcla se extrajo con EtOAc (5x10 ml). Las capas orgánicas combinadas se secaron con Na₂SO₄ anhidro, se filtraron y se concentraron bajo presión reducida. El residuo resultante y el compuesto 1.3 (35,6 mg, 0,19 mmoles, 0,60 equiv) se combinaron. La mezcla se agitó a 100 °C durante 18 h, seguidamente se enfrió a temperatura ambiente y se concentró bajo presión reducida. El residuo resultante se purificó mediante RP-HPLC preparativa para proporcionar 28 mg (29%) del compuesto del título en forma de un sólido blanco apagado. LC/MS: m/z (ES⁺) 310 (M+H)⁺. ¹H-RMN (300 MHz, DMSO-d₆): δ ppm 9,83 (s, 1H), 7,06-7,12 (m, 3H), 6. 54 (d, J = 6. 6 Hz, 1H), 4,91-4,82 (m, 1H), 4,54-4,46 (m, 1H), 4,30 (m, 1H), 1,34 (d, J = 6. 6 Hz, 3H), 1,22 (d, J = 6. 9 Hz, 6H).

Ejemplo 6. Preparación de (S)-6-((Ciclopropil(fenil)metil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona

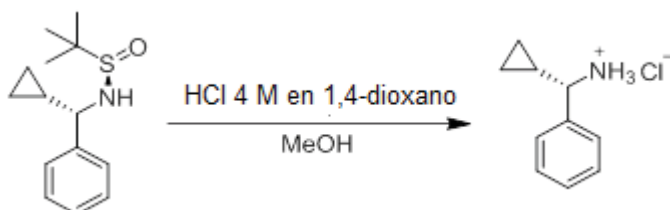


Compuesto 6.1. (R,E)-N-bencilideno-2-metilpropano-2-sulfonamida. El compuesto del título se preparó de la misma manera que 5.1 con la excepción de que se usó benzaldehído (5,0 g, 47,12 mmoles, 1,00 equiv) en lugar de 3,5-difluorobenzaldehído para proporcionar 2,8 g

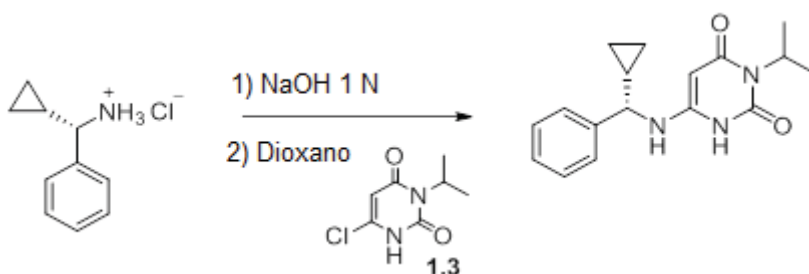
(28%) del compuesto del compuesto del título. . ^1H RMN (300 MHz, $\text{d}_6\text{-DMSO}$): δ ppm 8,62 (s, 1H), 7,89-7,87 (m, 2H), 7,55-7,49 (m, 3H), 1,31 (s, 9H).



Compuesto 6.2. (S)-N-((S)-Ciclopropil(fenil)metil)-2-metilpropano-2-sulfinamida. El compuesto del título se preparó usando un protocolo similar al usado para la preparación de 5.2 con la excepción de que usaron 6.1 (1,0 g, 4,78 mmoles, 1,00 equiv) y bromuro de ciclopropil-magnesio (9,6 ml, 1M, 2,00 equiv) en lugar de 5.1 y bromuro de metil-magnesio para proporcionar 0,5 g (35%) del compuesto del título en forma de un aceite amarillo. ^1H RMN (300 MHz, DMSO- d_6): δ ppm 7,36-7,23 (m, 5H), 3,67-3,51 (m, 2H), 1,31 (m, 10H), 0,85-0,15 (m, 4H).



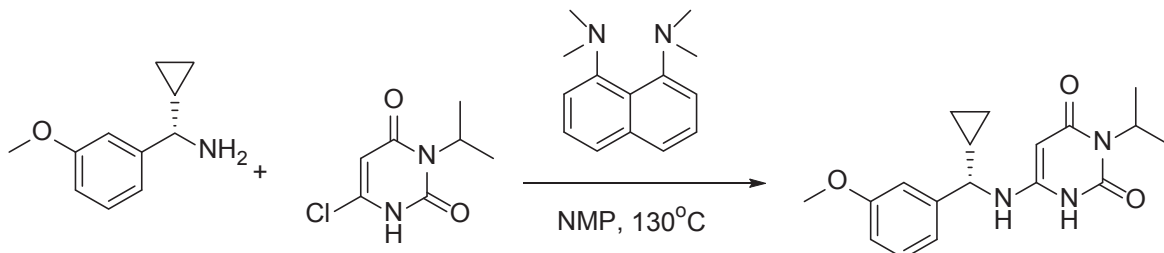
Compuesto 6.3. Hidrocloruro de (S)-Ciclopropil(fenil)metanamina. El compuesto del título se preparó usando un protocolo similar al usado para la preparación de 5.3 con la excepción de que usó 6.2 (500 mg, 1,69 mmoles, 1,00 equiv) en lugar de 5.2 para proporcionar 220 mg (88%) del compuesto del título en forma de un aceite amarillo. ^1H RMN (300 MHz, $\text{d}_6\text{-DMSO}$): δ ppm 7,37-7,31 (m, 5H), 3,53 (d, $J = 10,0$ Hz, 1H), 1,37-1,25 (m, 1H), 0,75-0,55 (m, 1H), 0,53-0,31 (m, 2H), 0,25-0,15 (m, 1H).



Compuesto 6. (S)-6-((Ciclopropil(fenil)metil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona. El compuesto del título se preparó usando un procedimiento similar al usado para la preparación de 5 con la excepción de que se usó 6.3 (200 mg, 1,36 mmoles, 1,00 equiv) en lugar de 5.3 y se utilizó 1,4-dioxano como disolvente. Después de una concentración bajo

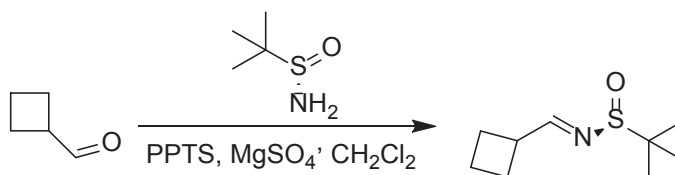
presión reducida, purificación usando una HPLC quiral (columna Phenomenex Lux 5 μ Cellulose-4,2.12*25,5 μ m) con una mezcla isocrática de EtOH:hexano (1:4) como eluyente se proporcionaron 22 mg (5%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES+) 300 (M+H)⁺. ¹H-RMN (300 MHz, DMSO-d₆) δ ppm 9,82 (s, 1H), 7,39-7,25 (m, 5H), 7,25-7,32 (m, 1H), 6. 72 (m, 1H), 4,90 (m, 1H), 4,22 (s, 1H), 3,78 (m, 1H), 1,27 (m, 6H), 1,57 (m, 1H), 0,60 (m, 1H), 0,56-0,32 (m, 2H).

Ejemplo 7. Preparación de (S)-6-((ciclopropil(3-metoxifenil)metil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona.



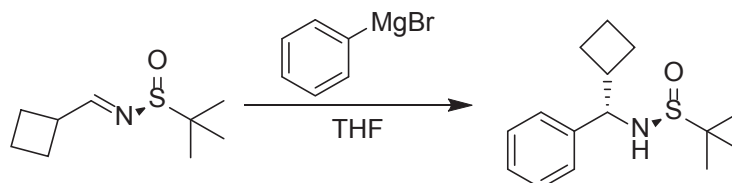
Una solución de 6-cloro-3-isopropilpirimidino-2,4(1H,3H)-diona (1,3. 50 mg, 0,265 mmol), (S)-ciclopropil-(3-metoxifenil)metilamina (Sigma-Aldrich, 104 mg, 0,587 mmol) y esponja de protones (85 mg, 0,397 mmol) en NMP (0,5 ml) se agitó a 130 °C durante 2 h. Después de enfriar a temperatura ambiente, la mezcla se purificó mediante RP-HPLC preparativa (sistema Shimadzu, Prominence LC-20AP equipado con una columna Phenomenex Gemini-NX C18) eluyendo con 20-90% de CH₃CN en H₂O (que contenían ambos 0,1% de TFA). Las fracciones que contenían compuesto puro se combinaron y se liofilizaron para proporcionar 10 mg (11%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES+) 330 (M+H)⁺. ¹H-RMN (400 MHz, CD₃OD): δ ppm 7,26 (t, J = 7,8 Hz, H), 6. 92-6. 79 (m, 3H), 5,00 (m, 1H), 3,79 (s, 3H), 3,74 (d, J = 8,6 Hz, 1H), 1,36 (d, J = 7,0 Hz, 6H), 1,23-1,13 (m, 1H), 0,68-0,60 (m, 1H), 0,58-0,50 (m, 1H), 0,50-0,42 (m, 1H), 0,41-0,34 (m, 1H).

Ejemplo 8. Preparación de (S)-6-((Ciclobutil(fenil)metil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona

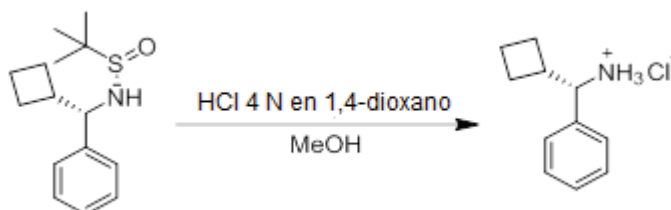


Compuesto 8.1. (S,E)-N-(ciclobutilmetileno)-2-metilpropano-2-sulfinamida. A una solución de ciclobutano carbaldehído (1,0 g, 11,89 mmoles, 1,00 equiv) en CH₂Cl₂ (10 ml) se añadieron p-toluenosulfonato de piridinio (0,143 g, 0,57 mmoles, 0,05 equiv), (S)-(-)-2-metilpropano-2-sulfinamida (1,22 g, 10,07 mmoles, 0,85 equiv) y sulfato de magnesio (7,14 g, 59,32

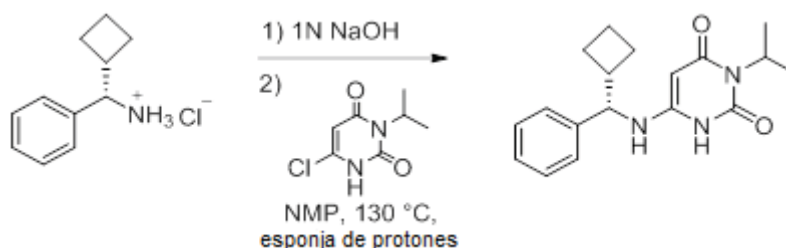
mmoles, 5,00 equiv). La mezcla resultante se agitó durante una noche a temperatura ambiente. La mezcla de reacción se filtró y se concentró bajo presión reducida. El residuo resultante se purificó mediante cromatografía rápida (gel de sílice, 30% de EtOAc en éter de petróleo) para proporcionar 2,0 g (90%) del compuesto del título en forma de un sólido blanco. ¹H RMN (400 MHz, CDCl₃) δ ppm 8,08 (d, J = 10,8 Hz, 1H), 3,36-3,32 (m, 1H), 2,25-2,16 (m, 4H), 2,03-1,90 (m, 2H), 1,15 (s, 9H).



Compuesto 8.2. (S)-N-((S)-ciclobutil(fenil)metil)-2-metilpropano-2-sulfonamida. Se añadió gota a gota bromuro de fenil-magnesio (3M en Et₂O, 15,3 ml, 2,00 equiv) a una solución de 8.1 (4,3 g, 22,96 mmoles, 1,00 equiv) en THF (40 ml). La mezcla de reacción se calentó durante 3 h a 65 °C. Seguidamente se enfrió a temperatura ambiente y se inactivó cuidadosamente con solución acuosa saturada de NH₄Cl (30 ml). La mezcla resultante se extrajo con EtOAc (3x30 ml) y las capas orgánicas combinadas se secaron con Na₂SO₄ anhidro y se concentraron bajo presión reducida para proporcionar 5,8 g (95%) del compuesto del título en forma de un sólido blanco. ¹H-RMN (300 MHz, CDCl₃) δ 7,30-7,21 (m, 5H), 4,23 (d, J = 9,6 Hz, 1H), 2,73-2,68 (m, 1H), 1,95-1,60 (m, 6H), 1,14 (s, 9H).



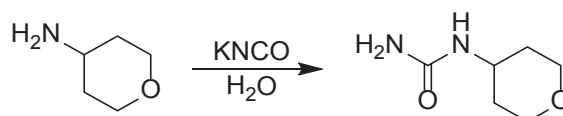
Compuesto 8.3. Hidrocloruro de (S)-Ciclobutil(fenil)metanamina. El compuesto del título se preparó usando un procedimiento similar al usado para la preparación 5.3 excepto que se usó 8.2 (5,8 g, 0,022 moles, 1,00 equiv) en lugar de 5.2 para proporcionar 3,20 g (91%) del compuesto del título en forma de un sólido blanco. ¹H RMN (300 MHz, D₂O): δ ppm 7,36-7,28 (m, 5H), 4,18 (m, 1H), 2,87-2,73 (m, 1H), 2,11-2,01 (m, 1H), 1,90-1,69 (m, 5H).



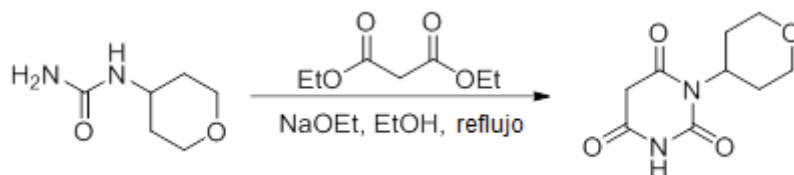
Compuesto 8. (S)-6-((Ciclobutil(fenil)metil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona. Se

disolvió el compuesto 8,3 (0,200 g, 1,24 mmoles, 1,00 equiv) en NaOH 1N (10 ml) y se agitó durante 1 h a 25 °C. La mezcla de reacción se extrajo con EtOAc (5x10 ml). Las capas orgánicas combinadas se secaron sobre Na₂SO₄ anhidro, se filtraron y se concentraron bajo presión reducida. El residuo resultante se disolvió en NMP y se combinó con 1.3 y esponja de protones y se calentó como se describió para la preparación de 7. El compuesto del título (35 mg, 9%) se aisló en forma de un sólido blanco. ¹H RMN (300 MHz, CD₃OD): δ ppm 7,38-7,26 (m, 5H), 5,08-4,97 (m, 1H), 4,25 (d, J = 6. 9 Hz, 1H), 2,68-2,58 (m, 1H), 2,19-2,13 (m, 1H), 1,98-1,83 (m, 5H), 1,36 (d, J = 6. 9 Hz, 6H).

Ejemplo 9. Preparación de (S)-6-((1-feniletil)amino)-3-(tetrahydro-2H-piran-4-il)pirimidino-2,4(1H,3H)-diona

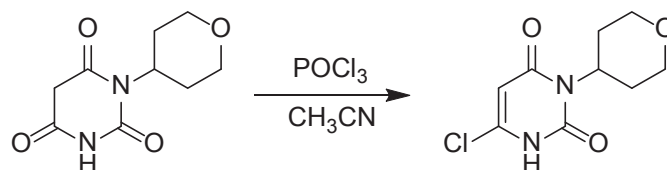


Compuesto 9.1. 1-(tetrahydro-2H-piran-4-il)urea. Una mezcla de tetrahydro-2H-piran-4-amina (5,0 g, 49,4 mmoles, 1,0 equiv) e isocianato de potasio (4,0 g, 49,5 mmoles, 1,0 equiv) se llevó a reflujo en H₂O (50 ml) durante una noche. La reacción se enfrió a temperatura ambiente y se añadió NaCl en exceso para ayudar a saturar la capa acuosa. El precipitado se aisló por filtración para proporcionar el producto deseado (1,28 g, 8,88 mmol). La capa acuosa se lavó con EtOAc (3x15 ml) y seguidamente se concentró y se sometió a destilación azeotrópica con tolueno (3x100 ml). El sólido resultante se puso en suspensión en CH₃OH:EtOAc 1:4 (100 ml) y se filtró un total de cuatro veces. Las fases orgánicas combinadas se concentraron bajo presión reducida y se combinaron con el precipitado aislado para proporcionar 5,01 g (70%) del compuesto del título. LC/MS: m/z (ES⁺) 145 (M+H)⁺. ¹H-RMN (400 MHz, DMSO-d₆): δ 6. 14 (d, J = 7,5 Hz, 1H), 5,47 (s, 2H), 3,85 (dt, J = 11,6. 3,6 Hz, 2H), 3,65-3,52 (m, 1H), 3,38 (td, J = 11,4. 2,2 Hz, 2H), 1,80-1,72 (m, 2H), 1,42-1,27 (m, 2H).

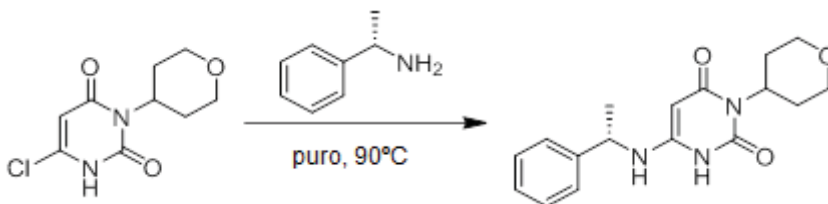


Compuesto 9.2. 1-(tetrahydro-2H-piran-4-il)pirimidino-2,4,6(1H,3H,5H)-triona. Se disolvió compuesto 9.1 (2,8 g, 19,4 mmol) en EtOH (30 ml) y malonato de dietilo (2,45 ml, 21,4 mmoles, 1,1 equiv) y se añadió NaOEt (7,55 ml, 23,3 mmoles, 1,2 equiv). La reacción se agitó a 85 °C durante una noche y seguidamente se enfrió a temperatura ambiente. La

mezcla de reacción se diluyó con H₂O (5 ml) y se añadió KHSO₄ en exceso para saturar la capa acuosa. La mezcla de reacción se extrajo con EtOAc (3x15 ml). Las capas orgánicas combinadas se secaron con MgSO₄ anhidro, se filtraron y se concentraron bajo presión reducida. El residuo resultante se purificó mediante cromatografía rápida (gel de sílice, 0-25% de CH₃OH en CH₂Cl₂) para proporcionar 1,57 g de una mezcla que contenía el compuesto del título que se usó sin purificación adicional. LC/MS: m/z (ES-) 211 (M-H)⁻.



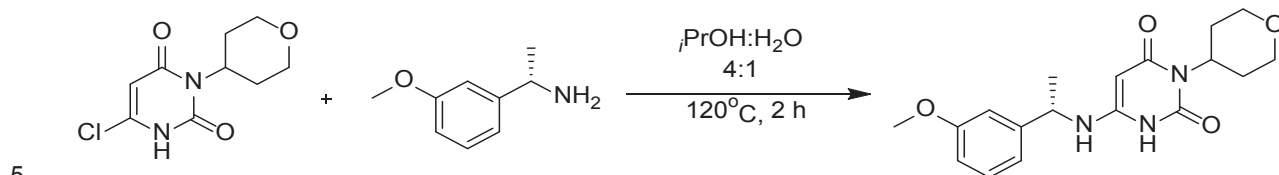
Compuesto 9.3. 6-cloro-3-(tetrahydro-2H-piran-4-il)pirimidino-2,4(1H,3H)-diona. A una solución de 9.2 (1,57 g, 7,4 mmoles, 1 equiv) en CH₃CN (15 ml) se añadió POCl₃ (0,551 ml, 5,9 mmoles, 0,8 equiv). La mezcla de reacción se agitó a 80 °C durante una noche. Se añadió una parte alícuota adicional de POCl₃ (0,4 equiv) y la mezcla de reacción se agitó a 80 °C durante 3 h. Se añadieron partes alícuotas adicionales de POCl₃ (0,4 equiv) después de 3 h y 5 h de agitación a 80 °C. La mezcla de reacción seguidamente se agitó a 90 °C durante 1 h. La reacción se enfrió a temperatura ambiente, se concentró, se removi6 con Et₂O (15 ml) y se sometió a decantación. El residuo resultante se aclaró con Et₂O (15 ml) y se sedimentó hasta que el Et₂O se sedimentó transparente. El residuo resultante se puso cuidadosamente en suspensión en CH₃OH (10 ml) y se filtró. El filtrado se concentró para obtener una mezcla de material de partida y el compuesto del título (~85% puro, 1,6 g). LC/MS: m/z (ES-) 229 (M-H)⁻.



Compuesto 9. (S)-6-((1-feniletil)amino)-3-(tetrahydro-2H-piran-4-il)pirimidino-2,4(1H,3H)-diona. Una mezcla de 9.3 (0,15 g, 0,65 mmoles, 1 equiv) y (S)-(-)-α-metilbencilamina (470 mg, 3,88 mmoles, 6,0 equiv) se agitó durante una noche a 90 °C. La mezcla de reacción se enfrió a temperatura ambiente y el residuo resultante se purificó mediante RP-HPLC preparativa (0-40% de CH₃CN en H₂O en 30 minutos) seguido de una segunda purificación en una placa de TLC preparatoria (200 μm) (7% de CH₃OH en CH₂Cl₂) para proporcionar 23 mg (11%) del compuesto del título. LC/MS: m/z (ES+) 316 (M+H)⁺. ¹H RMN (400 MHz, DMSO-d₆): δ ppm 10,23 (s, 1H), 7,40-7,32 (m, 4H), 7,31-7,17 (m, 1H), 6,93 (s, 1H), 4,84-

4,71 (m, 1H), 4,56-4,43 (m, 1H), 4,35 (s, 1H), 3,93-3,78 (m, 2H), 3,28 (t, J = 12,1 Hz, 2H), 2,63-2,39 (m, 2H), 1,40 (d, J = 6.7 Hz, 3H), 1,35-1,16 (m, 2H).

Ejemplo 10. Preparación de de (S)-6-((1-(3-metoxifenil)etil)amino)-3-(tetrahidro-2H-piran-4-il)pirimidino-2,4(1H,3H)-diona (10).

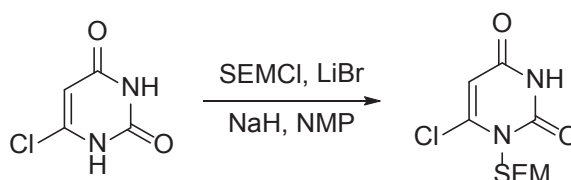


A una solución de 9.3 (0,58 g, 0,25 mmol) en una mezcla de 2-propanol y H₂O (4:1, 1 ml) se añadió (S)-1-(3-metoxifenil)-etilamina (0,113 g, 0,75 mmoles, 3,0 equiv). La mezcla de reacción se calentó a 120 °C durante 2 h. Después de enfriar, la mezcla de reacción se concentró bajo presión reducida, se disolvió en CH₃OH y se filtró. El filtrado se purificó mediante RP-HPLC preparativa (20-100% de CH₃CN en H₂O en 40 minutos a 25 ml/minuto) para proporcionar 18 mg (21%) del compuesto del título en forma de un sólido blanco apagado. . LC/MS: m/z (ES+) 346 (M+H)⁺. ¹H RMN (400 MHz, acetona-d₆) δ 8,90 (s, 1H), 7,15 (dd, J = 8,3. 8,1 Hz, 1H), 6. 88 (s, 1H), 6. 86 (d, J = 8,3 Hz, 1H), 6. 68 (d, J = 8,1 Hz, 1H), 6. 15 (s, 1H), 4,74 (m, 1H), 4,48 (m, 1H), 4,35 (s, 1H), 3,82 (m, 2H), 3,68 (s, 3H), 3,2 (m, 2H), 2,55 (m, 2H) 1,44 (d, J = 6. 6 Hz, 3H) , 1,15 (m, 2H).

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Ejemplo 11. Preparación de 6-(((S)-1-feniletil)amino)-3-(tetrahydrofuran-3-il)pirimidino-2,4(1H,3H)-diona.

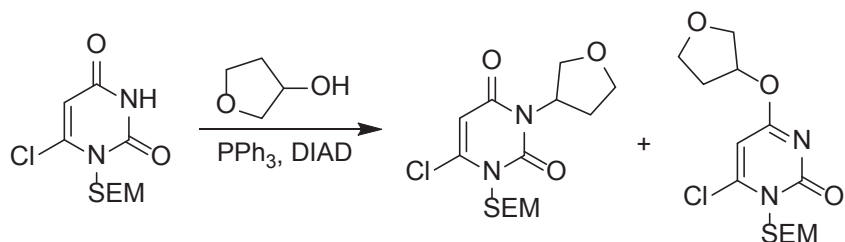


Compuesto 11.1. 6-cloro-1-((2-(trimetilsilil)etoxi)metil)pirimidino-2,4(1H,3H)-diona. A una mezcla de 6-cloro-uracilo (3,0 g, 20,47 mmoles, 1,00 equiv) y LiBr (1,78 g, 20,5 mmoles, 1,00 equiv) en NMP (70 ml) a 0 °C se añadió NaH (dispersión al 60% en aceite mineral, 0,82 g, 20,5 mmoles, 1,00 equiv). La mezcla de reacción se agitó a 0 °C durante 10 minutos y se añadió lentamente cloruro de 2-(trimetilsilil)etoximetilo (3,75 g, 22,5 mmoles, 1,1 equiv) a través de un embudo de adición. La mezcla de reacción se agitó durante una noche a temperatura ambiente y seguidamente se diluyó con EtOAc (150 ml). La mezcla se lavó con una solución acuosa saturada de NH₄Cl (50 ml), NaHCO₃ acuoso saturado (50 ml) y salmuera (50 ml). La capa orgánica se secó con Na₂SO₄ y se concentró bajo reducida para proporcionar 3,2 g (57%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z

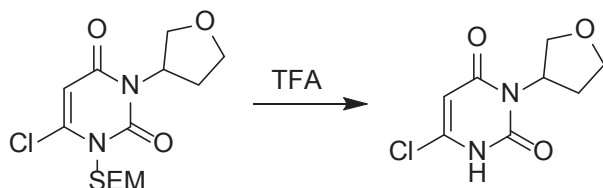
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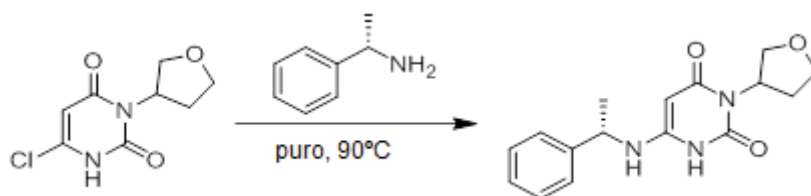
(ES+) 299 (M+Na)⁺. ¹H RMN (400 MHz, CDCl₃): δ ppm 9,00-8,80 (br-s, 1H), 5,95 (s, 1H), 5,45 (s, 2H), 3,63 (t, J = 7,0 Hz, 2H), 1,48 (t, J = 7,0 Hz, 2H), 0,01 (s, 9H).



Compuesto 11.2. 6-cloro-3-(tetrahidrofuran-3-il)-1-((2-(trimetilsilil)etoxi)metil)pirimidino-2,4(1H,3H)-diona. A una solución de 11.1 (277 mg, 1,0 mmoles, 1,00 equiv), 3-hidroxitetrahidrofurano (106 mg, 1,2 mmoles, 1,2 equiv) y trifenilfosfina (320 mg, 1,2 mmoles, 1,2 equiv) en THF (7,5 ml) a 0 °C se añadió azodicarboxilato de diisopropilo (0,240 g, 1,2 mmoles, 1,2 equiv) gota a gota. La mezcla de reacción se agitó a temperatura ambiente durante 30 minutos. La mezcla de reacción se concentró bajo presión reducida y el residuo resultante se purificó mediante RP-HPLC preparativa (2-100% de CH₃CN en H₂O) con 0,1% de tampón de ácido fórmico en 40 minutos a 25 ml/min, para proporcionar 102 mg (29%) del compuesto del título. LC/MS: m/z (ES+) 347 (M+H)⁺. ¹H RMN (400 MHz, CDCl₃) δ 5,92 (s, 1H), 5,58 (m, 1H), 5,41(s, 2H), 4,20 (m, 1H), 4,00-3,85 (m, 3H), 3,65 (t, J = 7,0 Hz, 2H), 2,35-2,20 (m, 1H), 2,20-2,08 (m, 1H), 0,95 (t, 2H), 0,01 (s, 9H); ¹³C RMN (CDCl₃) δ 160,7, 150,7, 145,6. 102,0, 74,8, 68,7, 67,9, 67,5. 51,9, 28,7, 18,0, 0,0.



Compuesto 11.3. 6-cloro-3-(tetrahidrofuran-3-il)pirimidino-2,4(1H,3H)-diona. Se disolvió compuesto 11.2 (0,50 g, 1,4 mmoles, 1,0 equiv) en ácido trifluoroacético (1 ml). La mezcla de reacción se agitó a temperatura ambiente 30 minutos y seguidamente se concentró bajo presión reducida. El residuo resultante se purificó mediante RP-HPLC preparativa (10% de CH₃CN en H₂O en 40 minutos a 25 ml/minuto para proporcionar 300 mg (96%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES+) 217 (M+H)⁺. ¹H RMN (400 MHz, DMSO-d₆): δ ppm 5,90 (s, 1H), 5,35 (m, 1H), 4,00 (m, 1H), 3,85-3,68 (m, 3H), 2,20 (m, 1H), 2,01 (m, 1H).



Compuesto 11. 6-(((S)-1-feniletil)amino)-3-(tetrahydrofuran-3-il)pirimidino-2,4(1H,3H)-diona.

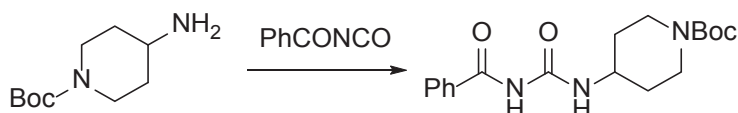
El compuesto del título se preparó usando un procedimiento similar al usado para la preparación de 9 excepto que se usó 11.3 (22 mg, 0,10 mmoles, 1,00 equiv) en lugar de 9.3

5 para proporcionar 15 mg (50%) del compuesto del título en forma de un sólido blanco.

LC/MS: m/z (ES+) 302 (M+H)⁺. ¹H RMN (400 MHz, CDCl₃): δ ppm 10,50 (1H), 7,50-7,20 (m, 5H), 5,90 (m, 1H), 5,60 (m, 1H), 4,78 (m, 1H), 4,45 (s, 1H), 4,20 (m, 1H), 4,05-3,90 (m, 2H), 3,90-3,80 (m, 1H), 2,45-2,10 (m, 2H), 1,55 (d, J = 6.7 Hz, 3H).

Ejemplo 12. Preparación de (S)-3-(1-(metilsulfonil)piperidin-4-il)-6-(1-feniletilamino)pirimidino-2,4(1H,3H)-diona.

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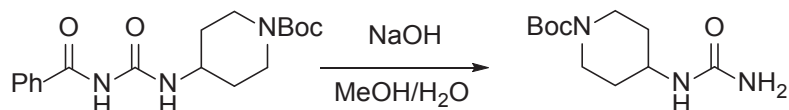


Compuesto 12.1. 4-(3-Benzoilureido)piperidino-1-carboxilato de terc-butilo. A una solución de isocianato de benzoilo (4,8 g, 32,6 mmol) en CH₂Cl₂ (180 ml) a 0 °C se añadió 4-amino-1-N-boc-piperidina (6,0 g, 30 mmol). La mezcla de reacción se agitó a temperatura ambiente

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durante 4 h y se concentró. El residuo se trató Et₂O (100 ml). El precipitado se filtró y se lavó con Et₂O para producir 5,70 g (55%) del compuesto del título en forma de un sólido blanco.

LC/MS: m/z (ES+) 337 (M+H)⁺.



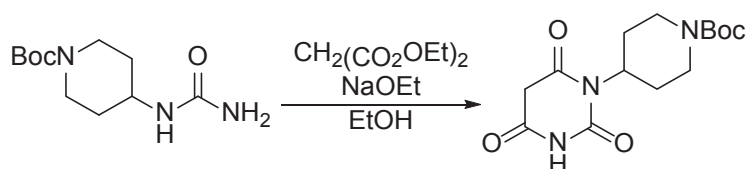
Compuesto 12.2. 4-Ureidopiperidino-1-carboxilato de terc-butilo. A una mezcla de 12.1 (5,60 g, 16,1 mmol) en CH₃OH (70 ml) y H₂O (70 ml) se añadió hidróxido de sodio (11,6 g, 290 mmol) por partes. La mezcla de reacción se agitó a temperatura ambiente durante una

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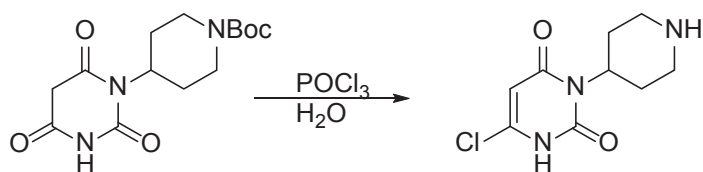
noche y seguidamente se llevó a reflujo durante 1 h. La mezcla se enfrió a temperatura ambiente y se concentró bajo presión reducida para separar CH₃OH. El precipitado se filtró, se lavó con H₂O y se secó para producir 3,2 g (82%) del compuesto del título en forma de un

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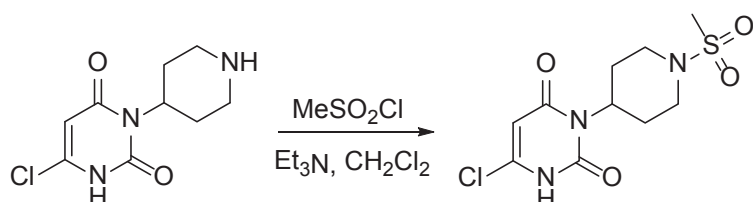
sólido blanco. LC/MS: m/z (ES+) 266 (M+Na)⁺.



Compuesto 12.3. 4-(2,4,6-Trioxo-tetrahidropirimidin-1(2H)-il)piperidino-1-carboxilato de terc-butilo. A una mezcla de 12.2 (3,63 g, 14,9 mmol), malonato de dietilo (2,6 ml, 16,5 mmoles, 1,1 equiv) y etanol anhidro (60 ml) se añadió NaOEt (21% en EtOH, 6,6 ml, 17,7 mmoles, 1,2 equiv). La mezcla se llevó a reflujo durante 14 h y se concentró. El residuo se recogió en H₂O (15 ml) y se lavó con EtOAc (2x30 ml). La capa acuosa se separó y se ajustó a pH = 5 con HCl concentrado. El precipitado se filtró, se lavó con H₂O y se secó para proporcionar 3,70 g (80%) del compuesto del título en forma de un sólido blanco apagado. LC/MS: m/z (ES+) 334 (M+Na)⁺.

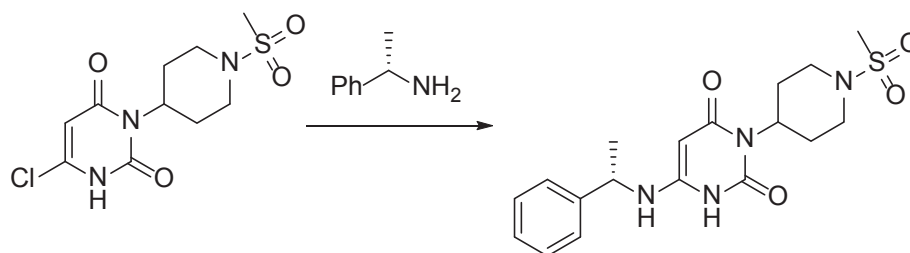


Compuesto 12.4. 6-cloro-3-(piperidin-4-il)pirimidino-2,4(1H,3H)-diona. A una mezcla de 12.3 (2,55 g, 8,19 mmol) y POCl₃ (10 ml, 100,65 mmol) se añadió H₂O (0,41 ml, 22,78 mmol) gota a gota. La mezcla se agitó a 120 °C durante 30 minutos y seguidamente se concentró. El residuo se recogió cuidadosamente en agua con hielo (20 g). A la mezcla se añadió K₂CO₃ (~8,0 g) por partes hasta que el pH era ~7. El precipitado se filtró, se lavó con H₂O (20 ml) y EtOAc (50 ml). El material resultante se secó para producir 1,45 g (77%) del compuesto del título en forma de un sólido blanco apagado. LC/MS: m/z (ES+) 230 (M+H)⁺.



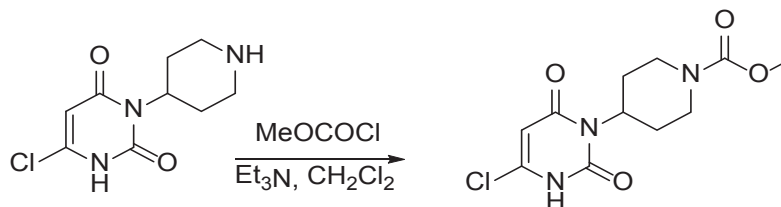
Compuesto 12.5. 6-Cloro-3-(1-(metilsulfonil)piperidin-4-il)pirimidino-2,4(1H,3H)-diona. A una mezcla de 12.4 (380 mg, 1,65 mmoles, 1,0 equiv) y CH₂Cl₂ (8 ml) se añadió Et₃N (0,70 ml, 4,95 mmoles, 3 equiv) y cloruro de metanosulfonilo (0,23 ml, 2,5 mmoles, 1,5 equiv). La mezcla se agitó a temperatura ambiente durante 2 h y seguidamente inactivó con H₂O (3 ml) para producir un precipitado. El precipitado se filtró y se lavó con CH₂Cl₂ (3x3 ml). El filtrado se concentró hasta ~1,5 ml. La filtración de un segundo precipitado estuvo seguida de un lavado con H₂O (2x1 ml) y CH₂Cl₂ (3x2 ml). Los precipitados se combinaron para proporcionar 320 mg (63%) del compuesto del título en forma de un sólido blanco apagado.

LC/MS: m/z (ES+) 308 (M+H)⁺.



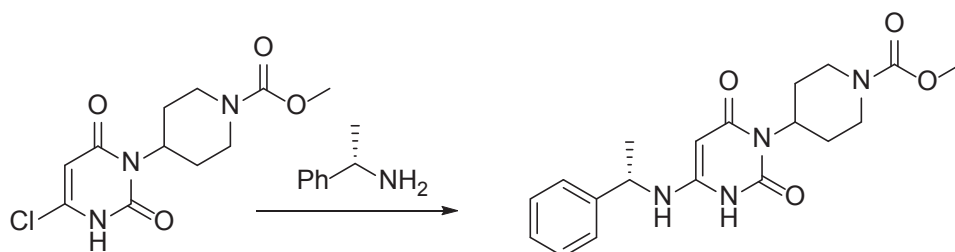
Compuesto 12. (S)-3-(1-(metilsulfonil)piperidin-4-il)-6-(1-feniletilamino)pirimidino-2,4(1H,3H)-
 5 diona. Una mezcla de 12.5 (20 mg, 0,065 mmol) y (S)-α-metilbencilamina (180 mg, 1,5
 mmoles, 23 equiv) se agitó a 125 °C durante 1 h. La mezcla se concentró bajo presión
 reducida, se disolvió en CH₃OH y se filtró. El filtrado se purificó usando RP-HPLC
 preparativa eluyendo con un gradiente lineal de 20% a 100% de CH₃CN en H₂O (tampón de
 ácido fórmico al 0,1%) durante 40 minutos para proporcionar 16 mg (63%) del compuesto
 del título en forma de un sólido blanco apagado. LC/MS: m/z (ES+) 393 (M+H)⁺. ¹H-RMN
 10 (400 MHz, DMSO-d₆): δ ppm 9,40 (s ancho, 1H), 7,35-7,25 (m, 4H), 7,15 (m, 1H), 6. 55 (s,
 1H), 4,58 (m, 1H), 4,42 (m, 1H), 4,30 (s, 1H), 3,52 (m, 2H), 2,79 (s, 3H), 2,70 -2,62 (m, 2H),
 2,50-2,48 (m, 2H), 1,48-1,38 (m, 2H), 1,32 (d, J = 6. 8 Hz, 3H).

Ejemplo 13. Preparación de (S)-4-(2,6-dioxo-4-(1-feniletilamino)-2,3-dihidropirimidin-1(6H)-
 il)piperidino-1-carboxilato de metilo



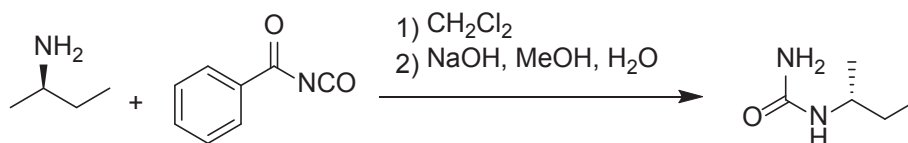
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Compuesto 13.1. 4-(4-Cloro-2,6-dioxo-2,3-dihidropirimidin-1(6H)-il)piperidino-1-carboxilato
 de metilo. A una mezcla de 12.4 (115 mg, 0,5 mmoles, 1,0 equiv) y CH₂Cl₂ (2 ml) se añadió
 Et₃N (0,14 ml, 1,5 mmoles, 3,0 equiv) seguido de cloroformiato de metilo (95 mg, 1,0
 mmoles, 2,0 equiv). La mezcla se agitó a temperatura ambiente durante 1 h, se diluyó con
 20 CH₂Cl₂ (8 ml), se lavó con una solución acuosa saturada de NaHCO₃ (1 ml), H₂O (1 ml),
 salmuera (1 ml), se secó con Na₂SO₄ anhidro y se concentró para producir 105 mg (73%) de
 un sólido blanco apagado. LC/MS: m/z (ES+) 288 (M+H)⁺.

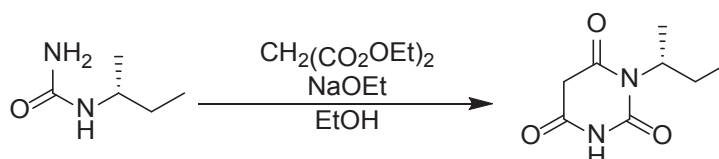


Compuesto 13. (S)-4-(2,6-dioxo-4-(1-feniletilamino)-2,3-dihidropirimidin-1(6H)-il)piperidino-1-carboxilato de metilo. Una mezcla de 13.1 (58 mg, 0,20 mmol) y (S)- α -metilbencilamina (240 mg, 1,5 mmol) se agitó a 120 °C durante 0,5 h. El compuesto del título se preparó usando un procedimiento similar al usado para la preparación de 9 para proporcionar 40 mg (63%) del compuesto del título en forma de un sólido blanco apagado. LC/MS: m/z (ES+) 373 (M+H)⁺. ¹H-RMN (400 MHz, CDCl₃): δ ppm 9,85 (s, 1H), 7,29-7,15 (m, 5H), 5,75 (s ancho, 1), 4,80 (m, 1H), 4,60 (s, 1H), 4,35 (m, 1H), 4,20 - 4,00 (m, 2H), 3,58 (s, 3H), 2,80 - 2,70 (m, 2H), 2,46 (m, 2H), 1,50 (m, 2H), 1,38 (d, J = 6. 7 Hz, 3H).

Ejemplo 14. Preparación de 3-(R)-sec-butil-6-((S)-1-(3-metoxifenil)etilamino)pirimidino-2,4(1H,3H)-diona.

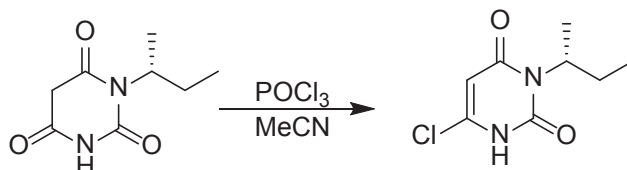


Compuesto 14.1. (R)-1-sec-butilurea. Se disolvió isocianato de benzoilo (5,36 g, 36,5 mmoles, 1,05 equiv) en CH₂Cl₂ (20 ml) y se enfrió a 0 °C en un baño con hielo. Se añadió cuidadosamente (R)-butan-2-amina (2,54 g, 34,7 mmoles, 1 equiv) en CH₂Cl₂ (10 ml) mientras se agitaba. La mezcla se dejó agitar durante 3 h a temperatura ambiente. Después de que la reacción se estimó completada, la mezcla se concentró. El residuo se puso en suspensión en Et₂O (20 ml) y se filtró. El sólido se recogió en una mezcla 1:1 de CH₃OH y H₂O (200 ml) seguido de la adición de NaOH (6,9 g, 174 mmoles, 5 equiv). La reacción se agitó durante una noche a temperatura ambiente. El CH₃OH se evaporó de la solución y el precipitado resultante (1,66 g, 39%) se recogió. LC/MS: m/z (ES+) 117 (M+H)⁺.

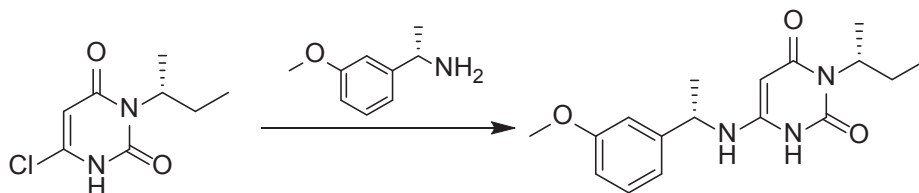


Compuesto 14.2. (R)-1-sec-butilpirimidino-2,4,6(1H,3H,5H)-triona. Se disolvió compuesto 14.1 (1,66 g, 14,3 mmoles, 1,0 equiv) en EtOH (10 ml) y se añadieron malonato de dietilo (1,8 ml, 15,7 mmoles, 1,1 equiv) y NaOEt (5,6 ml, 17,1 mmoles, 1,2 equiv). La reacción se

agitó a 80 °C durante 2 h y seguidamente se enfrió a temperatura ambiente. Se añadió agua (20 ml) y seguidamente se separó EtOH por evaporación. Se añadió KHSO₄ (exceso) para saturar la capa acuosa que seguidamente se extrajo con EtOAc. Las fases orgánicas combinadas se secaron con MgSO₄ anhidro y se concentraron para producir 1,6 g (61%) del compuesto del título en forma de un residuo en bruto que se usó sin purificación adicional. LC/MS: m/z (ES-) 183 (M-H)⁻.



Compuesto 14.3. (R)-3-sec-butil-6-cloropirimidino-2,4(1H,3H)-diona. Una mezcla de 14.2 (1,6 g, 8,7 mmoles, 1 equiv) y POCl₃ (648 µl, 7,0 mmoles, 0,8 equiv) en CH₃CN (10 ml) se agitó a 90 °C durante 2 h. Se añadió POCl₃ adicional (0,8 equiv) y se agitó a 90 °C durante 3 h. La reacción se enfrió a temperatura ambiente, se inactivó cuidadosamente con CH₃OH (10 ml), se agitó durante 30 minutos y se purificó con HPLC de fase normal, 0-25% de CH₃OH/CH₂Cl₂ seguido de barrido con CH₃OH. El producto y el material de partida se eluyeron conjuntamente. La mezcla se concentró, el residuo se recogió en CH₃CN (10 ml) y se añadió POCl₃ (648 µl). La reacción se agitó a 90 °C durante 3 h y seguidamente se enfrió a temperatura ambiente. La reacción se inactivó cuidadosamente con CH₃OH (10 ml) y se agitó durante 30 minutos. La mezcla de reacción se purificó mediante HPLC de fase normal con condiciones previas, se concentró y se secó bajo vacío para producir 450 mg (32%) del compuesto del título en forma de un sólido blanco apagado. LC/MS: m/z (ES-) 201 (M-H)⁻.



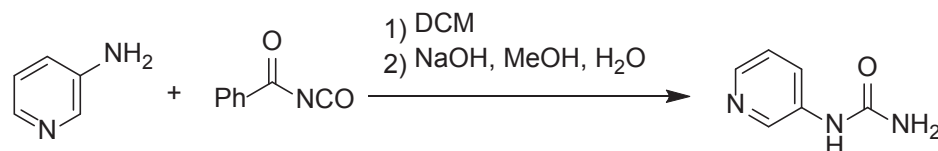
20

Compuesto 14. 3(R)-sec-butil-6-((S)-1-(3-metoxifenil)etilamino)pirimidino-2,4(1H,3H)-diona. Una mezcla de 14.3 (150 mg, 0,74 mmoles, 1,0 equiv) en (S)-1-(3-metoxifenil)etanamina pura (400 µl) se agitó durante una noche a 90 °C. La reacción se purificó usando RP-HPLC preparativa en un sistema Agilent con un gradiente de 0-40% de CH₃CN en H₂O durante 45 minutos para producir 13 mg (6%) del compuesto del título en forma de un sólido blanco apagado. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 9,79 (s, 1H), 7,28 (t, J = 8,1 Hz, 1H), 6,94-6,88 (m, 2H), 6,84 (dd, J = 8,2, 1,7 Hz, 1H), 6,51 (d, J = 6,4 Hz, 1H), 4,72-4,59 (m, 1H), 4,47 (m, 1H), 4,35 (s, 1H), 3,76 (s, 3H), 1,98-1,84 (m, 1H), 1,61 (m, 1H), 1,39 (d, J = 6,7 Hz,

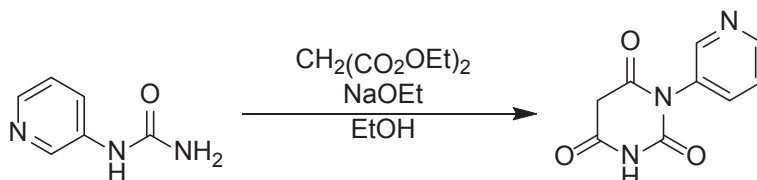
25

3H), 1,25 (d, J = 6.9 Hz, 3H), 0,70 (t, J = 7,4 Hz, 3H).

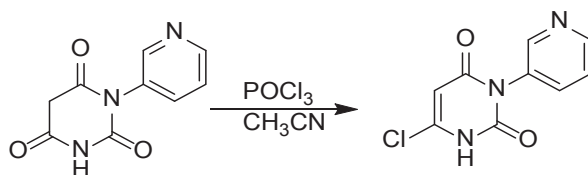
Ejemplo 15. Preparación de (S)-6-(1-feniletilamino)-3-(piridin-3-il)pirimidino-2,4(1H,3H)-diona.



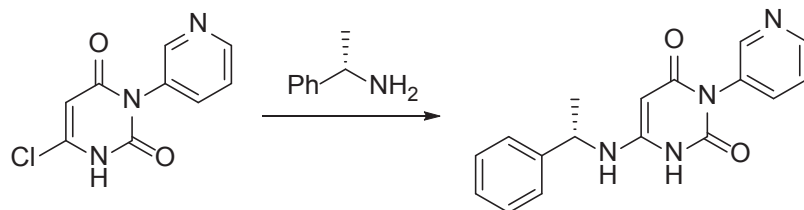
- 5 Compuesto 15.1. 1-(piridin-3-il)urea. Se recogió isocianato de benzoilo (3,28 g, 22,3 mmoles, 1,05 equiv) en CH₂Cl₂ (30 ml) y se enfrió a -100 °C. Se añadió piridin-3-amina (2 g, 21,2 mmoles, 1 equiv) por partes mientras se agitaba. La mezcla se dejó agitar durante 3 h a temperatura ambiente. Después de que la reacción se estimó completada, se concentró y se recogió en una mezcla 1:1 de CH₃OH y H₂O (100 ml) seguido de la adición de NaOH (4,25 g, 106,3 mmoles, 5 equiv). La reacción se dejó agitar durante una noche a temperatura ambiente, se concentró hasta sequedad y se sometió a destilación azeotrópica tres veces con tolueno. Se añadió una mezcla de 10% de CH₃OH en EtOAc (100 ml) al sólido y se agitó durante 10 minutos seguido de filtración. El sólido se puso en suspensión y se filtró dos veces adicionales. Los filtrados combinados se filtraron una vez más para separar
- 10 cualesquiera sólidos que pasaran a través del filtro y se concentraron. El residuo se trituró con EtOAc (5 ml) y se secó bajo vacío para producir 3,5 g de material en bruto (sólido blanco apagado) que se utilizó sin purificación adicional. LC/MS: m/z (ES+) 138 (M+H)⁺.



- Compuesto 15.2. 1-(piridin-3-il)pirimidino-2,4,6(1H,3H,5H)-triona. Se recogió compuesto 15.1
- 20 (3,0 g, 21,8 mmoles, 1,0 equiv) en EtOH (20 ml) seguido de la adición de malonato de dietilo (2,75 ml, 24,1 mmoles, 1,1 equiv) y NaOEt (8,5 ml, 26,3 mmoles, 1,2 equiv). La reacción se agitó a 85 °C durante una noche y seguidamente se enfrió a temperatura ambiente. Se añadió lentamente agua (100 ml) seguido de una adición cuidadosa de bicarbonato de sodio (8 g). La mezcla resultante se lavó tres veces con EtOAc. La capa acuosa se concentró
- 25 hasta 50 ml y se añadió CH₃OH (150 ml). El precipitado se separó por filtración y el filtrado se concentró. El residuo resultante se purificó por cromatografía rápida (gel de sílice, 0-25% CH₃OH/CH₂Cl₂) para proporcionar 1,70 g (38%) del compuesto del título en forma de un sólido amarillento claro. LC/MS: m/z (ES+) 206 (M+H)⁺.

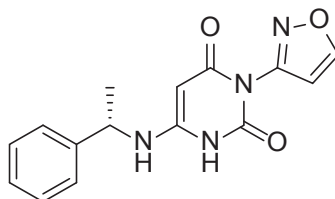


Compuesto 15.3. 6-cloro-3-(piridin-3-il)pirimidino-2,4(1H,3H)-diona. Una mezcla de 15.2 (700 mg, 3,41 mmoles, 1,0 equiv) y POCl₃ (255 µl, 2,7 mmoles, 0,8 equiv) en CH₃CN (10 ml) se agitó a 90 °C durante 2 h. Se añadió POCl₃ adicional (0,8 equiv) y se continuó la agitación a 90 °C durante 2 h. Se añadió POCl₃ adicional (1,6 equiv) seguido de una adición cuidadosa de H₂O (150 µl, 2,5 equiv). La reacción se agitó durante una noche a 90 °C. Después de enfriar a temperatura ambiente, la mezcla se filtró y el sólido se lavó cuidadosamente con CH₃OH (1 ml). Se añadió acetato de etilo al filtrado y el precipitado resultante se recogió por filtración y se secó bajo vacío para producir 230 mg (30%) del compuesto del título en forma de un sólido amarillento claro. LC/MS: m/z (ES⁺) 224 (M+H)⁺.



Compuesto 15. (S)-6-(1-feniletilamino)-3-(piridin-3-il)pirimidino-2,4(1H,3H)-diona. Una mezcla de 15.3 (100 mg, 0,45 mmoles, 1 equiv) en (S)-(-)-α-metilbencilamina pura (500 µl) se agitó durante una noche a 100 °C. Después de enfriar, la reacción se purificó usando RP-HPLC preparativa en un sistema Agilent con un gradiente de 0-40% de CH₃CN en H₂O durante 45 minutos, seguido de una segunda purificación en una placa de TLC preparatoria (2.000 µm) con 7% de CH₃OH/CH₂Cl₂ para producir 39,5 mg (28%) del compuesto del título. LC/MS: m/z (ES⁺) 309 (M+H)⁺. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 11,15 (s, 1H), 8,49 (dd, J = 4,8, 1,4 Hz, 1H), 8,34 (d, J = 2,4 Hz, 1H), 7,65-7,58 (m, 1H), 7,44 (dd, J = 8,1. 4,8 Hz, 1H), 7,37 (m, 5H), 7,26 (m, 1H), 4,61-4,53 (m, 1H), 4,48 (s, 1H), 1,39 (d, J = 6. 8 Hz, 3H).

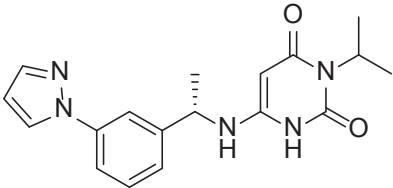
Ejemplo 16. Preparación de (S)-3-(Isoxazol-3-il)-6-(1-feniletilamino)pirimidino-2,4(1H,3H)-diona (16).



El compuesto del título se preparó usando procedimientos similares a los usados para la

preparación de compuesto 15 con la excepción de que se usó isoxazol-3-amina en lugar de piridin-3-amina. LC/MS: m/z (ES+) 299 (M+H)⁺. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 8,96 (s, 1H), 7,38 (d, J = 3,9 Hz, 4H), 7,28 (dd, J = 8,4. 4,3 Hz, 2H), 7,10 (s, 1H), 6. 63 (s, 1H), 4,74-4,52 (m, 1H), 4,48 (s, 1H), 1,44 (d, J = 6. 6 Hz, 3H).

5 Ejemplo 17. Preparación de (S)-6-((1-(3-(1H-pirazol-1-il)fenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona (17).



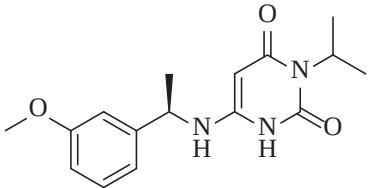
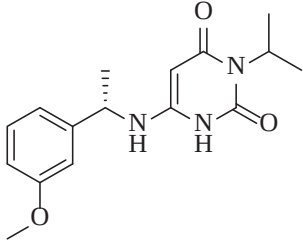
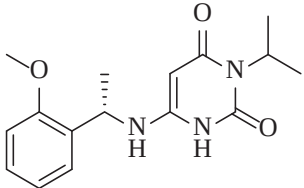
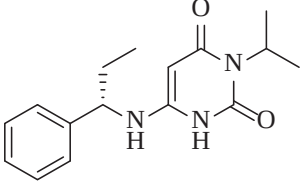
El compuesto del título se preparó mediante acoplamiento de Ullman (P.E. Fanta. "The Ullmann Synthesis of Biaryls". *Synthesis*, 1974, 9-21) de 35 con 1H-pirazol en presencia de yoduro de cobre, carbonato de cesio y trans-N,N'-dimetilciclohexano-1,2-diamina. LC/MS: m/z (ES+) 340 (M+H)⁺. ¹H-RMN (400 MHz, CD₃OD): δ ppm 8,26 (s, 1H), 7,70 (m, 2H), 7,66 (m, 1H), 7,51 (m, 1H), 7,34 (m, 1H), 6. 55 (s, 1H), 5,05 (m, 1H), 4,62 (m, 1H), 1,58 (d, J = 6. 8 Hz, 3H), 1,37 (m, 6H).

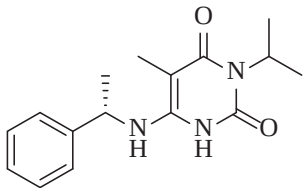
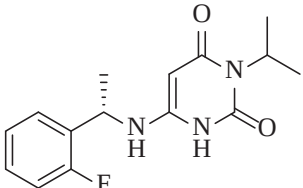
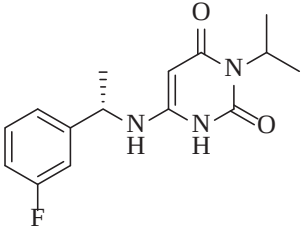
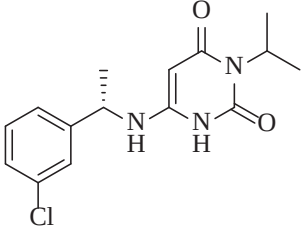
Ejemplo 18. Preparación de compuestos de pirimidino-diona adicionales

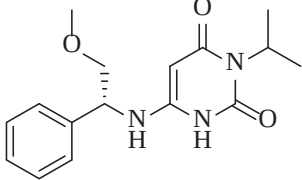
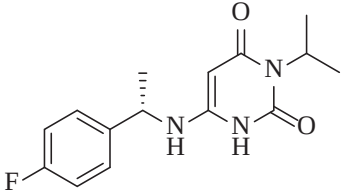
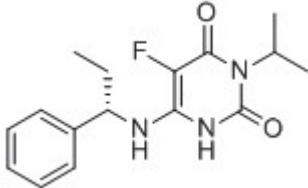
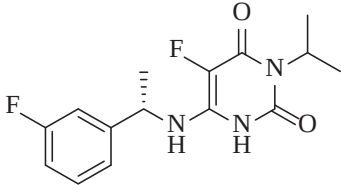
15 Los compuestos de la Tabla 1 se prepararon según los ejemplos anteriormente descritos.

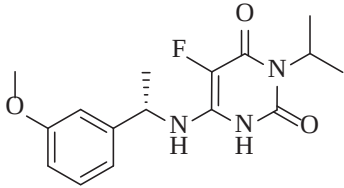
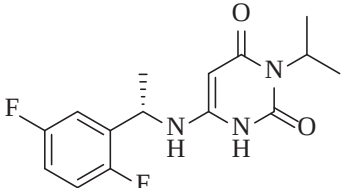
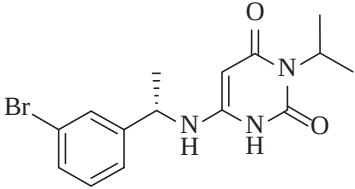
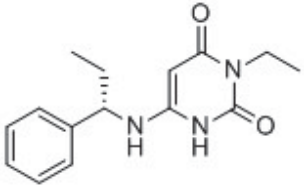
Tabla 1. Compuestos y datos analíticos

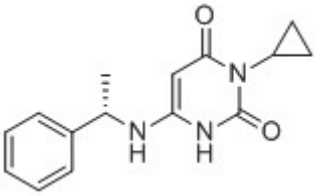
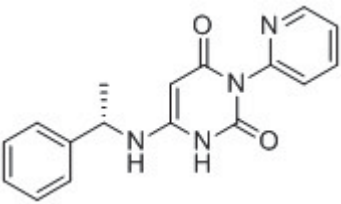
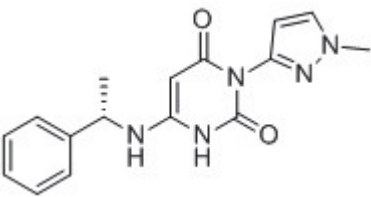
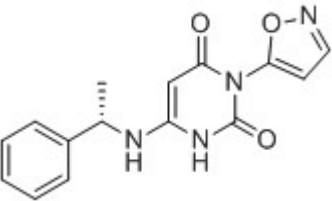
Estructura	Compuesto n° ---- Ejemplo de ref.	Peso observado y/o ¹ H RMN
	19R ---- 1	274 (M+H) ⁺ ¹ H-RMN (400 MHz, CD ₃ OD): δ ppm 7,42 - 7,22 (m, 5H), 5,06 - 4,94 (m, 1H), 4,49 (m, 1H), 1,49 (d, J = 7,0 Hz, 3H), 1,36 (m, 6H).

Estructura	Compuesto nº ---- Ejemplo de ref.	Peso observado y/o ¹ H RMN
	20R ---- 1	304 (M+H) ⁺ ¹ H-RMN (400 MHz, CDCl ₃): δ ppm 10,39 (s ancho, 1H), 7,29 - 7,23 (m, 1H), 6. 88 - 6. 79 (m, 3H), 5,31 (s ancho, 1H), 5,09 (m, 1H), 4,78 (s ancho, 1H), 4,48 - 4,34 (m, 1H), 3,80 (s, 3H), 1,51 (d, J = 7,0 Hz, 3H), 1,44 - 1,38 (m, 6H).
	21 ---- 1	304 (M+H) ⁺ ¹ H-RMN (400 MHz, CD ₃ OD): δ ppm 7,26 (t, J = 7,9 Hz, 1H), 6. 92 - 6. 85 (m, 2H), 6. 85 - 6. 80 (m, 1H), 5,01 (m, 1H), 4,45 (d, J = 7,0 Hz, 1H), 3,79 (s, 3H), 1,48 (d, J = 7,0 Hz, 3H), 1,37 (d, J = 7,0 Hz, 6H).
	22 ---- 1	304 (M+H) ⁺ ¹ H-RMN (400 MHz, CD ₃ OD): δ ppm 7,29 - 7,17 (m, 1 H), 7,00 (d, J=7,4 Hz, 1 H), 6. 93 (m, 1 H), 5,05 - 4,97 (m, 1 H), 4,83 (s, 1 H), 4,80 - 4,74 (m, 1 H), 3,89 (s, 3 H), 1,45 (d, J=6. 7 Hz, 3 H), 1,38 - 1,34 (m, 6 H).
	24 ---- 1	288 (M+H) ⁺ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 9,76 (s ancho, 1H), 7,41 - 7,13 (m, 5H), 6. 50 (d, J = 7,0 Hz, 1H), 4,88 (m, 1H), 4,31 (d, J = 2,4 Hz, 1H), 4,24 (m, 1H), 1,83 - 1,58 (m, 2H), 1,35 - 1,10 (m, 6H), 0,83 (m, 3H).

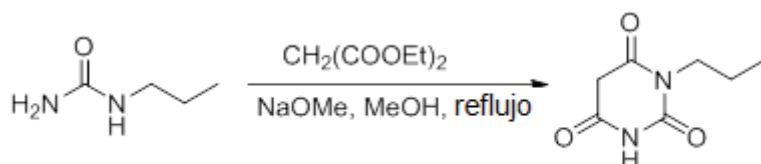
Estructura	Compuesto n° ---- Ejemplo de ref.	Peso observado y/o ¹ H RMN
	25 ---- 1	288 (M+H) ⁺ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 7,46 - 7,29 (m, 4H), 7,27 - 7,21 (m, 1H), 6. 27 (d, J = 9,0 Hz, 1H), 6. 08 (s ancho, 1H), 5,13 (m, 1H), 4,98 (m, 1H), 1,78 (s, 3H), 1,46 (m, 3H), 1,29 (m, 6H).
	26 ---- 1	292 (M+H) ⁺ ¹ H-RMN (400 MHz, CDCl ₃): δ ppm 10,45 (s ancho, 1H), 7,30 - 7,23 (m, 2H), 7,16 - 7,01 (m, 2H), 5,13 (dt, J = 13,8, 7,0 Hz, 1H), 4,99 (s ancho, 1H), 4,74 - 4,63 (m, 2H), 1,55 (d, J = 6. 7 Hz, 3H), 1,43 (m, 6H).
	27 ---- 1	292 (M+H) ⁺ ¹ H-RMN (400 MHz, CDCl ₃): δ ppm 10,28 (s ancho, 1H), 7,36 - 7,28 (m, 1H), 7,06 (d, J = 7,8 Hz, 1H), 7,02 - 6. 93 (m, 2H), 5,17 - 5,04 (m, 1H), 4,95 - 4,82 (m, 1H), 4,75 - 4,70 (m, 1H), 4,50 - 4,40 (m, 1H), 1,53 (d, J = 7,0 Hz, 3H), 1,46 - 1,37 (m, 6H).
	28 ---- 1	308 (M+H) ⁺ ¹ H RMN (400 MHz, CD ₃ OD): δ ppm 7,39 - 7,31 (m, 2H), 7,29 - 7,23 (m, 2H), 5,01 (m, 1H), 4,50 (q, J = 6. 7 Hz, 1H), 1,48 (d, J = 7,0 Hz, 3H), 1,37 (d, J = 7,0 Hz, 6H).

Estructura	Compuesto nº ---- Ejemplo de ref.	Peso observado y/o ¹ H RMN
	29 ---- 1	304 (M+H) ⁺ ¹ H RMN (400 MHz, CD ₃ OD): δ ppm 7,38-7,26 (m, 5H), 5,04-4,97 (m, 1H), 4,56 (dd, J = 7,4. 3,9Hz, 1H), 3,67-3,63 (m, 1H), 3,56-3,51 (m, 1H), 3,37 (s, 3H), 1,36 (m, 6H).
	30 ---- 1	292 (M+H) ⁺ ¹ H-RMN (400 MHz, CD ₃ OD): δ ppm 7,34 (m, 2H), 7,08 (m, 2H), 5,07 - 4,95 (m, 1H), 4,50 (q, J = 6. 8 Hz, 1H), 1,48 (d, J = 6. 7 Hz, 3H), 1,37 (m, 6H).
	31 ---- 4 & 5	306 (M+H) ⁺ ¹ H-RMN (400 MHz, CDCl ₃): δ ppm 9,70 (s ancho, 1H), 7,39 - 7,22 (m, 5H), 5,19 - 5,07 (m, 1H), 4,85 (s ancho, 1H), 4,73 - 4,61 (m, 1H), 1,88 (dq, J = 14,3. 7,0 Hz, 2H), 1,45 (m, 6H), 0,96 (t, J = 7,4 Hz, 3H).
	32 ---- 4 & 5	310 (M+H) ⁺ ¹ H-RMN (400 MHz, CDCl ₃): δ ppm 9,89 (s ancho, 1 H), 7,40 - 7,29 (m, 1 H), 7,13 - 6. 95 (m, 3 H), 5,12 (m, 1 H), 5,02 - 4,87 (m, 1 H), 4,82 - 4,69 (m, 1 H), 1,59 (d, J = 6. 7 Hz, 3 H), 1,42 (m, 6 H),

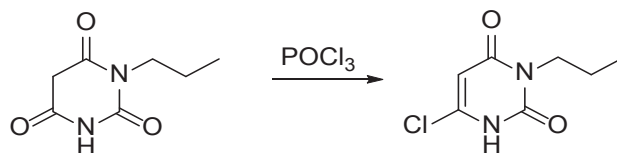
Estructura	Compuesto nº ---- Ejemplo de ref.	Peso observado y/o ¹ H RMN
	33 ---- 4 & 5	322 (M+H) ⁺ ¹ H-RMN (400 MHz, CDCl ₃): δ ppm 9,50 (s ancho, 1H), 7,30 (dd, J = 9,00, 7,83 Hz, 1H), 6. 93-6. 90 (m, 3H), 5,19 - 5,04 (m, 1H), 4,88 (m, 1H), 4,75 (m, 1H), 3,79 (s, 3H), 1,59 (d, J = 6. 7 Hz, 3H), 1,43 (d, J = 7,0 Hz, 6H).
	34 ---- 6	310 (M+H) ⁺ ¹ H-RMN (300 MHz, DMSO-d ₆): δ ppm 9,74 (s, 1H), 7,32 - 7,24 (m, 2H), 7,21 - 7,13 (m, 1H), 6. 60 (s, 1H), 4,95 - 4,86 (m, 1H), 4,69 - 4,62 (m, 1H), 4,32 (s, 1H), 1,49 - 1,42 (d, J = 6. 6 Hz, 3H), 1,28 - 1,26 (d, J = 6. 9 Hz, 6H).
	35 ---- 6	352 (M+H) ⁺ ¹ H-RMN (300 MHz, DMSO-d ₆): δ ppm 9,85 (s, 1H), 7,59 (s, 1H), 7,48 (m, 1H), 7,38 - 7,32 (m, 2H), 6. 59 (d, J = 5,4 Hz, 1H), 4,95 - 4,88 (m, 1H), 4,57 - 4,50 (m, 1H), 4,36 (s, 1H), 1,41 (d, J = 6. 6 Hz, 3H), 1,25 (d, J = 6. 9 Hz, 6H).
	36 ---- 1 & 5	274 (M+H) ⁺ ¹ H-RMN (300 MHz, DMSO-d ₆): δ ppm 9,96 (s ancho, 1H), 7,39-7,24 (m, 5H), 6. 58 (d, J = 6. 6 Hz, 1H), 4,38 (s, 1H), 4,28 (q, J = 6. 9 Hz, 1H), 3,65 (q, J = 6. 6 Hz, 2H), 1,78-1,66 (m, 2H), 0,99 (t, J = 6. 9 Hz, 3H), 0,86 (t, J = 7,2 Hz, 3H).

Estructura	Compuesto nº ---- Ejemplo de ref.	Peso observado y/o ¹ H RMN
	37 ---- 1 & 5	272 (M+H) ⁺ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 9,83 (s, 1H), 7,37 (m, 4H), 7,26 (m, 1H), 6. 52 (m, 1H), 4,50 (m, 1H), 4,33 (s, 1H), 2,37 (m, 1H), 1,41 (d, J = 6. 8 Hz, 3H), 0,85 (m, 2H), 0,60 (m, 2H).
	38 ---- 15	309 (M+H) ⁺ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 10,92 (s, 1H), 8,57 – 8,42 (m, 1H), 7,85 (ddd, J = 7,8, 7,8, 1,7 Hz, 1H), 7,46 – 7,31 (m, 5H), 7,32 – 7,19 (m, 2H), 7,13 (m, 1H), 4,67 – 4,52 (m, 1H), 4,41 (s, 1H), 1,39 (d, J = 6. 8 Hz, 3H).
	39 ---- 15	312 (M+H) ⁺ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 7,65 (d, J = 2,2 Hz, 1H), 7,41 – 7,35 (m, 5H), 7,32 – 7,24 (m, 1H), 6. 77 (d, J = 5,9 Hz, 1H), 6. 04 (d, J = 2,1 Hz, 1H), 4,63 – 4,55 (m, 1H), 4,42 (s, 1H), 3,79 (s, 3H), 1,44 (d, J = 6. 7 Hz, 3H).
	40 ---- 15	299 (M+H) ⁺ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 11,07 (s, 1H), 8,93 (s, 1H), 7,43 – 7,31 (m, 4H), 7,31 – 7,04 (m, 2H), 6. 59 (s, 1H), 4,62 (m, 1H), 4,43 (s, 1H), 1,40 (d, J = 6. 7 Hz, 3H).

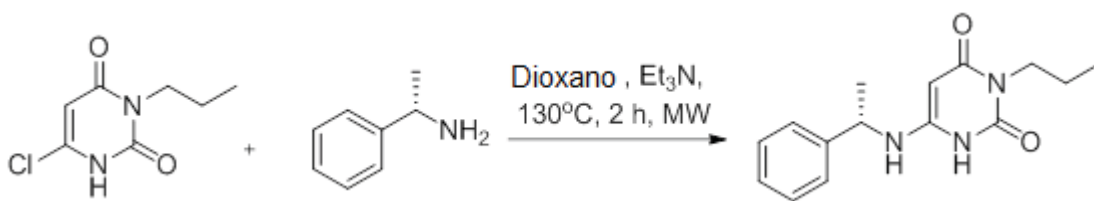
trimetilsililo (4,94 g (pureza de 85%), 36,5 mmoles, 1,00 equiv). La mezcla de reacción se agitó a temperatura ambiente durante 72 h y seguidamente se enfrió a 0 °C. La mezcla enfriada se inactivó mediante la adición gota a gota de CH₃OH (10 ml) y se concentró bajo presión reducida. El sólido resultante se puso en suspensión en Et₂O (30 ml) y se filtró. El sólido se lavó adicionalmente con Et₂O (30 ml) y se secó para proporcionar 2,0 g (38%) del compuesto del título en forma de un sólido blanco.



Compuesto 48.2. 1-Propilpirimidino-2,4,6(1H,3H,5H)-triona. A 48.1 (600 mg, 5,88 mmoles, 1,0 equiv) en CH₃OH (1 ml) se añadió malonato de dietilo (960 mg, 6,0 mmoles, 1,02 equiv) y metóxido de sodio (1 ml, 25% de NaOCH₃ en CH₃OH en peso). La mezcla de reacción se calentó en el reactor de microondas a 130 °C durante 1 h. La mezcla se enfrió y la mezcla se ajustó cuidadosamente a pH= 3 con HCl concentrado. Las partes volátiles se separaron y se añadió H₂O (10 ml). El sólido se precipitó y se filtró. Se lavó adicionalmente con H₂O adicional (10 ml) y se secó para proporcionar 560 mg (56%) del compuesto del título en forma de un sólido blanco.

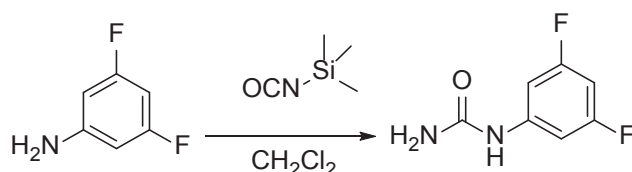


Compuesto 48.3. 6-Cloro-3-propilpirimidino-2,4(1H,3H)-diona. Se añadieron compuesto 48.2 (560 mg, 3,30 mmol) y POCl₃ (2 ml) a un recipiente a presión de paredes pesadas que posteriormente se cerró herméticamente. La solución resultante se calentó a 70 °C y se agitó durante 50 minutos detrás una protección para explosiones. La mezcla de reacción se enfrió y se concentró bajo presión reducida. Al residuo resultante se añadió CH₂Cl₂ (30 ml) que seguidamente se separó bajo presión reducida. La adición y evaporación de CH₂Cl₂ (30 ml) se realizó una vez adicional y seguidamente el residuo resultante se diluyó con CH₂Cl₂ (50 ml). A la capa orgánica se añadió cuidadosamente una solución acuosa saturada de NaHCO₃ (50 ml). Las capas se separaron y las fases orgánicas se lavaron adicionalmente con H₂O (30 ml) y salmuera (30 ml). La capa orgánica se concentró y se purificó por cromatografía de columna rápida (gel de sílice, utilizando 10% de EtOAc en CH₂Cl₂) para proporcionar 160 mg (26%) del compuesto del título en forma de un sólido blanco.

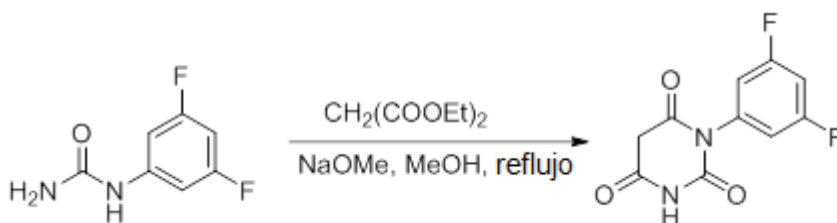


Compuesto 48. (S)-6-((1-feniletil)amino)-3-propilpirimidino-2,4(1H,3H)-diona. A 48.3 (160 mg, 0,85 mmoles, 1,0 equiv) en 1,4-dioxano (1,5 ml) se añadió Et₃N (200 µl) y (S)-α-metilbencilamina (235 mg, 1,94 mmoles, 2,3 equiv). La mezcla se calentó en un reactor de microondas a 130 °C durante 2 h. La mezcla se enfrió y se concentró. El residuo resultante se trató con una mezcla 8:3 de H₂O:CH₃CN que dio lugar a una precipitación. El sólido se filtró y se lavó sucesivamente con H₂O (10 ml) y EtOAc (10 ml). El sólido se secó para proporcionar 67 mg (29%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES⁺) 274 (M+H)⁺. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 9,92 (s ancho, 1H), 7,36-7,22 (m, 5H), 6. 54 (d, J = 7,0 Hz, 1H), 4,50 (quin, J = 6. 7 Hz, 1H), 4,35 (s, 1H), 3,54 (dd, J = 8,0, 6. 9 Hz, 2H), 1,42-1,36 (m, 5H), 0,76 (t, J = 7,6 Hz, 3H).

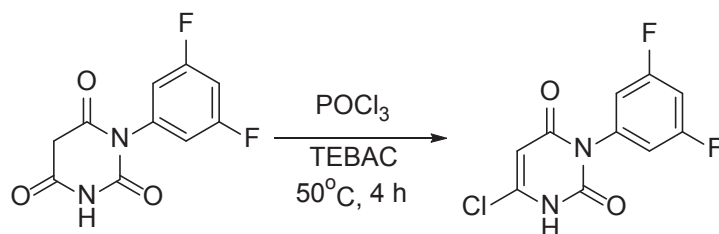
Ejemplo 49. Preparación de (S)-3-(3,5-difluorofenil)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona.



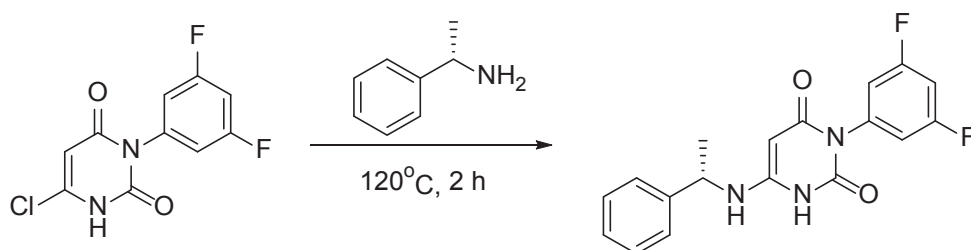
Compuesto 49.1. 1-(3,5-difluorofenil)urea. A una solución agitada del 3,5-difluoroanilina (4,0 g, 31 mmoles, 1,00 equiv) en CH₂Cl₂ (50 ml) bajo argón a temperatura ambiente se añadió gota a gota isocianato de trimetilsililo (3,56 g, 30,90 mmoles, 1,00 equiv). La mezcla de reacción se agitó durante 1 noche y se inactivó mediante la adición gota a gota de CH₃OH (50 ml). La mezcla de reacción se concentró bajo presión reducida y el residuo resultante se purificó por cromatografía rápida (gel de sílice, eluyendo con CHCl₃/CH₃OH (10:1 a 7:1)) para producir 2,0 g (38%) del compuesto del título en forma de un sólido blanco. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 8,96 (s, 1H), 7,16-7,10 (m, 2H), 6. 72-6. 66 (m, 1H), 6. 07 (s ancho, 2H).



Compuesto 49.2. 1-(3,5-Difluorofenil)pirimidino-2,4,6(1H,3H,5H)-triona. A una solución agitada de 49.1 (1,6 g, 0,0093 moles, 1,1 equiv) en CH₃OH (20 ml) se añadió malonato de dietilo (1,4 g, 0,0087 moles, 1,0 equiv) y metóxido de sodio (1,25 g, 0,0231 moles, 2,7 equiv). La mezcla resultante se agitó durante una noche a 65 °C. Después de enfriar a temperatura ambiente, el pH se ajustó cuidadosamente a 5 usando HCl acuoso 1N. La solución resultante se extrajo con EtOAc (3x50 ml). Las capas orgánicas se combinaron y se concentraron bajo presión reducida. El residuo se lavó con CH₃OH (50 ml) y el sólido resultante se aisló por filtración para proporcionar 700 mg (31%) del compuesto del título en forma de un sólido blanco. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 11,66 (s, 1H), 7,43-7,35 (m, 1H), 7,11-7,08 (m, 2H), 3,77 (s, 2H).



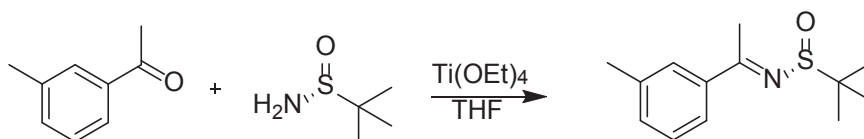
Compuesto 49.3. 6-Cloro-3-(3,5-difluorofenil)pirimidino-2,4(1H,3H)-diona. A un matraz de fondo redondo de 25 ml bajo argón que contenía 49.2 (740 mg, 3,08 mmoles, 1,00 equiv) se añadieron cloruro de trietilbencilamonio (840 mg, 1,20 equiv) y POCl₃ (3 ml). La solución resultante se agitó durante 4 h a 50 °C. La reacción se enfrió y se inactivó mediante la adición cuidadosa de agua/hielo (20 ml). El pH de la solución se ajustó a 5 con hidróxido de sodio 2N. La solución resultante se extrajo con EtOAc (2x10 ml) y las capas orgánicas se combinaron. La capa orgánica se lavó con salmuera (10 ml), se secó sobre MgSO₄ anhidro, se filtró y se concentró bajo presión reducida. Esto dio lugar a 500 mg (en bruto) del compuesto del título en forma de un sólido blanco. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 12,60 (br, 1H), 7,38-7,32 (m, 1H), 7,21-7,16 (m, 2H), 6.05 (s, 1H).



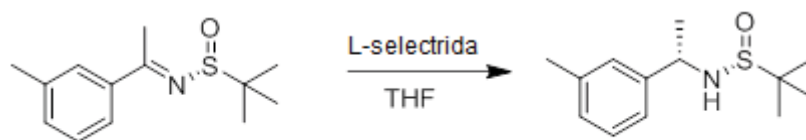
Compuesto 49. (S)-3-(3,5-difluorofenil)-6-((1-pheniletil)amino)pirimidino-2,4(1H,3H)-diona. A 49.3 (200 mg, 0,77 mmol) se añadió (S)-α-metilbencilamina (1,5 ml). La solución resultante se agitó durante 2 h a 120 °C. La mezcla de reacción se diluyó con DMF (3 ml) y el producto en bruto (100 mg) se purificó mediante RP-HPLC con las siguientes condiciones: columna

XBridge Prep C18 OBD, 5 μ m, 19x150 mm; fase móvil, H₂O con 0,05% TFA y CH₃CN (40,0% de CH₃CN a 90% en 10 minutos). Esto dio lugar a 21,6 mg (8%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES+) 344 (M+H)⁺. ¹H-RMN (300 MHz, DMSO-d₆): δ ppm 10,25 (s ancho, 1H), 7,38-7,35 (m, 4H), 7,28-7,21 (m, 2H), 7,03-6. 98 (m, 2H), 6. 76 (d, J = 6. 9 Hz, 1H), 4,59 (quin, J = 6. 7 Hz, 1H), 4,50 (d, J = 2,0 Hz, 1H), 1,42 (d, J = 6. 7 Hz, 3H).

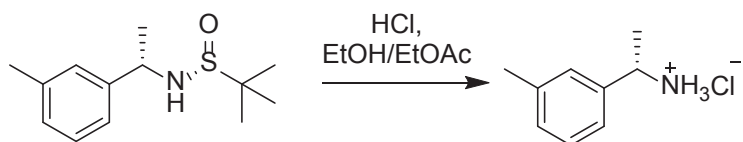
Ejemplo 50. Preparación de (S)-3-isopropil-6-((1-(m-tolil)etil)amino)pirimidino-2,4(1H,3H)-diona.



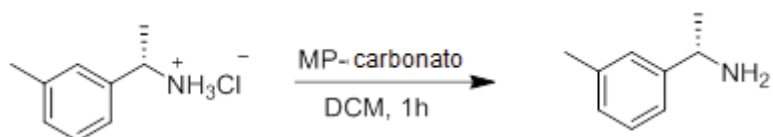
- Compuesto 50.1. (R,E)-2-metil-N-(1-(m-tolil)etilideno)propano-2-sulfinamida. A una solución agitada de 1-(3-metilfenil)etanona (1,61 g, 12,0 mmoles, 1,00 equiv) y (R)-(+)-2-metil-2-propanosulfinamida (1,94 g, 14 mmoles, 1,33 equiv) en THF (50 ml) se añadió Ti(OEt)₄ (3,19 g, 14 mmoles, 1,17 equiv) gota a gota. La mezcla de reacción se agitó durante 16 h a 60 °C, se enfrió a temperatura ambiente y se inactivó con una solución acuosa saturada de NaHCO₃ (50 ml). Las capas se separaron y la capa acuosa se extrajo adicionalmente con EtOAc (2x100 ml). Las fases orgánicas combinadas se concentraron y el residuo resultante se purificó mediante cromatografía rápida (gel de sílice, eluyendo con 0-5% de CH₃OH en CH₂Cl₂) para proporcionar 1,51 g (53%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES+) 238 (M+H)⁺.



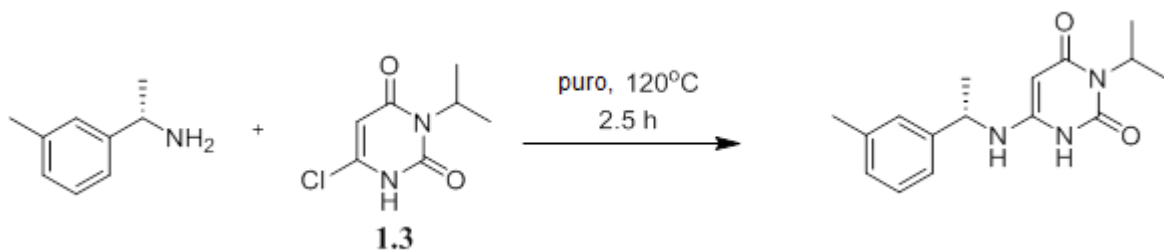
- Compuesto 50.2. (R)-2-metil-N-((S)-1-(m-tolil)etil)propano-2-sulfinamida. A una solución de 50.1 (1,51 g, 6,37 mmol) en THF (30 ml) a -78 °C bajo atmósfera de N₂ se añadió L-selectrida (gota a gota, 10 ml, 1,0M en THF, 10 mmol). La mezcla de reacción se calentó a 0 °C, se agitó durante 1 h y se inactivó cuidadosamente con una solución acuosa saturada de NH₄Cl (30 ml). Las capas se separaron y la capa acuosa se extrajo adicionalmente con EtOAc (2x50 ml). Las fases orgánicas combinadas se concentraron y el residuo resultante se purificó mediante cromatografía rápida (gel de sílice, eluida con 0-5% de CH₃OH en CH₂Cl₂) para proporcionar 0,85 g (56%) del compuesto del título. LC/MS: m/z (ES+) 240 (M+H)⁺.



Compuesto 50.3. Hidrocloruro de (S)-1-(m-tolil)etan-1-amina. A etanol absoluto (10 ml) se añadió AcCl (1,5 ml, gota a gota). La mezcla se agitó durante 10 minutos y seguidamente se añadió 50.2 (0,85 g, 3,56 mmol) en EtOH (3 ml). La mezcla de reacción se agitó durante 2 h a temperatura ambiente y se concentró. El sólido resultante se puso en suspensión en Et₂O y se filtró. El sólido se lavó con Et₂O adicional y se secó para proporcionar 402 mg (66%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES⁺) 136 (M+H)⁺.



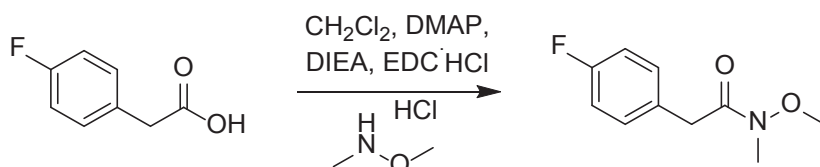
Compuesto 50.4. (S)-1-(m-tolil)etan-1-amina. A una solución agitada de 50.3 (205 mg, 1,20 mmol) en CH₂Cl₂ (10 ml) se añadió MP-carbonato (1,0 g, 3,18 mmol/g). La mezcla de reacción se agitó a temperatura ambiente durante 1 h y seguidamente se filtró. Los gránulos sólidos se lavaron con 10 ml adicionales de CH₂Cl₂ y los filtrados combinados se concentraron para proporcionar el compuesto del título que se extrajo sin purificación alguna.



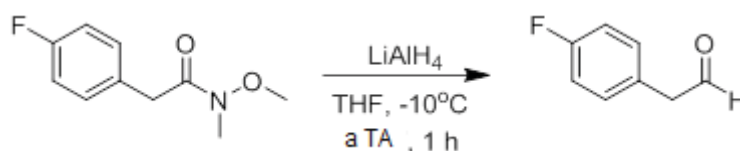
Compuesto 50. (S)-3-isopropil-6-((1-(m-tolil)etil)amino)pirimidino-2,4(1H,3H)-diona. A 50.4 (presumiblemente ~1,2 mmol de la reacción previa, 2,0 equiv) en un tubo de microondas de 0,5 a 2,0 ml se añadió compuesto 1.3 (110 mg, 0,59 mmoles, 1,0 equiv). El tubo de microondas se cerró herméticamente y se calentó a 120 °C por detrás de una protección para explosiones durante 2,5 h. Tras enfriar (a ~60 °C), se añadió NMP (2,5 ml) a la mezcla de reacción. La mezcla se sometió a ultrasonidos y se calentó (a ~60 °C) hasta que el sólido se disolvió completamente. La solución resultante se enfrió a 40 °C y se añadió una mezcla 3:1 de H₂O/CH₃CN (5 ml). Precipitó un sólido y se recogió a través de filtración. El sólido beige claro se lavó posteriormente con H₂O y se secó para proporcionar 97 mg (57%) del

compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES+) 288 (M+H)⁺. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 9,73 (s ancho, 1H), 7,22 (t, J = 8,0 Hz, 1H), 7,12-7,04 (m, 3H), 6,45 (d, J = 8,0 Hz, 1H), 4,90-4,86 (m, 1H), 4,42 (q, J = 6,7 Hz, 1H), 4,31 (d, J = 2,4 Hz, 1H), 2,29 (s, 3H), 1,36 (d, J = 6,7 Hz, 3H), 1,27-1,23 (m, 6H).

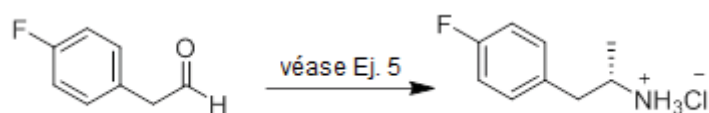
- 5 Ejemplo 51. Preparación de (S)-6-((1-(4-fluorofenil)propan-2-il)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona.



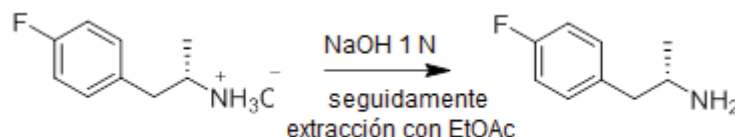
- Compuesto 51.1. 2-(4-fluorofenil)-N-metoxi-N-metilacetamida. A una solución agitada de ácido 2-(4-fluorofenil)acético (15 g, 97,32 mmoles, 1,00 equiv) en CH₂Cl₂ (300 ml) se añadió
 10 cloruro de metoxi(metil)amina (11,1 g, 113,70 mmoles, 1,20 equiv), 4-dimetilaminopiridina (12 g, 98,22 mmoles, 1,00 equiv), hidrocloreto de 1-etil-3-(3-dimetilaminopropil)carbodiimida (28,2 g, 147,10 mmoles, 1,50 equiv) y DIEA (37,5 g, 290,14 mmoles, 3,00 equiv). La solución resultante se agitó a temperatura ambiente durante 16 h y seguidamente se diluyó con EtOAc (150 ml). Las fases orgánicas se lavaron con HCl 1N acuoso (2x150 ml) y
 15 salmuera (2x150 ml). Seguidamente se secó sobre Na₂SO₄ anhidro y se concentró bajo presión reducida. El residuo en bruto se purificó por cromatografía rápida (gel de sílice, eluyendo con EtOAc/éter de petróleo (1:3)). Esto dio lugar a 18 g (88%) del compuesto del título en forma de un aceite amarillo. ¹H-RMN (400 MHz, CDCl₃): δ ppm 7,29-7,25 (m, 2H), 7,03-6,99 (m, 2H), 3,75 (s, 2H), 3,65 (s, 3H), 3,21 (s, 3H).



- 20 Compuesto 51.2. 2-(fluorofenil)acetaldehído. A una solución agitada de 51.1 (3 g, 15,21 mmoles, 1,00 equiv) en THF (60 ml) bajo argón a -10 °C se añadió LiAlH₄ (1,15 g, 30,30 mmoles, 2,00 equiv) en varias tandas (cuidado... reacción exotérmica). La solución resultante se agitó durante 1 h a temperatura ambiente antes de ser enfriada a -10 °C. La
 25 reacción se inactivó seguidamente mediante la adición cuidadosa de una solución acuosa saturada de NH₄Cl (50 ml). El sólido resultante se filtró y el filtrado se extrajo con EtOAc (3x50 ml). Las fases orgánicas se combinaron, se lavaron con salmuera (50 ml), se secaron con Na₂SO₄ anhidro y se concentraron bajo presión reducida para proporcionar 2,5 g (en bruto) del compuesto del título en forma de un aceite amarillo.



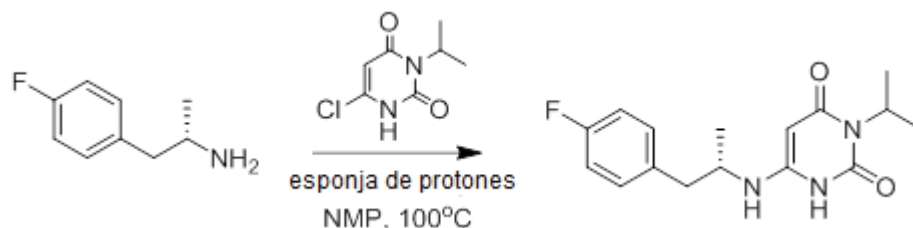
Compuesto 51.3. Hidrocloruro de (S)-1-(4-fluorofenil)propan-2-amina. El compuesto del título se sintetizó según los métodos descritos para la preparación de 5.3, utilizando 51.2 en lugar 3,5-difluorobenzaldehído. LC/MS: m/z (ES⁺) 154 (M+H)⁺.



5

Compuesto 51.4. (S)-1-(4-fluorofenil)propan-2-amina. A una solución acuosa de NaOH 1N (5 ml) se añadió 51.3 (300 mg, 1,59 mmol). La mezcla resultante se agitó durante una hora a 25 °C. La solución resultante se extrajo con EtOAc (2x10 ml). La capa orgánica se secó sobre sulfato de sodio anhidro y se concentró bajo presión reducida para producir 160 mg (65%) del compuesto del título. LC/MS: m/z (ES⁺) 154 (M+H)⁺.

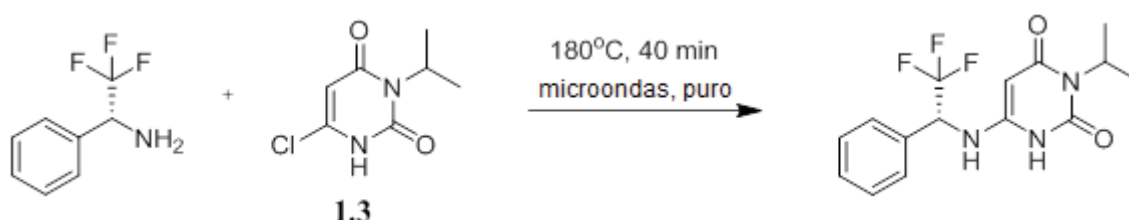
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Compuesto 51. (S)-6-((1-(4-fluorofenil)propan-2-il)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona. A una solución agitada de 51.4 (160 mg, 1,04 mmoles, 2,00 equiv) en NMP (0,5 ml) se añadió 1.3 (99 mg, 0,52 mmoles, 1,00 equiv) y esponja de protones (168 mg, 0,78 mmoles, 1,50 equiv). La solución resultante se agitó durante 5 h a 100 °C en un baño de aceite. La mezcla de reacción se concentró bajo presión reducida. El residuo (100 mg) se purificó mediante RP-HPLC preparativa para proporcionar 30 mg (19%) del compuesto del título en forma de un sólido gris. LC/MS: m/z (ES⁺) 306 (M+H)⁺. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 9,81 (s ancho, 1H), 7,27 (dd, J = 8,8, 5,6 Hz, 2H), 7,17-7,12 (m, 2H), 5,89 (d, J = 7,6 Hz, 1H), 5,00-4,92 (m, 1H), 4,58 (s, 1H), 3,69-3,65 (m, 1H), 2,74 (d, J = 6.4 Hz, 2H), 1,31 (d, J = 6.8 Hz, 6H), 1,08 (d, J = 6.4 Hz, 3H).

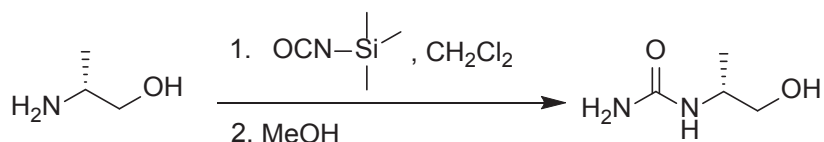
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Ejemplo 52. Preparación de (R)-3-isopropil-6-((2,2,2-trifluoro-1-feniletíl)amino)pirimidino-2,4(1H,3H)-diona (52).

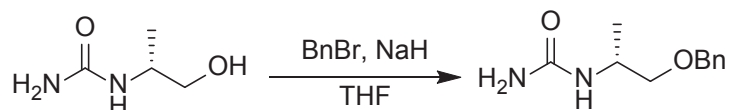


A un vial de microondas de 0,2-0,5 ml se añadió 1.3 (85 mg, 0,45 mmol) y (R)-2,2,2-trifluoro-1-feniletan-1-amina (200 μ l, en exceso). La mezcla de reacción se cerró herméticamente y se calentó a 180 °C en un reactor de microondas durante 40 minutos. La mezcla de reacción se enfrió a temperatura ambiente y seguidamente se añadió NMP (1 ml) para disolver completamente el sólido. Seguidamente se añadió una mezcla 2:1 de H₂O/CH₃CN (6 ml) que dio lugar a una precipitación. El sólido se aisló por filtración, se aisló con H₂O y se secó para proporcionar 50 mg (34% del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES⁺) 328 (M+H)⁺. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 9,79 (s ancho, 1H), 7,50-7,40 (m, 5H), 5,66-5,56 (m, 2H), 4,92-4,87 (m, 2H), 1,28-1,25 (m, 6H).

Ejemplo 53. Preparación de 3-((R)-1-(benciloxi)propan-2-il)-6-(((S)-1-feniletil)amino)pirimidino-2,4(1H,3H)-diona.

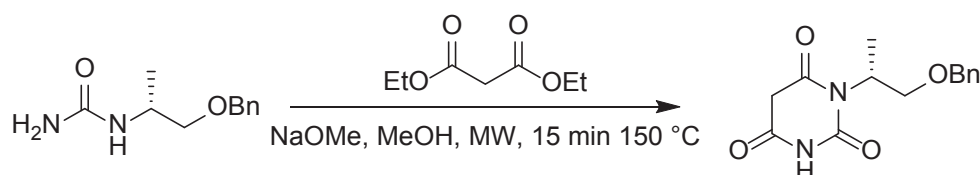


Compuesto 53.1. (R)-1-(1-(benciloxi)propan-2-il)urea. A una solución agitada de (R)-(-)-2-amino-1-propanol (0,65 g, 0,68 mmoles, 1 equiv) en CH₂Cl₂ (10 ml) bajo N₂ a 0 °C se añadió gota a gota isocianato de trimetilsililo (1,00 g, 8,68 mmoles, 1,00 equiv). La mezcla de reacción se agitó durante una noche mientras se calentaba lentamente a temperatura ambiente. Después de enfriar a 0 °C se añadió gota a gota CH₃OH (10 ml). La solución resultante se agitó durante 2 h a temperatura ambiente y seguidamente se concentró bajo presión reducida para proporcionar el compuesto del título (1,02 g, 99%) en forma de un sólido blanco.

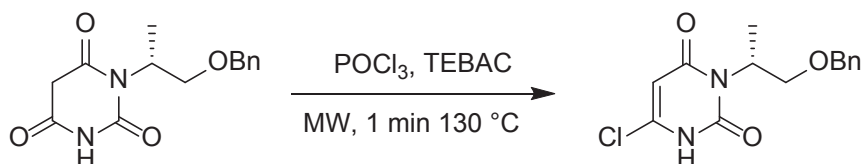


Compuesto 53.2. (R)-1-(1-(1-(benciloxi)propan-2-il)urea)urea. A una solución de hidruro de sodio (0,52 g, 13,2 mmoles, 1,5 equiv) en THF (10 ml) a 0 °C se añadió 53.1 (1,02 g, 1 equiv). La mezcla de reacción se agitó durante 20 minutos a 0 °C bajo N₂ antes de que se añadiera bromuro de bencilo (1,03 ml, 8,67 mmoles, 1 equiv). La mezcla de reacción se agitó durante

una noche mientras se calentaba lentamente a temperatura ambiente. La mezcla de reacción se inactivó con H₂O (3 ml) y se extrajo EtOAc (15 ml), se secó con Na₂SO₄ anhidro, se filtró y se concentró. El residuo resultante se purificó por cromatografía rápida (10% de CH₃OH en CH₂Cl₂) para proporcionar 510 mg (28%) del compuesto del título. LC/MS: m/z (ES+) 209 (M+H)⁺. ¹H-RMN (400 MHz, CDCl₃): δ ppm 7,42 - 7,27 (m, 5H), 4,79 (d, J = 6. 7 Hz, 1H), 4,52 (d, J = 2,7 Hz, 2H), 3,91 (s, 1H), 3,51 (dd, J = 9,4. 3,9 Hz, 1H), 3,40 (dd, J = 9,2. 5,3 Hz, 1H), 1,19 (d, J = 7,0 Hz, 3H).

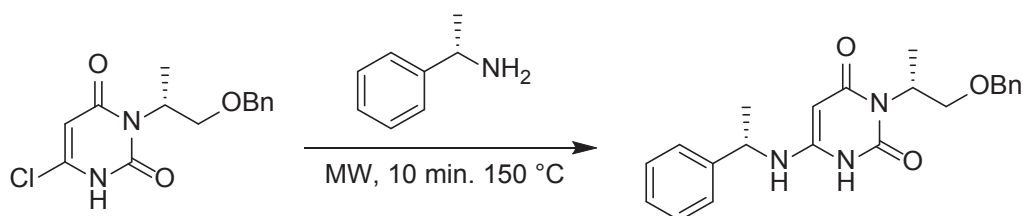


Compuesto 53.3. (*R*)-1-(1-(benciloxi)propan-2-il)pirimidino-2,4,6(1H,3H,5H)-triona. A un vial de microondas que contenía 53.2 (0,51 g, 2,42 mmoles, 1 equiv) en CH₃OH (10 ml) se añadió malonato de dietilo (2,55 g, 2,55 mmoles, 1,05 equiv) seguido de metóxido de sodio (solución al 25% p en CH₃OH, 1,31 g, 6,06 mmoles, 2,5 equiv). El vial se tapó y la mezcla de reacción se calentó en un reactor de microondas durante 15 minutos a 150 °C. Después de enfriar a temperatura ambiente, la mezcla de reacción se inactivó con H₂O (2 ml) y el pH se ajustó a 3 con HCl concentrado. La mezcla de reacción se transfirió a un matraz de fondo redondo y se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía rápida (5% de CH₃OH en CH₂Cl₂) para proporcionar 0,62 g (92%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES+) 277 (M+H)⁺. ¹H-RMN (400 MHz, CDCl₃): δ ppm 7,99 (s, 1H), 7,38-7,22 (m, 5H), 5,16-5,11 (m, 1H), 4,52 (d, J = 12,0 Hz, 1H), 4,45 (d, J = 12,0 Hz, 1H), 4,02 (t, J = 9,8 Hz, 1H), 3,56 (q, J = 1,57 Hz, 2H), 1,37 (d, J = 7,00 Hz, 3H).



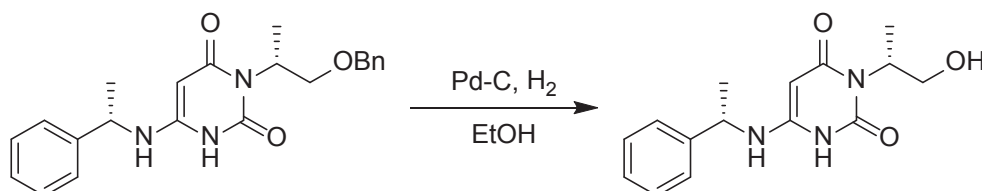
Compuesto 53.4. (*R*)-3-(1-(benciloxi)propan-2-il)-6-cloropirimidino-2,4(1H,3H)-diona. A un vial de microondas que contenía 53.3 (0,25 g, 0,91 mmoles, 1 equiv) se añadió cloruro de tribencilamonio (0,28 g, 1,26 mmoles, 1,4 equiv) y POCl₃ (1 ml). El vial se tapó y la mezcla de reacción se calentó en un reactor de microondas durante 1 minuto a 130 °C. La mezcla de reacción se transfirió a un matraz de fondo redondo y se concentró bajo presión reducida. El residuo resultante se disolvió en CH₂Cl₂ (5 ml) y se añadió cuidadosamente agua (2 ml). La mezcla se agitó durante 10 minutos. Las capas se separaron y la capa orgánica se secó

con Na₂SO₄, se filtró y se concentró bajo presión reducida. El residuo resultante se purificó por cromatografía rápida (gel de sílice, 5% CH₃OH en CH₂Cl₂) para proporcionar 150 mg (55%) del compuesto del título. LC/MS: m/z (ES+) 295 (M+H)⁺. ¹H-RMN (400 MHz, CDCl₃): δ ppm 10,27 (s, 1H), 7,36-7,20 (m, 5H), 5,32- 5,21 (m, 2H), 4,57 (d, J = 12,0 Hz, 1H), 4,48 (d, J = 12,0 Hz, 1H), 4,10 (dd, J = 10,0, 9,2 Hz, 1H), 1,40 (d, J = 7,0 Hz, 3H).



Compuesto 53. 3-((*R*)-1-(benziloxy)propan-2-il)-6-(((*S*)-1-feniletil)amino)pirimidino-2,4(1H,3H)-diona. A un vial de microondas que contenía (*S*)-α-metilbencilamina (1,5 ml) se añadió 53.4 (0,12 g, 0,42 mmol). El vial se tapó y la mezcla de reacción se calentó en un reactor de microondas durante 10 minutos a 150 °C. Después de enfriar, la mezcla de reacción se filtró a través de un cartucho de gel de sílice (10% de CH₃OH en CH₂Cl) y el filtrado se concentró bajo presión reducida. El residuo resultante se disolvió en CH₂Cl₂ (10 ml) y se lavó con HCl al 10% (5 ml). La capa orgánica se secó con Na₂SO₄ anhidro, se filtró y se concentró para proporcionar 150 mg (94%) del compuesto del título. LC/MS: m/z (ES+) 380 (M+H)⁺. ¹H-RMN (400 MHz, CDCl₃): δ ppm 9,96 (s ancho 1H), 7,35-7,24 (m, 10H), 4,70 (s ancho, 1H), 4,53-4,41 (m, 4H), 4,03-3,99 (m, 1H), 3,65-3,61 (m, 1H), 1,49 (d, J = 6. 7 Hz, 3H), 1,37 (d, J = 7,0 Hz, 3H).

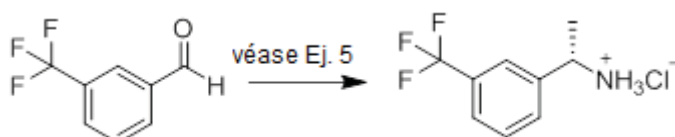
Ejemplo 54. Preparación de 3-((*R*)-1-hidroxipropan-2-il)-6-(((*S*)-1-feniletil)amino)pirimidino-2,4(1H,3H)-diona (54).



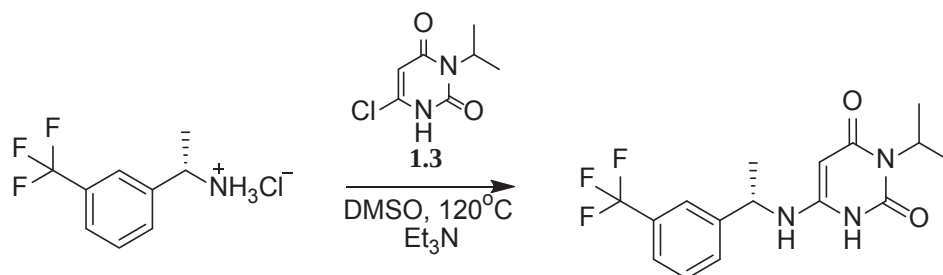
A una solución de 53 (0,10 g, 0,26 mmoles, 1 equiv) en EtOH (2 ml) se añadió paladio sobre carbono (contenido de 10% p (base seca), carbón activado con matriz, soporte húmedo, tipo Degussa, 0,025 g). El matraz de la reacción se purgó con nitrógeno y seguidamente se equipó con un balón de H_{2(g)}. La mezcla de reacción se sometió a vacío y seguidamente se rellenó con H_{2(g)} este procedimiento de bombeo/purga se repitió tres veces y la mezcla de reacción se agitó durante 4 h a temperatura ambiente. Después de purgar con nitrógeno, la mezcla de reacción se filtró y el filtrado se concentró bajo presión reducida. El residuo resultante se puso en suspensión en CH₃CN (2 ml) y el precipitado se aisló por filtración. El

precipitado se disolvió en $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$ (1:1, 2 ml) y se filtró a través de un filtro de 25 mm de PTFE 2 μM y se concentró bajo presión reducida para proporcionar 27 mg (35%) del compuesto del título. LC/MS: m/z (ES+) 290 ($\text{M}+\text{H}$)⁺. ¹H-RMN (400 MHz, CDCl_3): δ ppm 9,67 (s, 1H), 7,35-7,24 (m, 5H), 5,64 (d, $J = 5,5$ Hz, 1H), 5,08-5,04 (m, 1H), 4,66 (s, 1H), 4,42-4,35 (m, 1H), 4,24 (s, 1H), 4,04-3,91 (m, 1H), 3,78-3,68 (m, 1H), 1,50 (d, $J = 6,70$ Hz, 3H), 1,35 (d, $J = 7,00$ Hz, 3H).

Ejemplo 55. Preparación de (S)-3-isopropil-6-((1-(3-(trifluorometil)fenil)etil)amino) pirimidino-2,4(1H,3H)-diona.



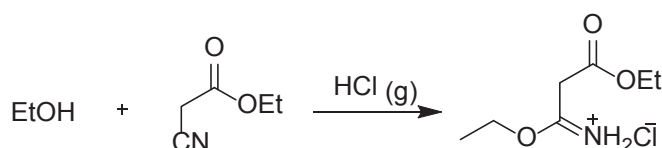
Compuesto 55.1. Hidrocloruro de (S)-1-(3-(trifluorometil)fenil)etan-1-amina. El compuesto del título se sintetizó según los métodos descritos para la preparación de 5.3, utilizando 3-(trifluorometil)benzaldehído en lugar de 3,5-difluorobenzaldehído.



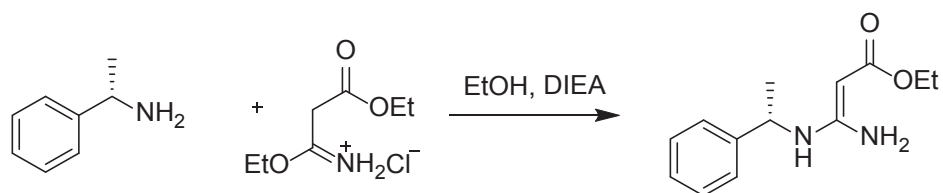
Compuesto 55. (S)-3-isopropil-6-((1-(3-(trifluorometil)fenil)etil)amino) pirimidino-2,4(1H,3H)-diona. A una solución agitada de 55.1 (59,8 mg, 0,27 mmoles, 1,00 equiv) en DMSO (1,5 ml) bajo una atmósfera de argón inerte se añadió Et_3N (0,2 ml) y 1.3 (50 mg, 0,27 mmoles, 1,00 equiv). La solución resultante se agitó durante 6 h a 120 °C en un baño de aceite. Después de enfriar, la mezcla se concentró bajo presión reducida y el residuo resultante (75 mg) se purificó mediante RP-HPLC preparativa para proporcionar 6,5 mg (7%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES+) 342 ($\text{M}+\text{H}$)⁺. ¹H-RMN (300 MHz, $\text{DMSO}-d_6$): δ ppm 7,78 (s, 1H), 7,74-7,60 (m, 3H), 7,20 (br, 1H), 6,02 (br, 1H), 4,96 (dt, $J = 10,1, 5,1$ Hz, 1H), 4,67-4,64 (m, 1H), 4,36 (s, 1H), 1,44 (d, $J = 6,8$ Hz, 3H), 1,31-1,28 (m, 6H).

Ejemplo 56. Preparación de (S)-3-isopropil-6-((1-(2-cyanofenil)etil)amino)pirimidino-2,4(1H,3H)-diona (56).

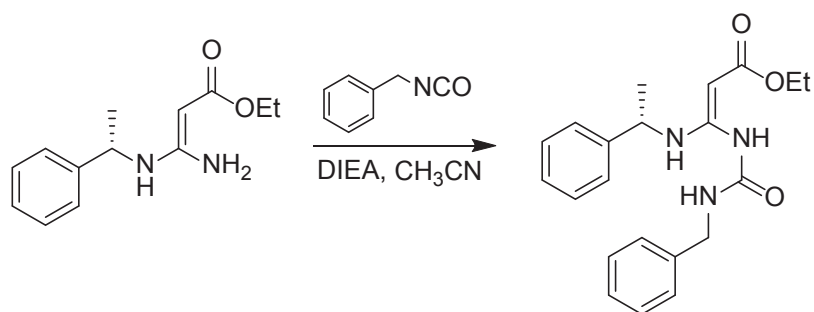
Ejemplo 57. Preparación de (S)-3-bencil-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona.



20 Compuesto 57.1. Cloruro de 3-etoxi-3-oxo-1-(1-etoxi)propan-1-iminio. A una solución agitada de cianoacetato de etilo (5,0 g, 44 mmol) en Et₂O anhidro (5 ml) se añadió EtOH absoluto (3 ml). La mezcla de reacción se enfrió a 0 °C y se hizo burbujear gas de HCl durante 10 minutos. La mezcla de reacción se calentó a temperatura ambiente y se agitó durante 16 h. El precipitado blanco que se formó se filtró y se lavó con Et₂O (40 ml) y se secó para
25 proporcionar el compuesto del título (6,99 g) en forma de un sólido blanco. LC/MS: m/z (ES+) 160 (M+H)⁺.

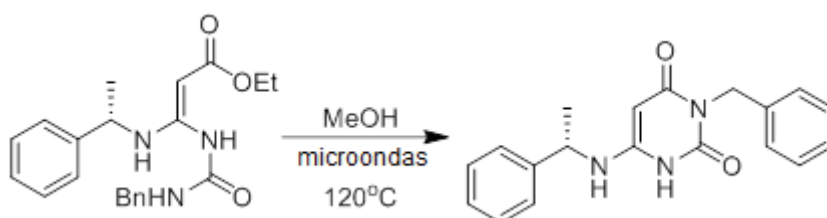


Compuesto 57.2. (S,E/Z)-3-amino-3-((1-pheniletil)amino)acrilato de etilo. A una solución agitada de 57.1 (585 mg, 3,0 mmol) en EtOH (15 ml) se añadió DIEA (0,8 ml) y (S)- α -metilbencilamina (290 mg, 2,4 mmol). La reacción se agitó durante 16 h y se concentró. El producto en bruto se purificó mediante cromatografía de columna rápida (gel de sílice, eluyendo con CH₃OH en CH₂Cl₂ (0 a 10%)) para proporcionar 0,57 g (98%) del compuesto del título en forma de un aceite claro. Un análisis RMN puso de manifiesto que el producto era una mezcla de isómeros E/Z. LC/MS: m/z (ES⁺) 235 (M+H)⁺.



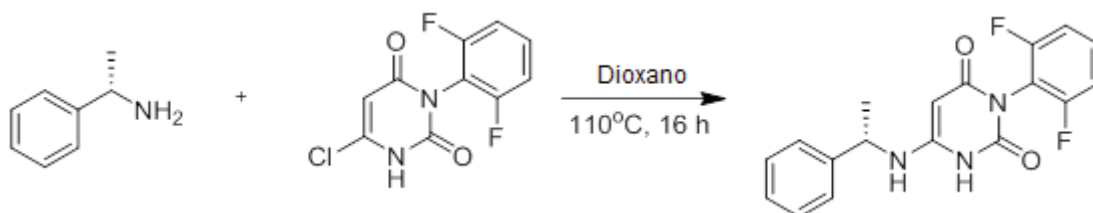
Compuesto 57.3. (S,Z)-3-(3-bencilureido)-3-((1-feniletil)amino)acrilato de etilo.

Se ajustaron dos reacciones en paralelo y posteriormente se combinaron ya que ambas dieron lugar a la formación de un producto (por HPLC). En la primera reacción, se añadió isocianato de bencilo (150 μ l, 1,2 mmol) a una solución agitada de 57.2 (143 mg, 0,61 mmol) en CH₃CN (1 ml). Después de 10 minutos, se añadió DIEA (300 μ l). La reacción se agitó durante 10 minutos adicionales y se inactivó con H₂O (12 ml). Precipitó un sólido y se separó por filtración. En la segunda reacción, se añadió isocianato de bencilo (150 μ l, 1,2 mmol) a una solución agitada de 57.2 (143 mg, 0,61 mmol) y DIEA (300 μ l) en CH₃CN (1 ml). Después de 10 minutos, la mezcla de reacción se inactivó con H₂O (10 ml). La mezcla resultante se diluyó con EtOAc (40 ml) y las capas se separaron. A la capa orgánica se añadió el filtrado de la primera reacción. Las capas se separaron y las fases orgánicas se concentraron para proporcionar el compuesto del título que se utilizó sin purificación adicional.



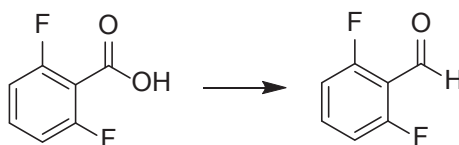
Compuesto 57. (S)-3-bencil-6-((1-feniletíl)amino)pirimidino-2,4(1H,3H)-diona. Se realizaron 2 reacciones y posteriormente se combinaron ya que ambas dieron lugar a la formación de un producto (por HPLC). La primera reacción utilizó 1/3 de 57.3 en bruto en CH₃OH (1 ml). Se calentó en un reactor de microondas a 120 °C durante 10 minutos. Los 2/3 restantes de 57.3 en bruto en CH₃OH (2 ml) se calentaron en un reactor de microondas a 120 °C durante 20 minutos. Después de enfriar a temperatura ambiente, las reacciones se combinaron y el CH₃OH se separó bajo presión reducida. Se añadió una mezcla 50/50 de CH₃CN/H₂O con 0,1% de TFA (5 ml) al residuo resultante. Precipitó un sólido y se filtró. El sólido marrón resultante se lavó con EtOAc para proporcionar 7 mg del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES⁺) 322 (M+H)⁺. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 10,05 (s ancho, 1H), 7,35-7,31 (m, 4H), 7,26-7,16 (m, 6H), 6. 61 (d, J = 7,0 Hz, 1H), 4,79 (s, 2H), 4,52 (quin, J = 6. 8 Hz, 1H), 4,42 (d, J = 2,3 Hz, 1H), 1,39 (d, J = 6. 7 Hz, 3H).

Ejemplo 58. Preparación de (S)-3-(2,6-difluorofenil)-6-((1-feniletíl)amino)pirimidino-2,4(1H,3H)-diona (58).

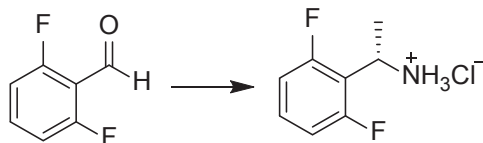


El compuesto del título se sintetizó según un procedimiento ligeramente modificado como se describió en el ejemplo 50. En este caso, se utilizó 1,4-dioxano como disolvente y la reacción se calentó a 110 °C durante 16 h. La mezcla resultante se enfrió y se concentró bajo presión reducida. El producto en bruto se purificó mediante RP-HPLC preparativa para proporcionar 19 mg del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES⁺) 344 (M+H)⁺. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 10,44 (s ancho, 1H), 7,52-7,42 (m, 2H), 7,39-7,36 (m, 3H), 7,34-7,16 (m, 3H), 6. 91 (s ancho, 1H), 4,65-4,56 (m, 1H), 4,52 (s, 1H), 1,43 (d, J = 6. 7 Hz, 3H).

Ejemplo 59. Preparación de (S)-6-((1-(2,6-difluorofenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona.

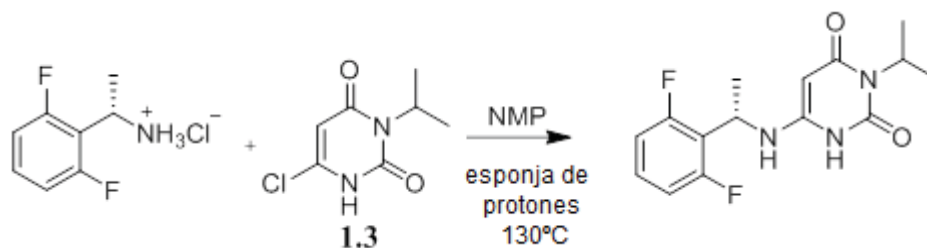


Compuesto 59.1. 2,6-difluorobenzaldehído. El compuesto del título se sintetizó según los métodos descritos para la preparación de 51.2. En este caso, se utilizó ácido 2,6-difluorobenzoico disponible en el comercio en lugar de ácido 2-(4-fluorofenil)acético.

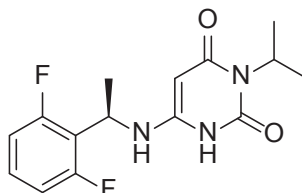


5

Compuesto 59.2. Hidrocloruro de (S)-1-(2,6-difluorofenil)etan-1-amina. El compuesto del título se sintetizó según los métodos descritos para la preparación 5.3. En este caso se utilizó 59.1 en lugar de 3,5-difluorobenzaldehído.

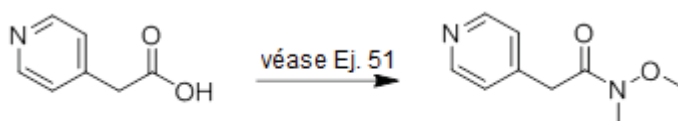


- 10 Compuesto 59. (S)-6-((1-(2,6-difluorofenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona. Se realizó la reacción de 59.1 con 1.3 de una manera similar al procedimiento descrito en el ejemplo 51. Sin embargo, en este caso la mezcla de reacción se calentó a 130 °C durante 5 h. Un análisis de la mezcla de reacción a través de HPLC quiral puso de manifiesto cantidades no despreciables del enantiómero. La separación de los enantiómeros se realizó
- 15 utilizando HPLC quiral con una mezcla isocrática de EtOH:hexano (1:4) como eluyente a partir de una columna de 30x150 mm Phenomenex Lux-2 5μ Cellulose-2 (pasada de 40 minutos). LC/MS: m/z (ES+) 310 (M+H)⁺. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 9,80 (s ancho, 1H), 7,45-7,41 (m, 1H), 7,18-7,14 (m, 2H), 6, 52 (d, J = 8,0 Hz, 1H), 4,94-4,88 (m, 1H), 4,79 (quint, J = 7,6 Hz, 1H), 4,41 (s, 1H), 1,56 (d, J = 6, 8 Hz, 3H), 1,30-1,26 (m, 6H).
- 20 Ejemplo 60. Preparación de (R)-6-((1-(2,6-difluorofenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona (60R).

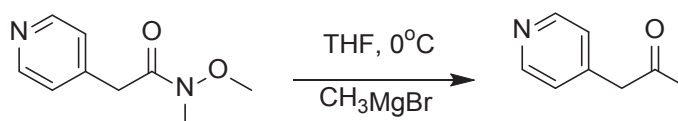


El compuesto del título se generó como un subproducto de la química realizada en el ejemplo 59. Se aisló a través de HPLC quiral preparativa con una mezcla isocrática de EtOH:hexano (1:4) como eluyente a partir de una columna de 30x150 mm Phenomenex Lux-2 5 μ Cellulose-2 (pasada de 40 minutos). LC/MS: m/z (ES+) 310 (M+H)⁺. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 9,98-9,61 (br, 1H), 7,45-7,41 (m, 1H), 7,18-7,14 (m, 2H), 6,52 (d, J = 8,0 Hz, 1H), 4,94-4,88 (m, 1H), 4,79 (quint, J = 7,6 Hz, 1H), 4,41 (s, 1H), 1,56 (d, J = 6,8 Hz, 3H), 1,30-1,26 (m, 6H).

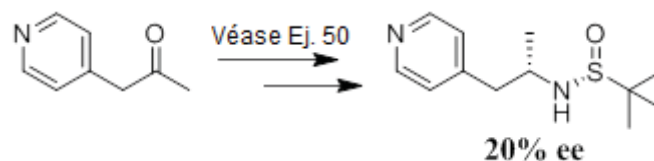
Ejemplo 61. Preparación de (S)-3-isopropil-6-((1-(piridin-4-il)propan-2-il)amino)pirimidino-2,4(1H,3H)-diona.



Compuesto 61.1. N-metoxi-N-metil-2-(piridin-4-il)acetamida. El compuesto del título se sintetizó según los métodos descritos para la preparación de 51.1. En este caso se utilizó ácido 4-piridinoacético disponible en el comercio en lugar de ácido 2-(4-fluorofenil)acético.

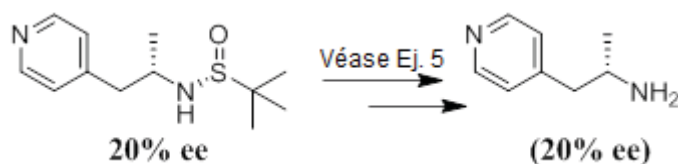


Compuesto 61.2. 1-(Piridin-4-il)propan-2-ona. A un matraz de fondo redondo de 3 bocas de 250 ml purgado y mantenido con una atmósfera de argón, se añadió THF (70 ml) y N-metoxi-N-metil-2-(piridin-4-il)acetamida (7,0 g, 0,39 moles, 1 equiv). La mezcla se enfrió a 0 °C y se añadió gota a gota CH₃MgBr (3M en THF, 65 ml, 5,0 equiv). La solución resultante se calentó a temperatura ambiente y se agitó durante 16 h. La mezcla de reacción se enfrió a 0 °C y se inactivó mediante la adición de NH₄Cl saturado (ac. 100 ml). La solución resultante se extrajo con EtOAc (3x200 ml). Las capas orgánicas se combinaron, se secaron sobre Na₂SO₄ anhidro y se concentraron bajo presión reducida. El producto en bruto se purificó mediante cromatografía rápida (gel de sílice, CH₂Cl₂/CH₃OH (20:1)) para producir 2,7 g (51%) del compuesto del título en forma de un aceite amarillo. ¹H-RMN (400 MHz, CDCl₃): δ ppm 8,58 (m, 2H), 7,17 (d, J = 0,4 Hz, 2H), 3,75 (s, 2H), 2,24 (s, 3H).

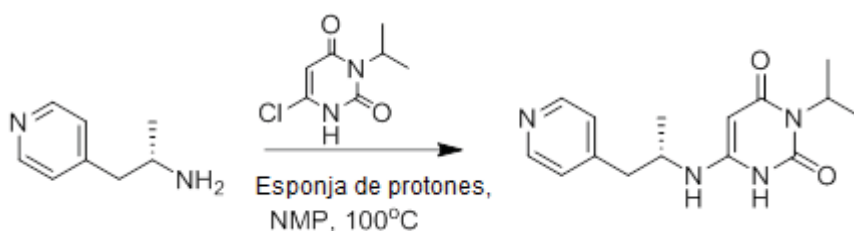


Compuesto 61.3. (R)-2-metil-N-((S)-1-(piridin-4-il)propan-2-il)propano-2-sulfinamida. El compuesto del título se preparó según los procedimientos descritos en el ejemplo 50

utilizando 61.2 en lugar de 1-(3-metilfenil)etanona. En este caso, la reducción utilizando L-selectrida dio lugar al aislamiento del compuesto del título (61.3) (exceso enantiómero de 20%).

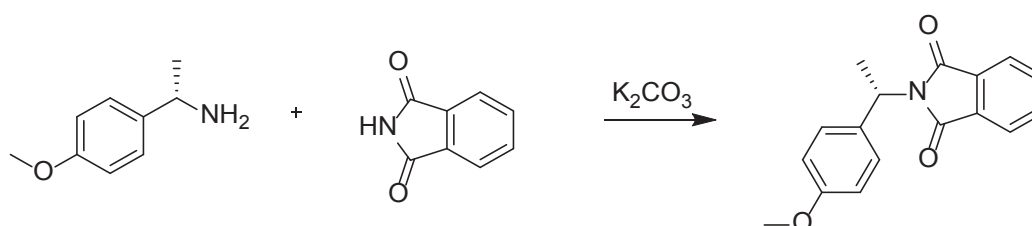


- 5 Compuesto 61.4. . (S)-1-(piridin-4-il)propan-2-amina. El compuesto del título se preparó utilizando un procedimiento en dos etapas como se describe en el ejemplo 5. En primer lugar, se convirtió la sulfonamida 61.3 en la sal de hidrocloreuro mediante tratamiento con HCl en 1,4-dioxano (véase el protocolo para el compuesto 5.3). La posterior basificación libre de la sal de hidrocloreuro (véase el protocolo para el compuesto 5) dio lugar al compuesto del
- 10 título (~20% ee).

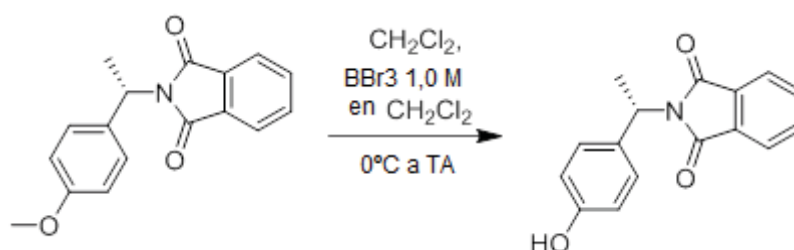


- Compuesto 61. (S)-3-isopropil-6-((1-(piridin-4-il)propan-2-il)amino)pirimidino-2,4(1H,3H)-diona. EL compuesto del título se preparó según el protocolo descrito para 51. En este caso, la mezcla de reacción se agitó a 100 °C durante 1 h. La mezcla de reacción se concentró
- 15 bajo presión reducida y el residuo (100 mg) se purificó mediante HPLC preparativa para proporcionar 13,1 mg del compuesto del título en forma de una mezcla de enantiómeros. Los enantiómeros (13,1 mg) se separaron por HPLC preparativa quiral con una columna de 5 µm, 2x25 cm Chiralpak IC, utilizando una mezcla isocrática de EtOH:hexano (1:3) como eluyente (pasada de 20 minutos). Esto dio lugar 8,2 mg (8%) del compuesto del título en
- 20 forma de un sólido amarillo claro. LC/MS: m/z (ES+) 289 (M+H)⁺. ¹H-RMN (300 MHz, CD₃OD): δ ppm 8,41 (d, J = 5,7 Hz, 2H), 7,29 (d, J = 6. 0 Hz, 2H), 5,06-4,96 (m, 1H), 4,68 (s, 1H), 3,82-3,75 (m, 1H), 2,87-2,83 (m, 2H), 1,36 (d, J = 7,2 Hz, 6H), 1,12 (d, J = 7,2 Hz, 3H).

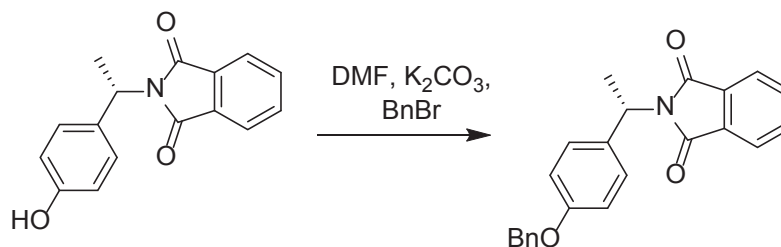
- Ejemplo 62. Preparación de (S)-6-((1-(4-(benciloxi)fenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona.
- 25



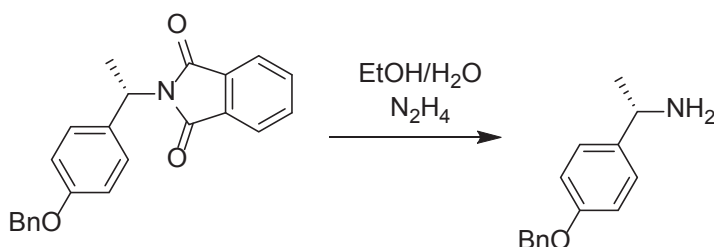
Compuesto 62.1. (S)-2-(1-(4-(metoxi)fenil)etil)isoindolino-1,3-diona. A ftalimida (1,3 g, 0,0088 mol) en una vial de microondas de 2-5 ml se añadió (S)-1-(4-metoxifenil)etan-1-amina (2,20 ml, 0,015 mol) y K_2CO_3 (1,2 g, 0,0087 mol). La mezcla de reacción se tapó y se calentó a 160 °C durante 2 minutos. El sólido en bruto resultante se puso en suspensión en n-BuOH y se filtró. El filtrado se apartó. El sólido se lavó con H_2O y el filtrado se desechó. El sólido se lavó con CH_2Cl_2 y el filtrado resultante se dividió en partes con H_2O . Las fases orgánicas (capa de n-BuOH y CH_2Cl_2) se combinaron y se concentraron. El residuo en bruto se purificó mediante cromatografía de columna de gel de sílice usando CH_2Cl_2 como eluyente para producir 1,6 g (64%) del compuesto del título. LC/MS: m/z (ES+) 282 (M+H)⁺.



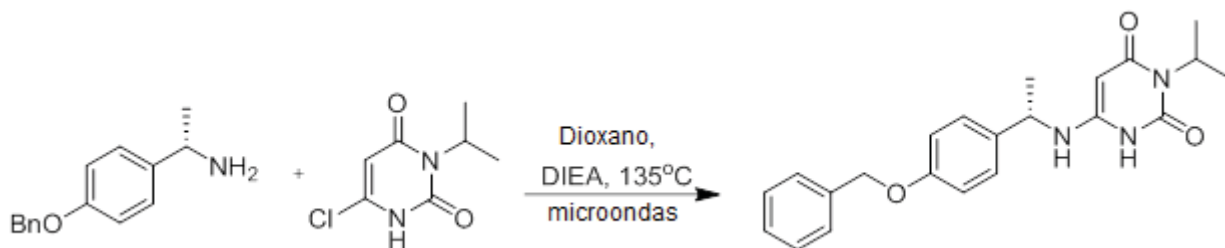
Compuesto 62.2. (S)-2-(1-(4-hidroxifenil)etil)isoindolino-1,3-diona. A una solución agitada de 62.1 (640 mg, 2,28 mmol) en CH_2Cl_2 (8 ml) a 0 °C se añadió BBr_3 (1M en CH_2Cl_2 , 3 ml, gota a gota). La reacción se dejó calentar a temperatura ambiente durante 30 minutos. Permaneció una cantidad significativa de material de partida, por lo que la reacción se volvió a enfriar a 0 °C. Se añadió BBr_3 adicional (2 ml, 1,0M en CH_2Cl_2) y la reacción se dejó calentar a temperatura ambiente durante 30 minutos. La mezcla de reacción se vertió sobre $NaHCO_3$ al 5% (ac en hielo). Las capas se separaron y la capa acuosa se extrajo adicionalmente con CH_2Cl_2 . Las fases orgánicas combinadas se lavaron con salmuera, se secaron con Na_2SO_4 anhidro y se concentraron para proporcionar 500 mg (82%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES+) 268 (M+H)⁺.



Ejemplo 62.3. (S)-2-(1-(4-(benciloxi)fenil)etil)isoindolino-1,3-diona. A una solución agitada de 62.2 (500 mg, 1,87 mmol) en DMF (10 ml) se añadió K₂CO₃ (560 mg, 4,05 mmoles, 2,17 equiv) y bromuro de bencilo (0,30 ml, 420 mg, 2,45 mmoles, 1,3 equiv). La reacción se agitó a 120 °C durante 5 h. La reacción se enfrió y se filtró. Se añadió agua (20 ml) y se utilizó EtOAc (60 ml) para extraer producto. La capa orgánica se lavó sucesivamente con H₂O, Na₂CO₃ al 10% (ac), H₂O y salmuera (2x). Las fases orgánicas se secaron sobre MgSO₄ anhidro y se concentraron. El residuo en bruto se purificó por cromatografía rápida (gel de sílice, eluyendo CH₂Cl₂) para producir 480 mg (72%) del compuesto del título. LC/MS: m/z (ES⁺) 358 (M+H)⁺.



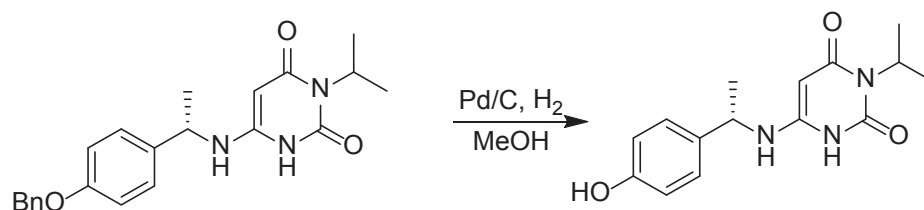
Compuesto 62.4. (S)-1-(4-(benciloxi)fenil)etan-1-amina. A una solución agitada de 62.3 (480 mg, 1,34 mmol) en una mezcla de EtOH/H₂O 70/30 (20 ml) se añadió N₂H₄·H₂O (1,5 ml). La reacción se agitó durante 16 h y se concentró. El material resultante se dividió en partes entre EtOAc y Na₂CO₃ al 5% (ac). Las capas se separaron y la capa de EtOAc se lavó con salmuera y se concentró para proporcionar 280 mg (92%) del compuesto del título que se usó sin purificación adicional. LC/MS: m/z (ES⁺) 228 (M+H)⁺.



Compuesto 62. (S)-6-((1-(4-(benciloxi)fenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona. A un vial de microondas de 0,5-2,0 ml se añadió 1,4-dioxano (1 ml), 62.4 (280 mg, 1,23 mmol), 1.3 (250 mg, 1,33 mmol) y DIEA (400 µl). La mezcla de reacción se tapó, se calentó a 135 °C en un reactor de microondas durante 1,5 h, se dejó enfriar y seguidamente se concentró. La mezcla de reacción en bruto se trató con CH₃CN/H₂O 50/50 (TFA al 0,1%) que condujo a una precipitación. El sólido se aisló por filtración y se secó para proporcionar 45 mg (10%) de un sólido blanco. LC/MS: m/z (ES⁺) 380 (M+H)⁺. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 9,73 (br, 1H), 7,43-7,29 (m, 5H), 7,23 (d, J = 14,5 Hz, 2H), 6. 97 (d, J = 14,5 Hz, 2H), 6. 42 (d, J = 7,0 Hz, 1H), 5,06 (s, 2H), 4,93-4,85 (m, 1H), 4,42 (quin, J = 6. 8

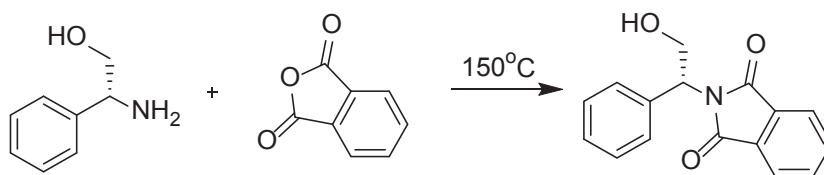
Hz, 1H), 4,32 (d, J = 1,6 Hz, 1H), 1,35 (d, J = 6. 7 Hz, 3H), (m, 1H) 1,27-1,23 (m, 6H).

Ejemplo 63. Preparación de (S)-6-((1-(4-hidroxifenil)etil)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona (63).

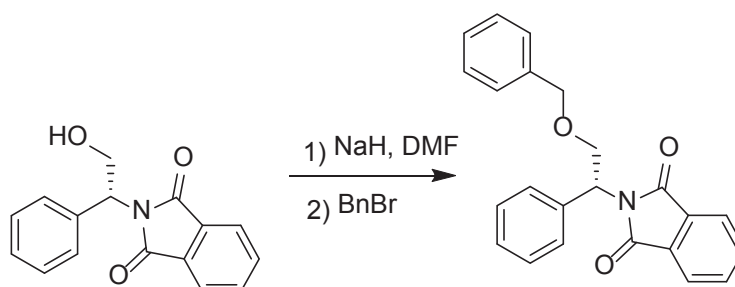


5 A una solución agitada de 62 (43 mg, 0,11 mmol) en CH₃OH (20 ml) se añadió paladio sobre carbono (50 mg, contenido de 10% p (base seca), carbono activado en matriz, soporte húmedo, tipo Degussa). El recipiente se purgó nitrógeno seguido de hidrógeno. La mezcla de reacción se agitó bajo una atmósfera de H₂ durante 2 h. Después de purgar el sistema con nitrógeno, la mezcla se filtró a través de celite y se concentró. El sólido resultante se
10 disolvió en 8 ml de CH₃CN y seguidamente se añadieron 20 ml de H₂O (TFA AL 0,1%). La solución se congeló y se liofilizó para proporcionar 29 g (90%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES+) 290 (M+H)⁺. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 9,70 (br, 1H), 9,32 (s, 1H), 7,10 (d, J = 8,6 Hz, 2H), 6. 71 (d, J = 8,6 Hz, 2H), 6. 36 (d, J = 7,0 Hz, 1H), 4,92-4,85 (m, 1H), 4,37-4,33 (m, 2H), 1,33 (d, J = 6. 7 Hz, 3H), 1,27-1,23 (m,
15 6H).

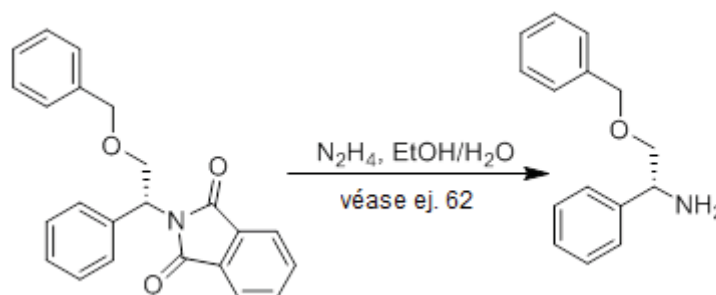
Ejemplo 64. Preparación de (R)-6-((2-(benciloxi)-1-fenilet)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona.



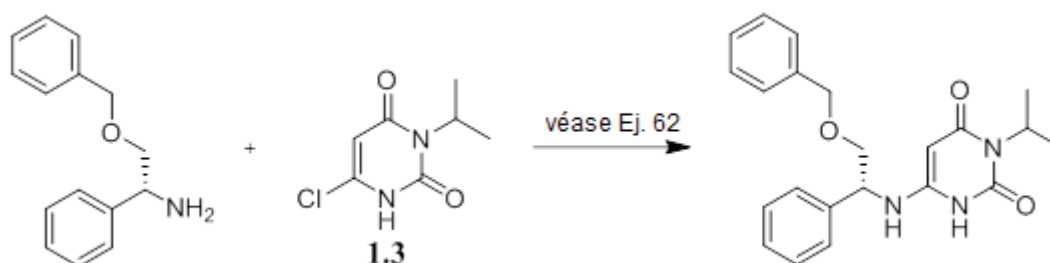
Compuesto 64.1. (R)-2-(2-hidroxi-1-fenilet)isoindolino-1,3-diona. A un vial de microondas de
20 2,0-5,0 ml se añadió (R)-2-amino-2-feniletan-1-ol (1,53 g, 0,0112 mol) y anhídrido ftálico (1,65 g, 0,0112 mol). La mezcla de reacción se tapó y se calentó a 150 °C durante 2 minutos en un reactor de microondas. La mezcla se enfrió y se diluyó con CH₃CN (2 ml), se volvió a tapar y se calentó en el reactor de microondas una segunda vez a 140 °C durante 20 minutos. Los componentes volátiles se separaron bajo presión reducida y el sólido resultante
25 se puso en suspensión en EtOAc (50 ml). La capa orgánica se lavó con NaHCO₃ al 5% (ac), H₂O y salmuera, se secó con MgSO₄ anhidro y se concentró. El residuo en bruto se purificó por cromatografía rápida (gel de sílice) eluyendo con CH₃OH en CH₂Cl₂ (0 a 5%) para producir 2,81 g (94%) del compuesto del título. LC/MS: m/z (ES+) 268 (M+H)⁺.



Compuesto 64.2. (*R*)-2-(2-(benciloxi)-1-feniletíl)isoindolino-1,3-diona. El compuesto del título se preparó de una manera similar al procedimiento descrito para 62.3. Sin embargo, en este caso se usó NaH (dispersión al 60% en aceite mineral, 1,2 equiv) en lugar de K₂CO₃. Específicamente, se añadió NaH a 0 °C y se agitó a temperatura ambiente durante 45 minutos. La reacción se volvió a enfriar a 0 °C y seguidamente se añadió bromuro de bencilo (1,2 equiv). Un procedimiento de tratamiento como se describió para 62.3 seguido de cromatografía rápida (gel de sílice eluyendo con CH₂Cl₂) produjo el compuesto del título con un rendimiento de 59%. LC/MS: *m/z* (ES⁺) 358 (M+H)⁺. ¹H-RMN (400 MHz, CDCl₃): δ ppm 7,84-7,79 (m, 2H), 7,72-7,67 (m, 2H), 7,52-7,48 (m, 2H), 7,37-7,20 (m, 8H), 5,62 (dd, *J* = 10,2. 5,9 Hz, 1H), 4,63 (t, *J* = 10,2 Hz, 1 H), 4,58 (s, 2H), 4,06-4,01 (m, 1H).



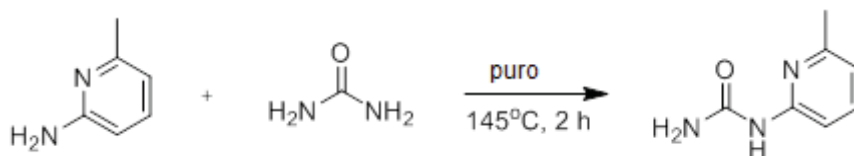
Compuesto 64.3. (*R*)-2-(benciloxi)-1-feniletan-1-amina. El compuesto del título se preparó de una manera similar al procedimiento descrito para 62.4. LC/MS: *m/z* (ES⁺) 228 (M+H)⁺. ¹H-RMN (400 MHz, CDCl₃): δ ppm 7,40-7,24 (m, 10H), 4,56 (d, *J* = 2,0 Hz, 2H), 4,25 (dd, *J* = 8,8, 3,7 Hz, 1 H), 3,65-3,60 (m, 1H), 3,49-3,44 (m, 1H).



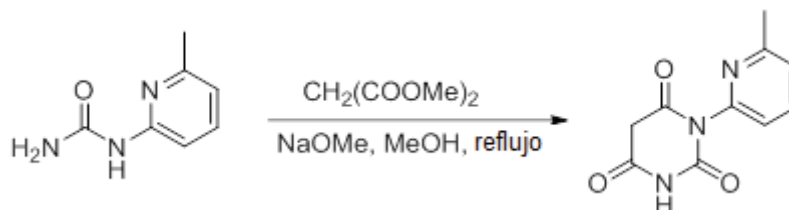
Compuesto 64. (*R*)-6-((2-(benciloxi)-1-feniletíl)amino)-3-isopropilpirimidino-2,4(1H,3H)-diona. El compuesto del título se preparó de una manera similar al procedimiento descrito para 62. Sin embargo, en esta ocasión la reacción se calentó a 140 °C durante 1 h. Después de

enfriar, la mezcla de reacción en bruto se trató con CH₃CN/H₂O 50/50 (TFA al 0,1%) que condujo a una precipitación. LC/MS: m/z (ES+) 380 (M+H)⁺. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 10,01 (br, 1H), 7,36-7,26 (m, 10H), 6. 62 (d, J = 6. 7 Hz, 1H), 4,93-4,83 (m, 1H), 4,67-4,62 (m, 1H), 4,50 (dd, J = 12,0, 2,0 Hz, 2H), 4,30 (s, 1H), 3,68-3,64 (m, 1H), 3,60-3,55 (m, 1H) 1,27-1,23 (m, 6H).

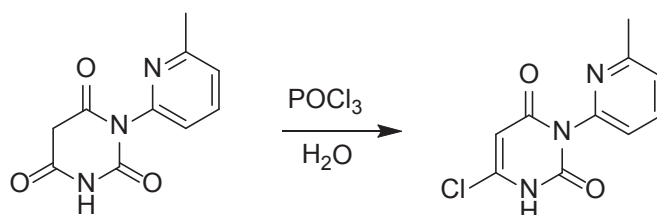
Ejemplo 65. Preparación de (S)-3-(6-metilpiridin-2-il)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona.



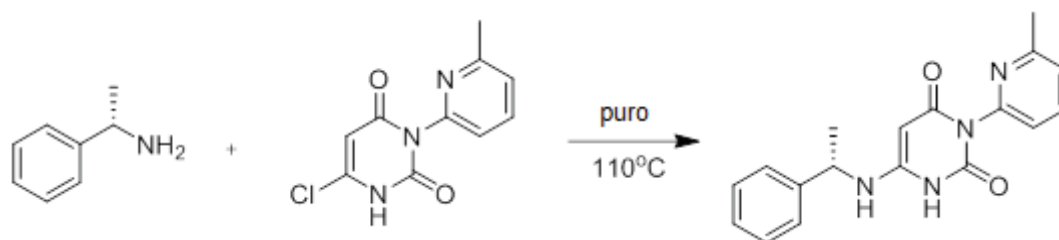
Compuesto 65.1. 1-(6-metilpiridin-2-il)urea. A un matraz de fondo redondo de 25 ml purgado y mantenido con una atmósfera inerte de argón, se añadió urea (1,48 g, 24,64 mmoles, 1,00 equiv) y 6-metilpirin-2-amina (3 g, 27,74 mmoles, 1,00 equiv). La mezcla resultante se agitó durante 2 h a 145 °C. Después de enfriar, el producto en bruto (4 g) se purificó usando una columna CombiFlash: gel de sílice C18; utilizando una fase móvil de CH₃CN:H₂O = 0:100 a CH₃CN:H₂O = 50:50 durante 40 minutos. Esto dio lugar al aislamiento de 1,2 g (32%) del compuesto del título en forma de un sólido blanco. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 9,07 (s, 1H), 7,56-7,52 (m, 1H), 7,18-7,14 (m, 1H), 6. 80-6. 75 (m, 1H), 2,36 (s, 3H).



Compuesto 65.2. 1-(6-metilpiridin-2-il)pirimidino-2,4,6(1H,3H,5H)-triona. El compuesto del título se preparó de una manera similar al procedimiento descrito para 1.2. Sin embargo, en este caso, después de agitar durante 1 noche a 65 °C, la mezcla de reacción se concentró bajo presión reducida y el producto en bruto se dividió en partes entre CH₃OH:Et₂O (1:50). El sólido se recogió por filtración y se disolvió en CH₃OH (50 ml). El valor del pH de la solución se ajustó a 7 con una resina de intercambio de iones catiónicos (Dowex 50WX8-100, 5 g). Los sólidos se filtraron y el filtrado se concentró bajo presión reducida dando lugar a 0,5 g (29%) del compuesto del título en forma de un sólido blanco. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 9,27 (s ancho, 1H), 7,69 (t, J = 7,6 Hz, 1H), 7,17 (d, J = 7,6 Hz, 1H), 6. 93 (d, J = 7,6 Hz, 1H), 3,18 (s, 2H), 2,44 (s, 3H).

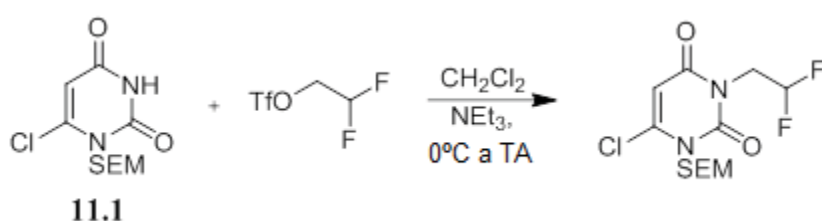


Compuesto 65.3. 6-Cloro-3-(6-metilpiridin-2-il)pirimidino-2,4(1H,3H)-diona. A una solución agitada de 65.2 (500 mg, 2,28 mmoles, 1,00 equiv) en POCl₃ (5 ml) a 0 °C se añadió una gota (~20 µl) de H₂O. La solución resultante se calentó a temperatura ambiente, se agitó durante 30 minutos, se calentó a 70 °C y se agitó durante 2 h. Después de enfriar, la mezcla resultante se concentró bajo presión reducida. El residuo resultante se disolvió cuidadosamente en 10 ml de agua con hielo. El pH se ajustó a 7 con una resina de intercambio iónico de aniones (resina de intercambio aniónico de estireno de base fuerte 201x4 (711) activada, 20 g, y los sólidos se filtraron. El filtrado se concentró bajo presión reducida dando lugar a 0,2 g (37%) del compuesto del título en forma de un sólido amarillo.

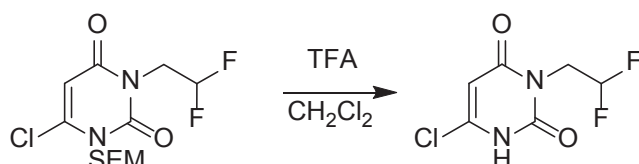


Compuesto 65. (S)-3-(6-metilpiridin-2-il)-6-((1-feniletíl)amino)pirimidino-2,4(1H,3H)-diona. A un matraz de fondo redondo de 10 ml purgado y mantenido con una atmósfera inerte de argón se añadió (S)-α-metilbencilamina (0,5 ml) y 65.3 (200 mg, 0,84 mmoles, 1,00 equiv). La solución resultante se agitó durante 3 h a 110 °C. Después de enfriar, la mezcla resultante se concentró bajo vacío. El residuo (100 mg) se purificó mediante RP-HPLC preparativa con las siguientes condiciones: columna, XBridge Prep C18 OBD Column, 5µm, 19x150 mm, fase móvil, H₂O con 0,05% de Na₄(HCO₃) y CH₃CN (15% de CH₃CN hasta 80% en 8 minutos. Esto dio lugar a 28,8 mg (11%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES⁺) 323 (M+H)⁺. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 7,76 (t, J = 7,6 Hz, 1H), 7,39- 7,22 (m, 7H), 7,05 (d, J = 7,6 Hz, 1H), 6. 82 (br, 1H), 4,63-4,59 (m, 1H), 4,46 (s, 1H), 2,43 (s, 3H), 1,44 (d, J = 6. 4 Hz, 3H).

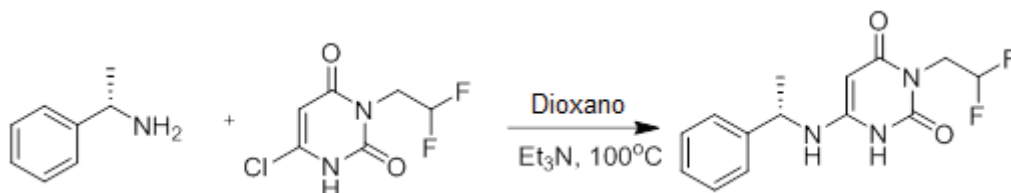
Ejemplo 66. Preparación de (S)-3-(2,2-difluoroetil)-6-((1-feniletíl)amino)pirimidino-2,4(1H,3H)-diona.



Compuesto 66.1. 6-Cloro-3-(2,2-difluoroetil)-1-((2-(trimetilsilil)etoxi)metil) pirimidino-2,4(1H,3H)-diona. A una solución agitada de 11.1 (1,30 mg, 0,47 mmol) y Et₃N (0,2 ml) en CH₂Cl₂ (2M), a 0 °C se añadió a trifluorometanosulfonato de 2,2-difluoroetilo (0,10 ml). La reacción se calentó a temperatura ambiente y se agitó durante 30 minutos. La mezcla se concentró para proporcionar el compuesto en una mezcla en bruto.

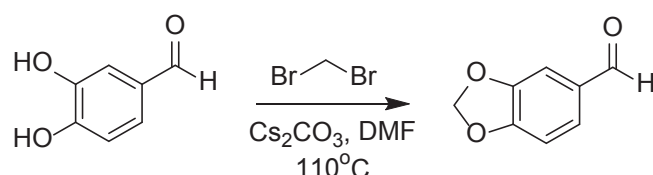


Compuesto 66.2. 6-Cloro-3-(2,2-difluoroetil)pirimidino-2,4(1H,3H)-diona. Se disolvió 65.1 en bruto en CH₂Cl₂/TFA (1:1, 4 ml) y se agitó durante 3 h y se concentró. El material resultante se trató con NaHCO₃ al 5% (ac) hasta que el pH fue 7. Se añadió acetato de etilo a la mezcla y las capas se separaron. La capa acuosa se concentró. El sólido resultante se puso en suspensión en CH₃CN (15 ml) y se separó por filtración. El filtrado se concentró para proporcionar 52 mg del compuesto del título.

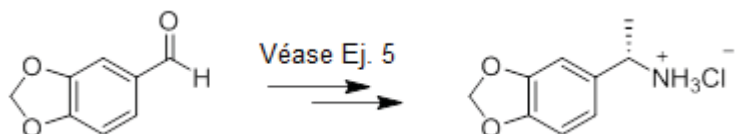


Compuesto 66. (S)-3-(2,2-difluoroetil)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona. A 66.2 (52 mg, 0,25 mmol) en 1,4-dioxano (15 ml) se añadió Et₃N (100 µl) y (S)-α-metilbencilamina (188 mg, 1,55 mmol). La mezcla de reacción se calentó en un reactor de microondas a 100 °C durante 32 minutos, se enfrió a temperatura ambiente y seguidamente se concentró. El residuo resultante se disolvió en CH₃CN/H₂O 2:3 (10 ml) con 2 gotas de TFA (~40 µl). La mezcla se purificó mediante RP-HPLC preparativa para proporcionar 8 mg (11%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES⁺) 296 (M+H)⁺. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 10,20 (s ancho, 1H), 7,37-7,32 (m, 4H), 7,26-7,23 (m, 1H), 6,71 (d, J = 7,0 Hz, 1H), 6,07 (tt, J = 56,0, 4,5 Hz, 1H), 4,54 (quin, J = 6,8 Hz, 1H), 4,43 (d, J = 2,3 Hz, 1H), 4,02 (td, J = 14,3, 4,7 Hz, 2H), 1,40 (d, J = 6,7 Hz, 3H).

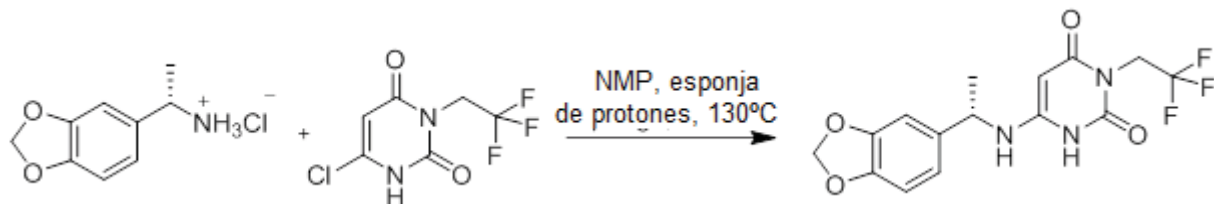
Ejemplo 67. Preparación de (S)-6-((1-(benzo[d][1,3]dioxol-5-yl)etil)amino)-3-(2,2,2-trifluoroetil)pirimidino-2,4(1H,3H)-diona.



Compuesto 67.1. 2H-1,3-benzodioxole-5-carbaldehído. A una solución agitada de 3,4-dihidroxibenzaldehído (10 g, 72,40 mmoles, 1,00 equiv) en DMF (150 ml) se añadió carbonato de cesio (35,5 g, 108,31 mmoles, 1,50 equiv) y dibromometano (18,7 g, 107,57 mmoles, 1,50 equiv). La solución resultante se agitó durante 2 h a 110 °C. La solución se enfrió a temperatura ambiente y el sólido se separó por filtración. El filtrado se diluyó con H₂O (300 ml). La solución resultante se extrajo con EtOAc (2x300 ml). Las capas orgánicas se combinaron, se secaron sobre sulfato de sodio y se concentraron bajo presión reducida. El residuo en bruto se purificó mediante cromatografía de columna de gel de sílice, se eluyó con EtOAc/éter de petróleo (1:9) para proporcionar 8 g (74%) del compuesto del título en forma de un sólido amarillo. ¹H-RMN (300 MHz, CDCl₃): δ ppm 9,81 (s, 1H), 7,41 (d, J = 8,1 Hz, 1H), 7,34 (s, 1H), 6. 93 (d, J = 8,1 Hz, 1H), 6. 08 (s, 2H).



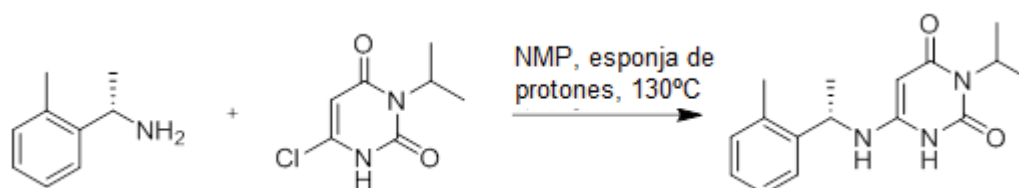
Compuesto 67.2. Hidrocloruro de (S)-1-(benzo[d][1,3]dioxol-5-yl)etan-1-amina. El compuesto del título se sintetizó según los métodos descritos para la preparación de 5.3. En este caso, se utilizó 67.1 en lugar de 3,5-difluorobenzaldehído. LC/MS: m/z (ES⁺) 166 (M+H)⁺.



Compuesto 67. (S)-6-((1-(benzo[d][1,3]dioxol-5-yl)etil)amino)-3-(2,2,2-trifluoroetil)pirimidino-2,4(1H,3H)-diona. El compuesto del título se sintetizó según los métodos descritos en el ejemplo 59. En este caso, se utilizó 67.2 en lugar de hidrocloruro de (S)-1-(2,6-difluorofenil)etan-1-amina y se utilizó 6-cloro-3-(2,2,2-trifluoroetil)pirimidino-2,4(1H,3H)-diona (sintetizada según los métodos descritos en el ejemplo 1) en lugar de 1.3. LC/MS: m/z (ES⁺) 358 (M+H)⁺. ¹H-RMN (300 MHz, DMSO-d₆): δ ppm 10,27 (s ancho, 1H), 6. 94 (d, J= 1,2 Hz, 1H), 6. 89-6. 82 (m, 3H), 6. 72 (d, J = 6. 9 Hz, 1H), 5,99 (s, 2H), 4,48-4,40 (m, 4H), 1,38 (d, J

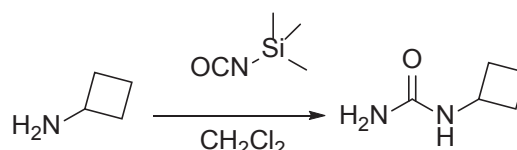
= 6.9 Hz, 3H).

Ejemplo 68. Preparación de (S)-3-isopropil-6-((1-(o-tolil)etil)amino)pirimidino-2,4(1H,3H)-diona (68).



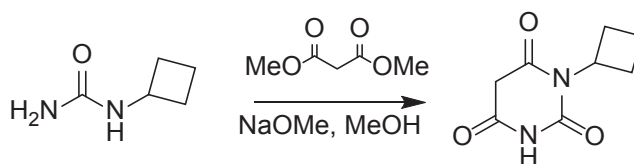
- 5 A una solución agitada de (1S)-1-(2-metilfenil)etan-1-amina (310 mg, 2,29 mmoles, 1,50 equiv) en NMP (1 ml) se añadió una esponja de protones (491,4 mg, 2,30 mmoles, 1,50 equiv) y 1.3 (288 mg, 1,53 mmoles, 1,00 equiv). La solución resultante se agitó durante 1 h a 130 °C en un baño de aceite, se enfrió a temperatura ambiente y seguidamente se diluyó con DMSO (2 ml). Los sólidos se filtraron y el filtrado se purificó mediante HPLC preparativa
- 10 rápida con las siguientes condiciones: columna: X Bridge C18, 19x150 mm, 5 µm; fase móvil A: H₂O/0,05% TFA, fase móvil B: CH₃CN; caudal: 20 ml/minuto; gradiente (30% B a 70% B en 10 minutos). Esto proporcionó 50 mg del producto en bruto que posteriormente se separó mediante HPLC preparativa quiral con las siguientes condiciones: columna Chiralpak IC, 2x25 cm, 5 µm; fase móvil, hexanos y etanol (9:1, 15 minutos). Esto dio lugar a 35,6 mg
- 15 (8%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES+) 288 (M+H)⁺. ¹H-RMN (300 MHz, DMSO-d₆): δ ppm 9,76 (s ancho, 1H), 7,28 (d, J = 7,2 Hz, 1H) 7,24-7,14 (m, 3H), 6.48 (d, J = 6.3 Hz, 1H), 4,95-4,86 (m, 1H), 4,60 (quin, J = 6.9 Hz, 1H), 4,19 (s, 1H), 2,34 (s, 3H), 1,37 (d, J = 6.6 Hz, 3H), 1,27 (d, J = 6.9 Hz, 6H).

Ejemplo 69. Preparación de (S)-3-ciclobutil-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona.

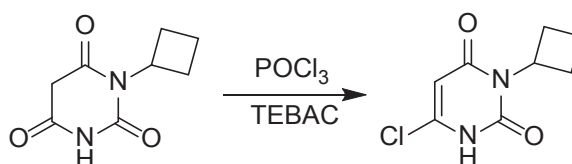


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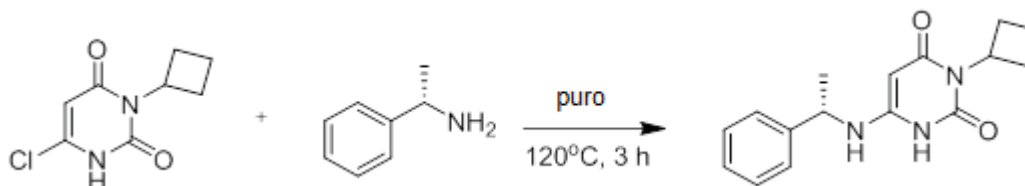
- Compuesto 69.1. 1-ciclobutilurea. A una solución agitada de ciclobutanamina (40 g, 562,42 mmoles, 1,00 equiv) en CH₂Cl₂ (400 ml) a 0 °C se añadió isocianato de trimetilsililo (67,40 g, 561,60 mmoles, 1,00 equiv) por partes. La solución resultante se agitó durante una noche a temperatura ambiente y se inactivó mediante la adición de CH₃OH (80 ml). La mezcla
- 25 resultante se agitó durante 1 h a temperatura ambiente y seguidamente se concentró bajo presión reducida. El residuo se lavó con Et₂O (2x100 ml) y se filtró, lo que proporcionó 53 g (83%) del compuesto del título en forma de un sólido blanco. ¹H-RMN (300 MHz, DMSO-d₆): δ ppm 6.17 (d, J = 9,0Hz, 1H), 5,33 (s, 2H), 3,99-3,91 (m, 1H), 2,16-2,07 (m, 2H), 1,81-1,68 (m, 2H), 1,61-1,45 (m, 2H).



Compuesto 69.2. 1-ciclobutilpirimidino-2,4,6(1H,3H,5H)-triona. A una solución agitada de metóxido de sodio (62,43 g, 1,156 moles, 2,40 equiv) en CH₃OH (500 ml) se añadió malonato de dimetilo (76,42 g, 0,578 moles, 1,20 equiv) y 69.1 (55 g, 0,48 moles, 1,00 equiv). La solución resultante se calentó a 65 °C y se agitó durante 1 noche. La reacción se enfrió y se inactivó mediante la adición de H₂O (100 ml). El pH de la solución se ajustó a 1 con HCl concentrado. La mezcla resultante se concentró bajo presión reducida. El residuo se purificó mediante cromatografía de columna de gel de sílice con CH₂Cl₂/ CH₃OH (20:1) como eluyente para proporcionar 60 g (68%) del compuesto del título en forma de un sólido blanco. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 11,20 (s, 1H), 4,95-4,86 (m, 1H), 3,56 (s, 2H), 2,72-2,62 (m, 2H), 2,16-2,09 (m, 2H), 1,78-1,60 (m, 2H).



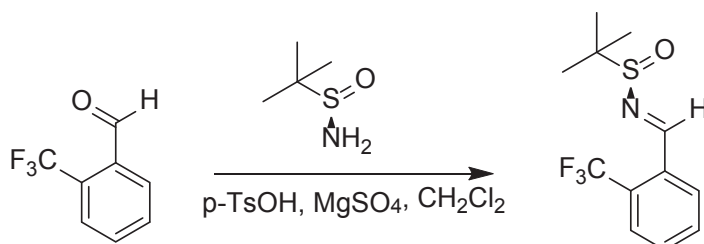
Compuesto 69.3. 6-cloro-3-ciclobutilpirimidino-2,4(1H,3H)-diona. A 69.2 (80 g, 0,44 moles, 1,00 equiv) se añadió cloruro de trietilbencilamonio (140,2 g, 0,615 moles, 1,40 equiv). La reacción se agitó durante 1 h a 65 °C y seguidamente se concentró bajo presión reducida. La reacción se inactivó mediante la adición cuidadosa de 1 l de agua/hielo y seguidamente el valor del pH de la solución se ajustó con NaOH 2N (ac). El sólido se filtró, se lavó con CH₃OH (300 ml) y Et₂O (2x300 ml) y se secó. Esto dio lugar a 78 g (89%) del compuesto del título en forma de un sólido amarillo claro. ¹H-RMN (300 MHz, DMSO-d₆): δ ppm 12,23 (s, 1H), 5,82 (s, 1H), 5,13-5,01 (m, 1H), 2,87-2,73 (m, 2H), 2,13-2,03 (m, 2H), 1,80-1,56 (m, 2H).



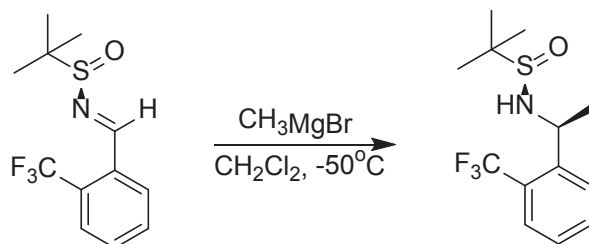
Compuesto 69. (S)-3-ciclobutil-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona. A un matraz de fondo redondo de 500 ml purgado y mantenido con una atmósfera inerte de argón, se añadió 69.3 (78 g, 388,79 mmoles, 1,00 equiv) y (S)-α-metilbencilamina (150 ml, 2,00 equiv). La mezcla de reacción se agitó durante 3 h a 120 °C. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con CH₃OH (1 l) y se enfrió adicionalmente a 0 °C. El sólido

resultante se filtró, se lavó con Et₂O (2x300 ml) y se secó bajo vacío para proporcionar 57,25 (52%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES⁺) 286 (M+H)⁺. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 9,94 (s ancho, 1H), 7,40-7,32 (m, 4H), 7,30-7,26 (m, 1H), 6. 40 (s ancho, 1H), 5,19-5,10 (m, 1H), 4,56-4,49 (m, 1H), 4,35 (s, 1H), 2,91-2,81 (m, 2H), 2,02-1,95 (m, 2H), 1,76-1,58 (m, 2H), 1,42 (d, J = 6. 8Hz, 3H).

Ejemplo 70. Preparación de (S)-3-isopropil-6-((1-(2-(trifluorometil)fenil)etil)amino) pirimidino-2,4(1H,3H)-diona.

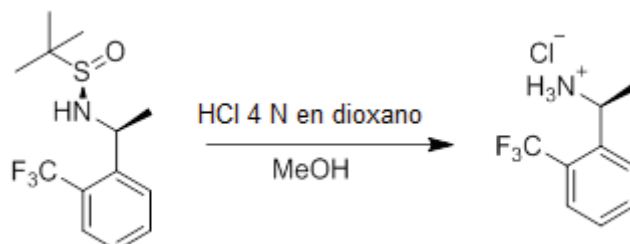


Compuesto 70.1. (R,E)-2-metil-N-(2-(trifluorometil)bencilideno)propano-2-sulfinamida. A un matraz de fondo redondo de 100 ml purgado y mantenido con una atmósfera inerte de argón se añadió CH₂Cl₂ (50 ml), 2-(trifluorometil)benzaldehído (2,0 g, 11,54 mmoles, 1,00 equiv), (R)-(+)-2-metilpropano-2-sulfinamida (1,68 g, 13,86 mmoles, 1,20 equiv), p-toluenosulfonato de piridinio (0,145 g, 0,05 equiv) y sulfato de magnesio (6,93 g, 5,00 equiv). La solución resultante se agitó durante 48 h a 40 °C. La mezcla se enfrió a temperatura ambiente y el sólido se filtró. El filtrado se concentró bajo presión reducida y el residuo resultante se purificó mediante cromatografía de columna rápida (gel de sílice, eluyendo con EtOAc/éter de petróleo (1:20)). Esto dio lugar a 0,96 g (30%) del compuesto del título en forma de un sólido amarillo claro. LC/MS: m/z (ES⁺) 278 (M+H)⁺. ¹H-RMN (300 MHz, DMSO-d₆): δ ppm 8,82-8,80 (m, 1H), 8,24 (d, J = 7,2 Hz, 1H), 7,95-7,80 (m, 3H), 1,22 (s, 9H).

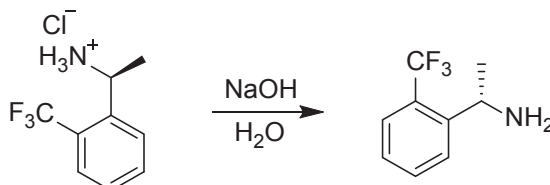


Compuesto 70.2. (R)-2-metil-N-((1S)-1-(2-(trifluorometil)fenil)-etil)propano-2-sulfinamida. A una solución agitada de 70.1 (578 mg, 2,08 mmoles, 1,00 equiv) en THF (20 ml) a -50 °C se añadió bromuro de metilmagnesio 3M en Et₂O (1,4 ml, 4,20 mmoles, 2,0 equiv) gota a gota. La solución resultante se agitó a -50 °C durante 2,5 h y a temperatura ambiente durante 10 h adicionales. La reacción se inactivó mediante la adición de una solución acuosa saturada de NH₄Cl (10 ml) y seguidamente se concentró bajo presión reducida. El residuo resultante se

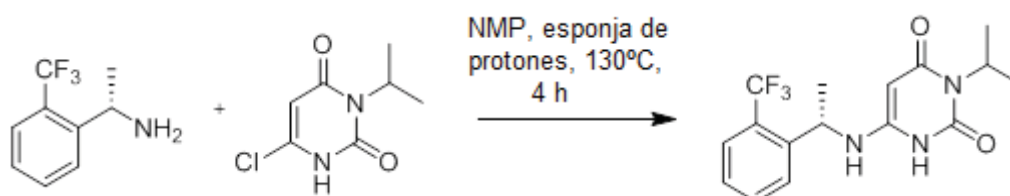
trató con H₂O (50 ml) y se extrajo con CH₂Cl₂ (2x50 ml). Las capas orgánicas se combinaron, se secaron sobre Na₂SO₄ y se concentraron bajo presión reducida. Esto dio lugar a 700 mg (60% de) del compuesto del título en forma de un sólido amarillo. LC/MS: m/z (ES+) 294 (M+H)⁺. ¹H-RMN (300 MHz, DMSO-d₆): δ ppm 7,77-7,74 (m, 1H), 7,67-7,60 (m, 2H), 7,43-7,38 (m, 1H), 5,53 (d, J = 4,5Hz, 1H), 4,70-4,60 (m, 1H), 1,42 (d, J = 6.6 Hz, 3H), 1,02 (s, 9H).



Compuesto 70.3. Hidrocloruro de (S)-1-(2-(trifluorometil)fenil)etan-1-amina. A una solución agitada de 70.2 (700 mg, 2,39 mmoles, 1,00 equiv) en CH₃OH (4 ml) se añadió HCl 4N en 1,4-dioxano (2 ml) gota a gota. La solución resultante se agitó durante 1 h a temperatura ambiente y seguidamente se concentró bajo presión reducida. Precipitó un sólido mediante la adición de Et₂O (5 ml). El sólido se filtró y se secó proporcionando el compuesto del título en forma de un sólido blanco (0,32 g, 60%).



Compuesto 70.4. (S)-1-(2-(trifluorometil)fenil)etan-1-amina. A un matraz de fondo redondo de 50 ml se añadió 70.3 (320 mg, 1,43 mmoles, 1,00 equiv) e hidróxido de sodio (80 mg, 2,00 mmoles, 1,40 equiv) en H₂O (20 ml). La solución resultante se agitó durante 1 h a temperatura ambiente y seguidamente se extrajo con EtOAc (20 ml). La capa orgánica se combinó y se concentró bajo presión reducida. Esto proporcionó 190 mg (70%) del compuesto del título en forma de un aceite amarillo claro.

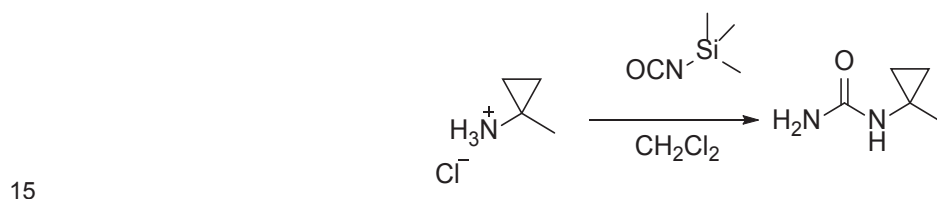


Compuesto 70. (S)-3-isopropil-6-((1-(2-(trifluorometil)fenil)etil)amino) pirimidino-2,4(1H,3H)-diona. A un matraz de fondo redondo de 10 ml purgado y mantenido con una atmósfera inerte de argón, se añadió NMP (2 ml), 70.4 (160 mg, 0,85 mmoles, 1,00 equiv), 1.3 (160 mg,

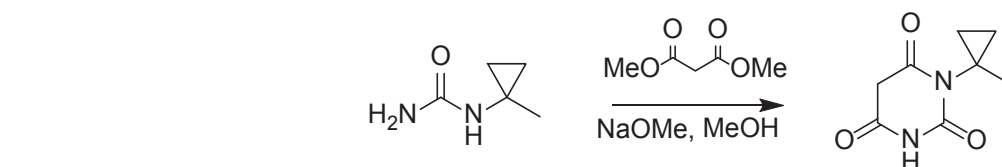
0,85 mmoles, 1,00 equiv) y esponja de protones (273 mg, 1,28 mmoles, 1,5 equiv). La solución resultante se agitó durante 4 h a 130 °C. El producto en bruto (200 mg) se purificó mediante HPLC preparativa quiral con las siguientes condiciones: columna, Phenomenex Lux-2 5µ Cellulose-2, 30x150 mm; fase móvil, hexano-HPLC y etanol-HPLC (mantenido a 20% de etanol-HPLC en 14 minutos); detector UV 254/220 nm. Se obtuvieron 160 mg de producto en bruto. El material obtenido (60 mg) se purificó adicionalmente usando HPLC preparativa quiral con las siguientes condiciones: columna: Phenomenex Lux-2 5µ Cellulose-2, 30x150 mm; fase móvil y gradiente: hexano:EtOH =80:20; tiempo de retención (pico 2) (minutos): 11,106. Esto dio lugar a 30 mg del compuesto del título en forma de un sólido blanco.

LC/MS: m/z (ES+) 342 (M+H)⁺. ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 9,84 (br, 1H), 7,78-7,68 (m, 3H), 7,56-7,52 (m, 1H), 6. 75 (s ancho, 1H), 4,93-4,86 (m, 1H), 4,68-4,63 (m, 1H), 4,13 (s, 1H), 1,46 (d, J = 6. 8 Hz, 3H), 1,25 (d, J = 7,2 Hz, 6H).

Ejemplo 71. Preparación de (S)-3-(1-metilciclopropil)-6-((1-feniletil)amino)pirimidino-2,4(1H,3H)-diona.

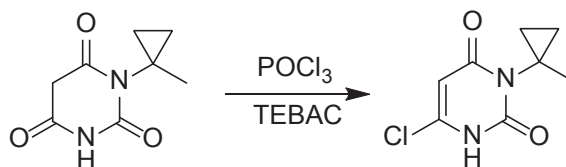


Compuesto 71.1. 1-(1-Metilciclopropil)urea. A una solución agitada de sal de hidrocloreto de 1-metilciclopropan-1-amina (429 mg, 3,99 mmoles, 1,00 equiv) y trietilamina (268 mg, 2,65 mmoles, 1,00 equiv) en CH₂Cl₂ (6 ml) se añadió isocianato de trimetilsililo (366 mg, 3,18 mmoles, 1,20 equiv). La mezcla resultante se agitó a temperatura ambiente durante 1 h y se inactivó mediante la adición gota a gota de CH₃OH (2 ml) a 0 °C. La solución resultante se calentó a temperatura ambiente y se agitó durante 1 h adicional. La mezcla resultante se concentró bajo presión reducida. El producto en bruto se precipitó en CH₃OH:Et₂O (1:40) proporcionando 300 mg (66%) del compuesto del título en forma de un sólido blanco.

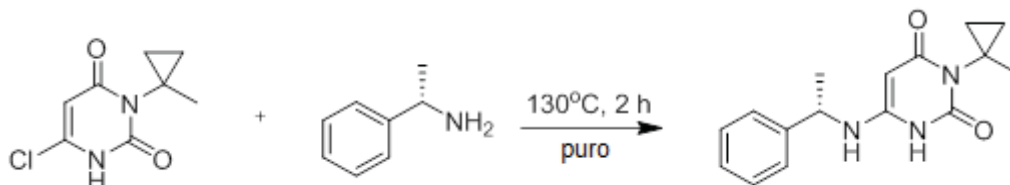


Compuesto 71.2. 1-(1-Metilciclopropil)pirimidino-2,4,6(1H,3H,5H)-triona. A una solución agitada de 71.1 (320 mg, 2,80 mmoles, 1,0 equiv) en CH₃OH (2 ml) se añadió metóxido de sodio (390 mg, 7,2 mmoles, 2,5 equiv) y malonato de dimetilo (380 mg, 2,88 mmoles, 1,0 equiv). La solución resultante se agitó durante una noche a 65 °C. Después de enfriar, la reacción se inactivó mediante la adición de H₂O (100 ml). El pH de la solución se ajustó a 2

con HCl concentrado y la mezcla resultante se concentró bajo presión reducida. El residuo en bruto se purificó mediante cromatografía de columna de gel de sílice con EtOH/éter de petróleo (1:3) como eluyente. Esto proporcionó 100 mg (20%) del compuesto del título en forma de un sólido blanco. ¹H-RMN (300 MHz, CDCl₃): δ ppm 8,04 (br, 1H), 3,61 (s, 2H), 1,41 (s, 3H), 1,00-, 0,86 (m, 4H).



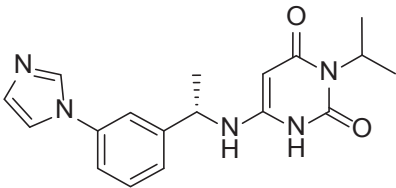
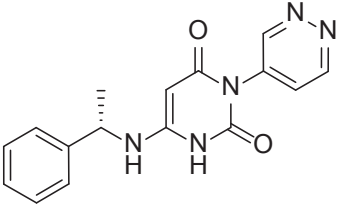
Compuesto 71.3. 6-Cloro-3-(1-metilciclopropil)pirimidino-2,4(1H,3H)-diona. A 71.2 (100 mg, 0,55 mmoles, 1,00 equiv) y cloruro de trietilbencilamonio (180 mg, 0,79 mmoles, 1,00 equiv) se añadió POCl₃ (2 ml). La solución resultante se agitó durante 3 h a 50 °C y seguidamente se concentró bajo presión reducida. El residuo se inactivó cuidadosamente mediante la adición de 10 ml de agua/hielo y se extrajo con EtOAc (2x30 ml). Las capas orgánicas se combinaron y se concentraron bajo presión reducida. El residuo en bruto se purificó mediante cromatografía de columna de gel de sílice con CH₂Cl₂/CH₃OH (10:1) como eluyente para proporcionar 40 mg (36%) del compuesto del título en forma de un sólido amarillo.

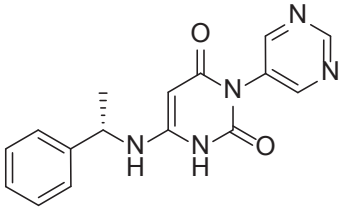
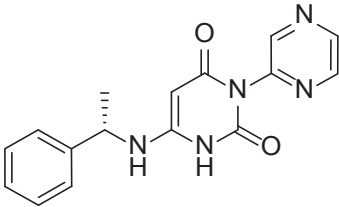
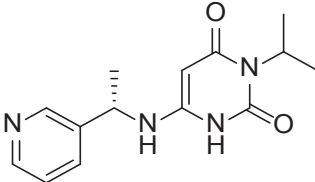


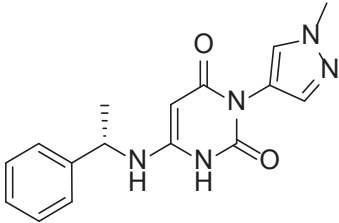
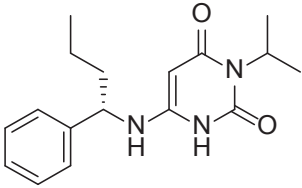
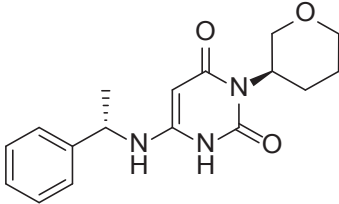
Compuesto 71. (S)-3-(1-Metilciclopropil)-6-((1-feniletíl)amino)pirimidino-2,4(1H,3H)-diona. A 71.3 (40 mg, 0,20 mmoles, 1,00 equiv) se añadió (S)-α-metilbencilamina (0,5 ml). La mezcla de reacción se agitó durante 2 h a 130 °C y seguidamente se concentró bajo presión reducida. El residuo resultante se purificó mediante RP-HPLC preparativa con las siguientes condiciones: columna: X Bridge C18, 19x150 mm, 5μ; fase móvil A: H₂O/0,05% de TFA, fase móvil B: CH₃CN, caudal: 20 ml/minuto, gradiente: 30% de B a 70% de B en 10 minutos. Esto proporcionó 15,1 mg (27%) del compuesto del título en forma de un sólido blanco. LC/MS: m/z (ES⁺) 286 (M+H)⁺. ¹H-RMN (300 MHz, CD₃CN): δ ppm 8,41 (br, 1H), 7,42-7,29 (m, 5H), 5,79 (br, 1H), 4,48-4,44 (m, 1H), 4,30 (s, 1H), 1,47 (d, J = 6. 9 Hz, 3H), 1,27 (s, 3H), 0,87-0,77 (m, 4H).

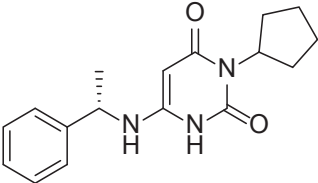
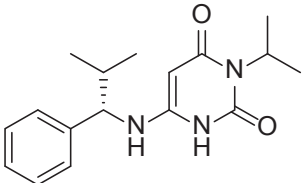
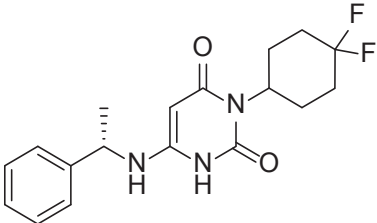
Ejemplo 72. Preparación de compuestos de pirimidino-diona adicionales

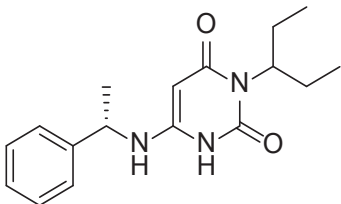
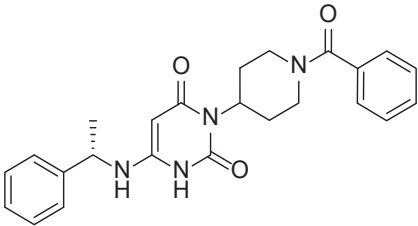
Los compuestos en la Tabla 1B se prepararon según los ejemplos anteriormente descritos (se proporcionan métodos ilustrativos como "Ej. n° de referencia").

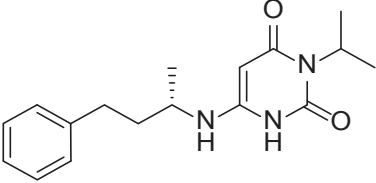
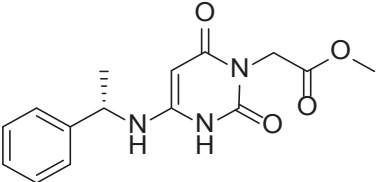
Estructura	Compuesto nº ----- Ej. referencia nº	Peso observado y/o ¹ H RMN
	72 ----- 17	340 (M+H) ⁺ ¹ H-RMN (300 MHz, DMSO-d ₆): δ ppm 9,89 (s ancho, 1H), 9,54 (s ancho, 1H), 8,22 (s ancho, 1H) 7,82 (s ancho, 1H), 7,75 (s, 1H) 7,66-7,54 (m, 2H), 7,48 (d, J = 7,5 Hz, 1H), 6. 60-6. 58 (m, 1H), 4,90-4,83 (m, 1H), 4,55-4,48 (m, 1H), 4,30 (s, 1H), 1,42 (d, J = 6. 9 Hz, 3H), 1,27-1,21 (m, 6H).
	73 ----- 15	310 (M+H) ⁺ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 9,20 (m, 1H), 9,04 (s ancho, 1H), 7,57 (m, 1H), 7,38-7,32 (m, 4H), 7,26-7,21 (m, 1H), 6. 76 (m, 1H), 4,69-4,62 (m, 1H), 4,46 (s, 1H), 1,40 (d, J = 6. 8 Hz, 3H).

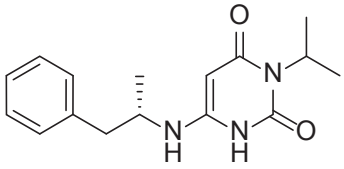
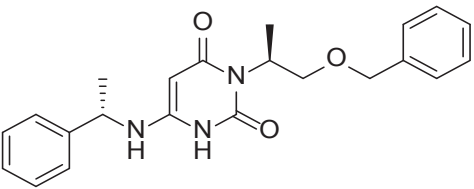
	74 ---- 15	310 (M+H) ⁺ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 8,56 (m, 1H), 8,49 (m, 1H), 8,37 (m, 1H), 7,37-7,31 (m, 4H), 7,26-7,22 (m, 1H), 6. 68 (m, 1H), 4,71-4,65 (m, 1H), 4,34 (s, 1H), 1,37 (d, J = 6. 8 Hz, 3H).
	75 ---- 15	310 (M+H) ⁺ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 8,60 (m, 1H), 8,57 (m, 1H), 8,49 (s ancho, 1H), 7,39-7,32 (m, 4H), 7,26-7,22 (m, 1H), 6. 68 (m, 1H), 4,69-4,64 (m, 1H), 4,41 (s, 1H), 1,39 (d, J = 6. 8 Hz, 3H).
	76 ---- 5 y 58	275 (M+H) ⁺ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 9,70 (br, 1H), 8,60 (d, J = 2,0 Hz, 1H) 8,50 (dd, J = 4,8, 1,6 Hz, 1H), 7,76 (d, J = 8,0 Hz, 1H), 7,41 (dd, J = 7,6. 4,8 Hz, 1H), 6. 67 (s ancho, 1H), 4,94-4,88 (m, 1H), 4,62-4,58 (m, 1H), 4,38 (s, 1H), 1,45 (d, J = 6. 4 Hz, 3H), 1,30-1,28 (m, 6H).

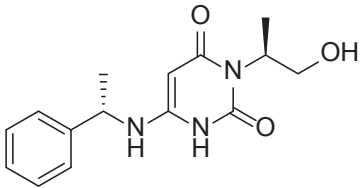
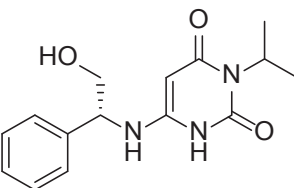
	77 ---- 15	312 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 10,69 (s ancho, 1H), 7,65 (s, 1H), 7,40-7,20 (m, 7H), 4,52 (quin, J = 6. 8 Hz, 1H), 4,40 (s, 1H), 3,30 (s ancho, 3H), 1,39 (d, J = 7,0 Hz, 3H).
	78 ---- 1	302 (M+H)+ ¹ H-RMN (400 MHz, CDCl ₃): δ ppm 10,58 (s ancho, 1H), 7,36-7,23 (m, 5H), 5,16 (m, 2H), 4,69 (s, 1H), 4,26 (m, 1H), 1,82-1,71 (m, 2H), 1,44-1,38 (m, 6H), 1,36-1,25 (m, 2H), 0,92 (t, J = 8,0 Hz, 3H).
	79 ---- 11	316 (M+H)+ ¹ H-RMN (400 MHz, CD ₃ CN): δ ppm 7,30-7,20 (m, 4H), 7,16-7,11(m, 1H), 6. 32 (m, 1H), 4,69-4,62 (m, 1H), 4,43 (quin, J = 6. 7 Hz, 1H), 4,29 (s, 1H), 4,00 (t, J = 10,5 Hz, 1H), 3,67-3,59 (m, 1H), 3,44-3,40 (m, 1H), 3,14-3,08 (m, 1H), 2,48-2,38 (m, 1H), 1,56-1,45 (m, 3H), 1,38(d, J = 6. 8 Hz, 3H).

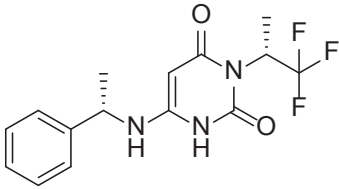
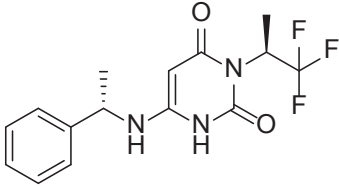
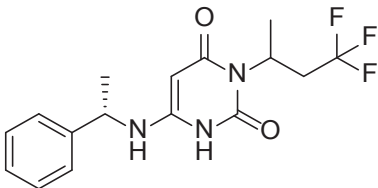
	80 ---- 1	300 (M+H) ⁺ ¹ H RMN (400 MHz, DMSO-d ₆) δ ppm 9,82 (s ancho, 1H), 7,41-7,19 (m, 5H), 6.50 (d, J = 6.7 Hz, 1H), 5,05-5,01 (m, 1H), 4,50-4,46 (m, 1H), 4,34 (s, 1H), 2,01-1,84 (m, 2H), 1,83-1,64 (m, 2H), 1,63-1,51 (m, 2H), 1,49-1,34 (m, 5H).
	81 ---- 5	302 (M+H) ⁺ ¹ H-RMN (400 MHz, CD ₃ OD): δ ppm 7,39-7,35 (m, 2H), 7,30-7,28 (m, 3H), 5,06-5,00 (m, 1H), 4,53 (s, 1H), 4,12 (d, J = 7,2 Hz, 1H), 2,10-2,01 (m, 1H), 1,40-1,37 (m, 6H), 1,02 (d, J = 6.8 Hz, 3H), 0,93 (d, J = 6.8 Hz, 3H).
	82 ---- 7	350 (M+H) ⁺ ¹ H-RMN (400 MHz, CD ₃ OD): δ ppm 7,43-7,33 (m, 4H), 7,30-7,26 (m, 1H), 4,82-4,75 (m, 1H), 4,54-4,49 (m, 2H), 2,74-2,65 (m, 2H), 2,15-2,05 (m, 2H), 1,93-1,79 (m, 2H), 1,61-1,57 (m, 2H), 1,51 (d, J = 6.8 Hz, 3H).

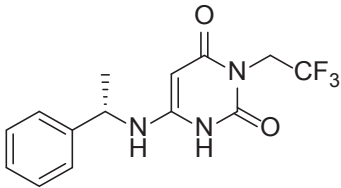
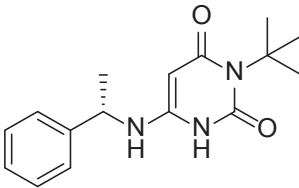
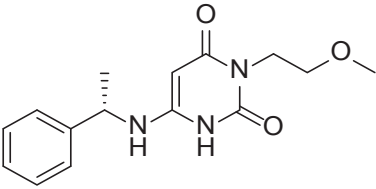
	83 ---- 1	302 (M+H) ⁺ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 9,73 (s ancho, 1H), 7,40 - 7,22 (m, 5H), 6.50 (d, J = 5,1 Hz, 1H), 4,57-4,44 (m, 2H), 4,34 (s ancho, 1H), 1,90 (ddd, J = 13,3. 9,8, 7,4 Hz, 2H), 1,61-1,50 (m, 2H), 1,38 (d, J = 6.7 Hz, 3H), 0,74-0,60 (m, 6H).
	84 ---- 12	419 (M+H) ⁺ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 9,88 (s ancho, 1H), 7,45-7,41 (m, 3H), 7,37-7,29 (m, 6H), 7,27-7,22 (m, 1H), 6.54 (d, J = 6.7 Hz, 1H), 4,84-4,79 (m, 1H), 4,52-4,47 (m, 1H), 4,36 (d, J = 2,4 Hz, 1H), 3,57 (m, 2H), 3,05 (m, 2H), 2,38 (m, 2H), 1,50 (m, 2H), 1,38 (d, J = 6.7 Hz, 3H).

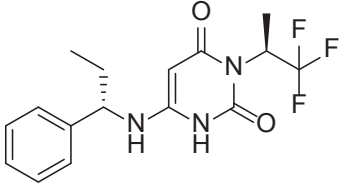
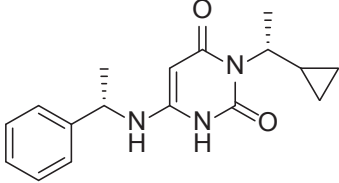
	85 ---- 1	302 (M+H) ⁺ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 9,73 (s ancho, 1H), 7,31-7,22 (m, 2H), 7,21-7,12 (m, 3H), 5,93 (d, J = 8,2 Hz, 1H), 5,00-4,87 (m, 1H) 4,44 (s, 1H), 4,30 (s, 1H), 3,37-3,31 (m, 1H), 2,65-2,53 (m, 2H), 1,70 (dtd, J = 9,0, 6.9, 6.9, 2,0 Hz, 1H), 1,29 (d, J = 7,0 Hz, 6H), 1,11 (d, J = 6.3 Hz, 3H).
	86 ---- 11	304 (M+H) ⁺ ¹ H-RMN (400 MHz, CD ₃ OD + CDCl ₃): 7,22-7,15 (m, 2H), 7,13-7,07 (m, 3H), 6.28 (d, J = 6.1 Hz, 1H), 4,44 (s, 1H), 4,38 (s, 2H), 4,30-4,23 (m, 1H), 3,55 (s, 3H), 1,35 (d, J = 6.8 Hz, 3H).

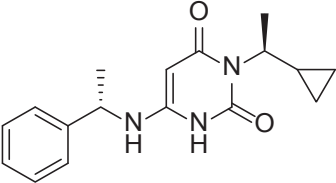
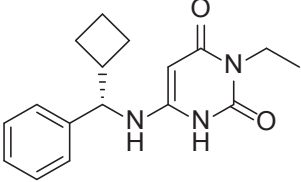
	90 ---- 1	288 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 9,77 (s ancho, 1H), 7,32-7,26 (m, 2H), 7,23-7,12 (m, 3H), 5,85 (d, J = 7,9 Hz, 1H), 4,97-4,87 (m, 1H), 4,55 (s, 1H), 3,77-3,65 (m, 1H), 2,76-2,68 (m, 2H), 1,27 (d, J = 7,0 Hz, 6H), 1,05 (d, J = 6. 7 Hz, 3H).
	91 ---- 53	380 (M+H)+ ¹ H-RMN (400 MHz, CDCl ₃): δ ppm 9,77 (s ancho, 1H), 7,33-7,23 (m, 10H), 5,23 (s ancho, 1H), 4,67 (s ancho, 1H), 4,57 (d, J = 12,0 Hz, 1H), 4,47 (d, J = 12,0 Hz, 1H), 4,44-4,37 (m, 1H), 4,09 (t, J = 9,2 Hz, 1H), 3,63 (dd, J = 9,8, 5,9 Hz, 1H), 1,48 (d, J = 6. 7 Hz, 3H), 1,35 (d, J = 7,0 Hz, 3H).

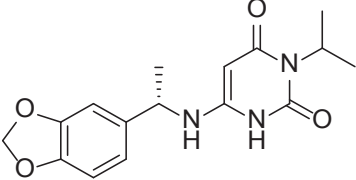
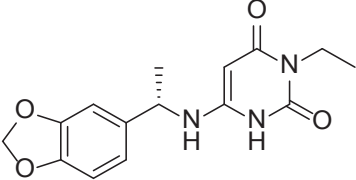
	92 ----- 54	290 (M+H)+ 1H-RMN (400 MHz, CDCl3): δ ppm 9,68 (s, 1H), 7,41 - 7,22 (m, 5H), 5,62 (s, 1H), 5,08 (td, J = 7,3. 2,9 Hz, 1H), 4,67 (s, 1H), 4,48 - 4,35 (m, 1H), 3,98 (dd, J = 11,9, 7,6 Hz, 1H), 3,75 (dd, J = 11,7, 3,1 Hz, 1H), 1,52 (d, J = 7,0 Hz, 3H), 1,36 (d, J = 7,0 Hz, 3H).
	93 ----- 1	290 (M+H)+ 1H-RMN (400 MHz, DMSO-d6): δ ppm 10,01 (d, J = 2,0 Hz, 1H), 7,37-7,23 (m, 5H), 6. 61 (d, J = 6. 3 Hz, 1H), 5,19 (t, J = 5,1 Hz, 1H), 4,93-4,83 (m, 1H), 4,40- 4,33 (m, 1H), 4,24 (d, J = 2,4 Hz, 1H), 3,66 (dt, J = 11,1. 4,7 Hz, 1H), 3,52- 3,44 (m, 1H), 1,25 (dd, J= 6. 9, 2,2 Hz, 6H).

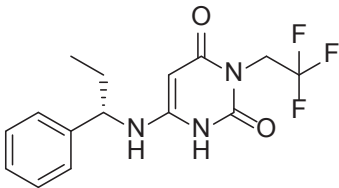
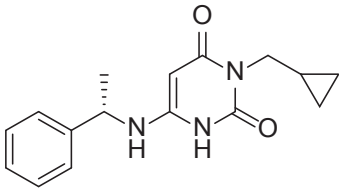
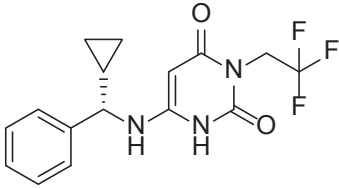
	94 ---- 1 y 50	328 (M+H)+ ¹ H RMN (400 MHz, DMSO-d ₆ a 75 °C): δ ppm 9,91 (s ancho, 1H), 7,44-7,23 (m, 5H), 6. 58 (s ancho, 1H), 5,52 (s ancho, 1H), 4,59-4,51 (m, 1H), 4,46 (s ancho, 1H), 1,52 (d, J = 7,0 Hz, 3H), 1,43 (d, J = 7,0 Hz, 3H).
	95 ---- 1 y 50	328 (M+H)+ ¹ H RMN (400 MHz, DMSO-d ₆ a 75 °C): δ ppm 9,91 (s ancho, 1H), 7,44-7,23 (m, 5H), 6. 58 (s ancho, 1H), 5,52 (s ancho, 1H), 4,59-4,51 (m, 1H), 4,46 (s ancho, 1H), 1,52 (d, J = 7,0 Hz, 3H), 1,43 (d, J = 7,0 Hz, 3H).
	99 ---- 1	342 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆ a 50 °C): δ ppm 9,79 (s ancho, 1H), 7,46-7,23 (m, 5H), 6. 51 (d, J = 6. 7 Hz, 1H), 5,13 (s ancho, 1H), 4,50 (quin, J = 6. 9 Hz, 1 H), 4,37 (s, 1H), 3,15-3,01 (m, 1H), 2,60-2,50 (m, 1H), 1,40 (d, J = 6. 7 Hz, 3H), 1,31 (d, J = 7,0 Hz, 3H).

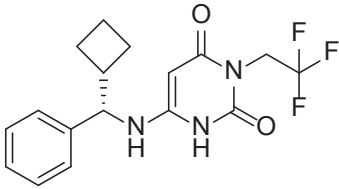
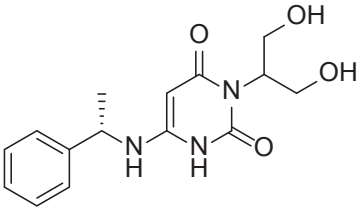
 <chem>CC(F)(F)FN1C(=O)NC(=C1)NC(C2=CC=CC=C2)C3=CC=CC=C3</chem>	100 ---- 1 y 50	314 (M+H)+ ¹ H-RMN (300 MHz, DMSO-d ₆): δ ppm 10,32 (s ancho, 1H), 7,40-7,34 (m, 4H), 7,29-7,25 (m, 1H), 6.81 (d, J = 6.6 Hz, 1H), 4,60-4,54 (m, 1H), 4,49-4,40 (m, 3H), 1,42 (d, J = 6.6 Hz, 3H).
 <chem>CC(C)(C)N1C(=O)NC(=C1)NC(C2=CC=CC=C2)C3=CC=CC=C3</chem>	101 ---- 1 y 50	288 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 9,50 (s ancho, 1H), 7,56-7,44 (m, 4H), 7,38-7,24 (m, 1H), 6.41 (d, J = 6.4 Hz, 1H), 4,45 (q, J = 6.8 Hz, 1H), 4,25 (s, 1H), 1,54 (s, 9H), 1,38 (d, J = 6.8 Hz, 3H).
 <chem>COCCN1C(=O)NC(=C1)NC(C2=CC=CC=C2)C3=CC=CC=C3</chem>	102 ---- 57	290 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 10,31 (s ancho, 1H), 7,35-7,23 (m, 5H), 5,72 (d, J = 4,7 Hz, 1H), 4,67 (s, 1H), 4,40 (quin, J = 6.6 Hz, 1H), 4,05 (t, J = 5,7 Hz, 2H), 3,56 (t, J = 5,7 Hz, 2H), 3,27 (s, 3H), 1,46 (dd, J = 6.7, 1,6 Hz, 3H).

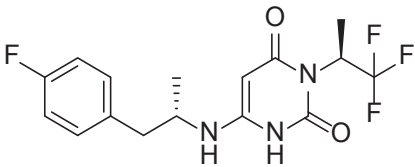
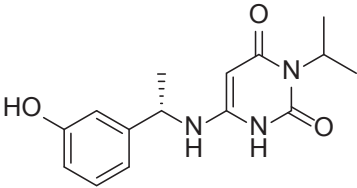
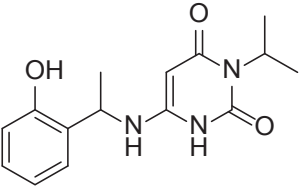
	103 ---- 1 y 59	342 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆ , a 75 °C): δ ppm 9,91 (s ancho, 1H), 7,37-7,24 (m, 5H), 6. 59 (s ancho, 1H), 5,51 (s ancho, 1H), 4,45 (s ancho, 1H), 4,31 (q, J = 6. 9 Hz, 1H), 1,83-1,67 (m, 2H), 1,52 (d, J = 7,4 Hz, 3H), 0,86 (t, J = 7,4 Hz, 3H).
	104 ---- 1 y 58	300 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 9,80 (s ancho, 1H), 7,37-7,31 (m, 4H), 7,27-7,22 (m, 1H), 6. 52 (br, 1H), 4,48 (q, J = 6. 7 Hz, 1H), 4,32 (s ancho, 1H), 3,93 (br, 1H), 1,62 (br, 1H), 1,38 (d, J= 6. 7 Hz, 3H), 1,33 (d, J = 7,0 Hz, 3H), 0,48-0,41 (m, 1H), 0,27-0,21 (m, 1H), 0,14 (dq, J = 9,4. 4,8 Hz, 1H), 0,02 (m, 1H).

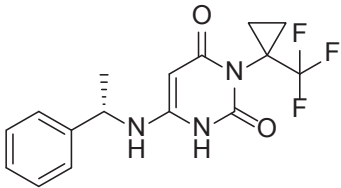
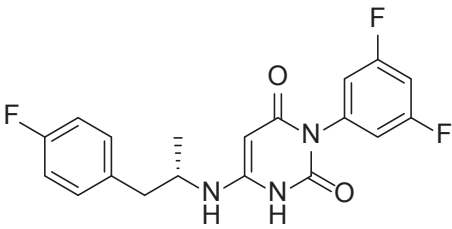
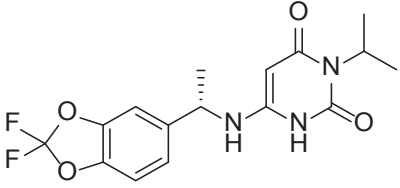
	105 ---- 1 y 58	300 (M+H)+ 1H-RMN (400 MHz, DMSO-d ₆): δ ppm 9,81 (s ancho, 1H), 7,37-7,30 (m, 4H), 7,26-7,22 (m, 1H), 6.53 (d, J = 5,9 Hz, 1H), 4,48 (q, J = 6.8 Hz, 1H), 4,32 (d, J = 1,6 Hz, 1H), 3,85 (m, 1H), 1,61 (m, 1H), 1,38 (d, J= 7,0 Hz, 3H), 1,32 (d, J = 6.7 Hz, 3H), 0,49-0,42 (m, 1H), 0,28-0,22 (m, 1H), 0,17-0,12 (m, 1H), 0,01- (-)0,05. (m, 1H).
	106 ---- 8	300 (M+H)+ 1H-RMN (300 MHz, DMSO-d ₆): δ ppm 9,96 (s ancho, 1H), 7,36-7,24 (m, 5H), 6.48 (d, J = 6.3 Hz, 1H), 4,40 (s, 1H), 4,36-4,27 (m, 1H), 3,63 (q, J = 6.6 Hz, 2H), 2,67-2,50 (m parcialmente oscurecido, 1H) 2,02-1,95 (m, 1H), 1,90-1,78 (m, 4H), 1,66-1,57 (m, 1H), 0,98 (t, J = 6.6 Hz, 3H).

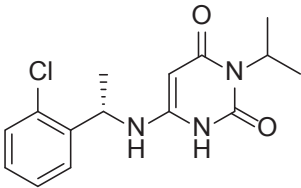
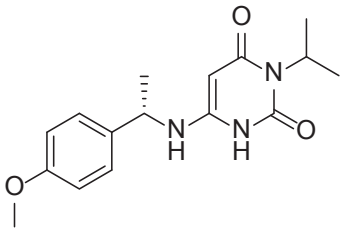
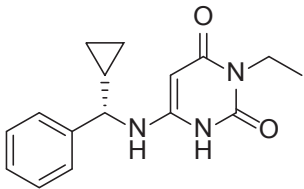
	107 ---- 67 y 59	318 (M+H)+ ¹ H-RMN (300 MHz, DMSO-d ₆): δ ppm 9,76 (s ancho, 1H), 6. 92 (d, J= 1,8 Hz, 1H), 6. 87 (d, J = 7,8 Hz, 1H), 6. 80 (dd, J = 6. 0, 1,8 Hz, 1H), 6. 44 (d, J = 7,2 Hz, 1H), 5,99 (s, 2H), 4,93-4,88 (m, 1H), 4,41-4,35 (m, 2H), 1,35 (d, J = 6. 6 Hz, 3H) 1,28 (d, J= 1,2 Hz, 3H) 1,26 (d, J = 1,2 Hz, 3H).
	108 ---- 67 y 59	304 (M+H)+ ¹ H-RMN (300 MHz, DMSO-d ₆): δ ppm 9,93 (s ancho, 1H), 6. 92 (d, J= 1,5 Hz, 1H), 6. 87 (d, J = 8,1 Hz, 1H), 6. 82-6. 79 (m, 1H), 6. 48 (d, J = 7,2 Hz, 1H), 5,99 (s, 2H), 4,45-4,39 (m, 2H), 3,65 (q, J = 6. 6 Hz, 2H), 1,36 (d, J = 6. 9 Hz, 3H) 0,99 (t, J= 6. 9 Hz, 3H).

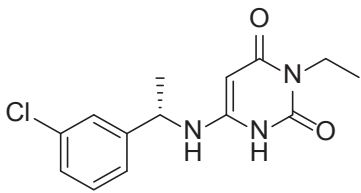
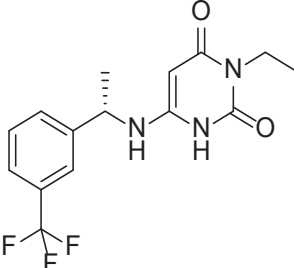
	109 ---- 1. 5 y 7	328 (M+H)+ ¹ H-RMN (300 MHz, DMSO-d ₆): δ ppm 10,28 (s ancho, 1H), 7,39-7,24 (m, 5H), 6. 81 (d, J = 6. 6 Hz, 1H), 4,47-4,33 (m, 4H), 1,80-1,67 (m, 2H), 0,85 (t, J = 7,2 Hz, 3H).
	110 ---- 1 y 50	286 (M+H)+ ¹ H-RMN (300 MHz, DMSO-d ₆): δ ppm 10,01 (s ancho, 1H), 7,39-7,33 (m, 4H), 7,30-7,23 (m, 1H), 6. 60 (d, J = 6. 0 Hz, 1H), 4,52 (q, J = 6. 6 Hz, 1H), 4,38 (s, 1H), 3,49 (d, J = 6. 9 Hz, 2H), 1,40 (d, J = 6. 9 Hz, 3H) 1,08-1,00 (m, 1H), 0,37-0,33 (m, 2H), 0,28-0,23 (m, 2H).
	111 ---- 7 y 59	340 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 10,29 (s ancho, 1H), 7,37-7,33 (m, 4H), 7,30-7,25 (m, 1H), 6. 98 (d, J = 5,6 Hz, 1H), 4,42 (q, J = 9,2 Hz, 2H), 4,35 (d, J= 1,6 Hz, 1H), 3,89-3,85 (m, 1H), 1,24-1,15 (m, 1H) 0,61-0,56 (m, 1H), 0,50-0,33 (m, 3H).

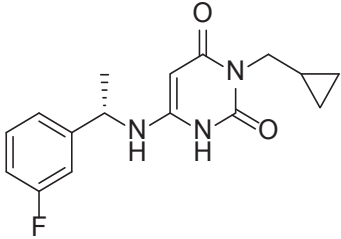
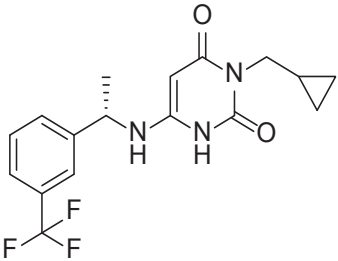
 <chem>C1CC[C@H](C1)C(NC2=CN(C(=O)N(C2)C(F)F)C3=CC=CC=C3)C4=CC=CC=C4</chem>	112 ---- 8 y 59	354 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 10,27 (s ancho, 1H), 7,45-7,25 (m, 5H), 6. 73 (s ancho, 1H), 4,46-4,35 (m, 4H), 2,67-2,50 (m parcialmente oscurecido, 1H), 2,04-2,01 (m, 1H), 1,90-1,79 (m, 4H), 1,68-1,62 (m, 1H).
 <chem>C1CC[C@H](C1)C(NC2=CN(C(=O)N(C2)CO)C3=CC=CC=C3)C4=CC=CC=C4</chem>	113 ---- 15	306 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆ a 90 °C): δ ppm 9,86 (s ancho, 1H), 7,39-7,31 (m, 4H), 7,29-7,25 (m, 1H), 6. 48 (d, J = 6. 7 Hz, 1H), 5,00-4,91 (m, 1H), 4,78 (m, 1H), 4,56-4,50 (m, 1H), 4,45-4,38 (m, 2H), 3,76-3,70 (m, 2H), 1,42 (d, J = 7,4 Hz, 3H).

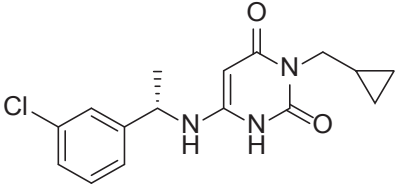
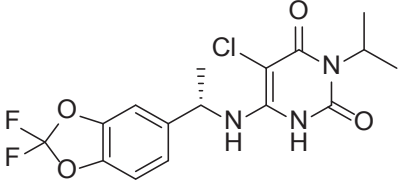
 <chem>Fc1ccc(cc1)CC[C@@H]2C(=O)N(C(=O)N2C(F)(F)F)N</chem>	114 ---- 1 y 51	360 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆ a 90 °C): δ ppm 9,86 (s ancho, 1H), 7,25 (dd, 8,4. 5,7 Hz, 2H), 7,10-7,04 (m, 2H), 5,94 (s ancho, 1H), 5,52 (s ancho, 1H), 4,62 (s ancho, 1H), 3,79-3,71 (m, 1H), 2,76 (d, J= 6. 7 Hz, 2H), 1,55 (d, J = 7,0 Hz, 3H), 1,11 (d, J = 6. 3 Hz, 3H).
 <chem>CC(C)N1C(=O)C=C(N[C@@H]1C2=CC=CC=C2O)N</chem>	115 ---- 62	290 (M+H)+
 <chem>CC(C)N1C(=O)C=C(N[C@@H]1C2=CC=CC=C2O)N</chem>	116 ---- 62	290 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 9,83 (s ancho, 1H), 9,68 (s ancho, 1H), 7,14 (dd, J = 7,4. 1,6 Hz, 1H), 7,05 (td, J = 7,6. 1,6 Hz, 1H), 6. 82-6. 74 (m, 2H), 6. 40 (d, J = 7,0 Hz, 1H), 4,92-4,85 (m, 1H), 4,60 (quin, J = 6. 9 Hz, 1H), 4,30 (d, J = 2,4 Hz, 1H), 1,35 (d, J = 6. 7 Hz, 3H), 1,27-1,22 (m, 6H).

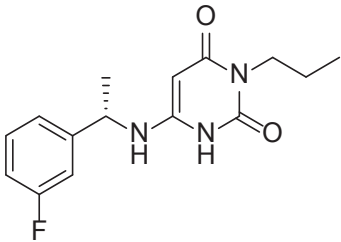
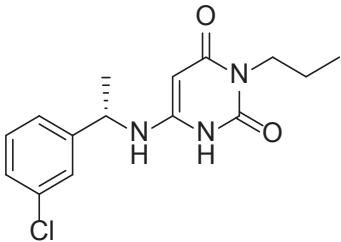
	117 ---- 1 y 59	340 (M+H)+ ¹ H-RMN (300 MHz, CDCl ₃): δ ppm 10,40 (s ancho, 1H), 7,44-7,26 (m, 5H), 6. 13 (s ancho, 1H), 4,80 (s ancho, 1H), 4,45 (m, 1H), 1,76-1,52 (m, 5H), 1,35-1,27 (m, 2H).
	118 ---- 1 y 51	376 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 10,27 (s ancho, 1H), 7,29-7,22 (m, 3H), 7,15-7,10 (m, 2H), 7,01 (dd, J = 8,2. 2,3 Hz, 2H), 6. 12 (s ancho, 1H), 4,72 (d, J = 2,0 Hz, 1H), 3,79-3,71 (m, 1H), 2,76 (d, J= 6. 7 Hz, 2H), 1,09 (d, J = 6. 7 Hz, 3H).
	119 ---- 5 y 59	354 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 9,84 (s ancho, 1H), 7,43 (d, J= 1,2 Hz, 1H), 7,38 (d, J = 8,0 Hz, 1H), 7,21 (dd, J = 8,4. 1,2 Hz, 1H), 6. 54 (d, J = 6. 8 Hz, 1H), 4,90 (q, J = 6. 8 Hz, 1H), 4,55-4,52 (m, 1H), 4,34 (d, J = 2,0 Hz, 1H), 1,39 (d, J = 6. 8 Hz, 3H) 1,31-1,26 (m, 6H).

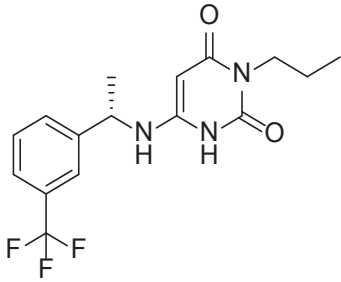
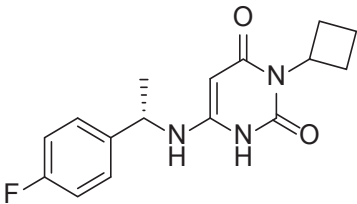
	120 ---- 5 y 59	308 (M+H)+ ¹ H-RMN (300 MHz, DMSO-d ₆): δ ppm 9,87 (m, 1H), 7,48-7,28 (m, 4H), 6.66 (d, J = 6.6 Hz, 1H), 4,93-4,84 (m, 1H), 4,70 (quin, J = 6.6 Hz, 1H), 4,08 (s, 1H), 1,41 (d, J = 6.6 Hz, 3H), 1,28-1,24 (m, 6H).
	121 ---- 5	304 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 9,68 (m, 1H), 7,25-7,21 (m, 2H), 6.91-6.87 (m, 2H), 6.43 (m, 1H), 4,92-4,85 (m, 1H), 4,41 (quin, J = 6.7 Hz, 1H), 4,32 (s, 1H), 3,71 (s, 3H), 1,35 (d, J = 6.7 Hz, 3H), 1,27-1,23 (m, 6H).
	122 ---- 7 y 59	286 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 7,38-7,33 (m, 4H), 7,28-7,25 (m, 1H), 6.80 (s ancho, 1H), 4,24 (s, 1H), 3,82-3,78 (m, 1H), 3,63 (q, J = 6.8 Hz, 2H), 1,17-1,13 (m, 1H), 0,97 (t, J = 6.8 Hz, 3H), 0,59-0,54 (m, 1H), 0,47-0,32 (m, 3H).

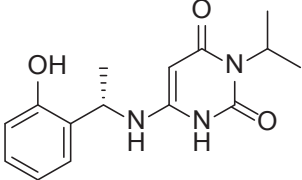
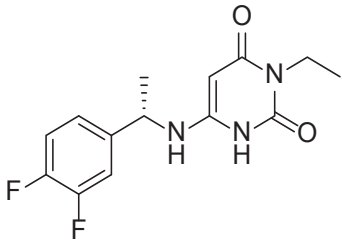
 <chem>CCN1C(=O)C=C(N[C@@H](c2ccc(Cl)cc2)C)NC1=O</chem>	123 ---- 1 y 59	294 (M+H) ⁺ ¹ H-RMN (300 MHz, DMSO-d ₆): δ ppm 10,00 (s ancho, 1H), 7,44 (s, 1H), 7,42-7,30 (m, 3H), 6. 61 (d, J = 6. 6 Hz, 1H), 4,57-4,53 (m, 1H), 4,38 (d, J = 1,8 Hz, 1H), 3,65 (q, J = 6. 9 Hz, 2H), 1,39 (d, J = 6. 9 Hz, 3H), 0,99 (t, J = 7,2 Hz, 3H).
 <chem>CCN1C(=O)C=C(N[C@@H](c2ccc(C(F)(F)F)cc2)C)NC1=O</chem>	124 ---- 1 y 59	328 (M+H) ¹ H-RMN (300 MHz, DMSO-d ₆): δ ppm 7,75 (s, 1H), 7,72-7,59 (m, 3H), 6. 99 (s ancho, 1H), 4,68-4,62 (m, 1H), 4,38 (s, 1H), 3,65 (q, J = 6. 6 Hz, 2H), 1,42 (d, J = 6. 6 Hz, 3H), 1,01 (t, J = 4,5 Hz, 3H).

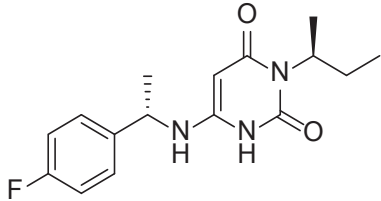
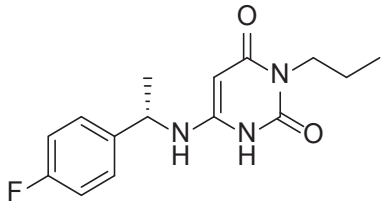
	125 ---- 1 y 59	304 (M+H)⁺ ¹H-RMN (300 MHz, DMSO-d₆): δ ppm 10,01 (s ancho, 1H), 7,42 (dd, J = 7,8, 6. 0 Hz, 1H), 7,20 (d, J = 7,5 Hz, 2H), 7,12-7,06 (m, 1H), 6. 62 (d, J = 7,2 Hz, 1H), 4,56 (quin, J = 6. 9 Hz, 1H), 4,39 (s, 1H), 3,49 (d, J = 6. 9 Hz, 2H), 1,40 (d, J = 6. 6 Hz, 3H), 1,07-0,99 (m, 1H), 0,37-0,34 (m, 2H), 0,30-0,22 (m, 2H).
	126 ---- 1 y 59	354 (M+H)⁺ ¹H-RMN (300 MHz, CD₃OD): δ ppm 7,73-7,50 (m, 4H), 4,63 (q, J = 6. 9 Hz, 1H), 3,62 (d, J = 7,2 Hz, 2H), 1,50 (d, J = 6. 9 Hz, 3H) 1,17-1,10 (m, 1H), 0,45-0,39 (m, 2H), 0,32-0,26 (m, 2H).

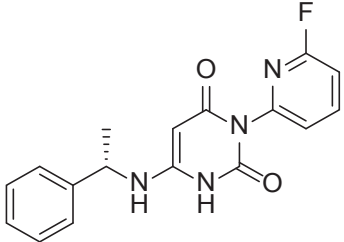
	127 ---- 1 y 59	320 (M+H)+ ¹H-RMN (300 MHz, DMSO-d₆): δ ppm 10,01 (s ancho, 1H), 7,45 (s, 1H), 7,42-7,30 (m, 3H), 6. 64 (d, J = 6. 9 Hz, 1H), 4,58-4,53 (m, 1H), 4,39 (s, 1H), 3,50 (d, J = 7,2 Hz, 2H), 1,40 (d, J = 6. 6 Hz, 3H) 1,07-1,03 (m, 1H), 0,37-0,31 (m, 2H), 0,25-0,22 (m, 2H).
	128 ---- 3	388(M+H)+ ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 9,50 (s ancho, 1H), 7,52- 7,22 (m, 3H), 4,87-4,72 (m, 1H), 4,52-4,41 (m, 1H), 1,60-1,48 (m, 3H), 1,41-1,27 (m, 6H).

	129 ---- 1 y 59	292 (M+H)+ ¹ H-RMN (300 MHz, DMSO-d ₆): δ ppm 10,00 (s ancho, 1H), 7,40 (dt, J = 7,8 Hz, 0,6 Hz, 1H), 7,26 (d, J = 7,8 Hz, 2H), 7,09-7,06 (m, 1H), 6. 60 (d, J = 6. 9 Hz, 1H), 4,46 (q, J = 6. 6 Hz, 1H), 4,38 (s, 1H), 3,60-3,55 (m, 2H), 1,47-1,39 (m, 5H), 0,79 (t, J = 7,5 Hz, 3H).
	130 ---- 1 y 59	308 (M+H)+ ¹ H-RMN (300 MHz, DMSO-d ₆): δ ppm 10,01 (s ancho, 1H), 7,44 (t, J = 0,9 Hz, 1H), 7,41-7,38 (m, 1H), 7,34-7,31 (m, 2H), 6. 62 (d, J = 5,1 Hz, 1H), 4,55 (q, J = 6. 7 Hz, 1H), 4,38 (s, 1H), 3,54 (dd, J = 6. 0, 5,7 Hz, 2H), 1,47-1,39 (m, 5H), 0,84 (t, J = 7,5 Hz, 3H).

	131 ---- 1 y 59	342 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 10,05 (s ancho, 1H), 7,74 (s, 1H), 7,68-7,56 (m, 3H), 6. 69 (d, J = 6. 4 Hz, 1H), 4,70-4,63 (m, 1H), 4,40 (s, 1H), 3,59-3,54 (m, 2H), 1,49-1,40 (m, 5H), 0,86 (t, J = 6. 0 Hz, 3H).
	132 ---- 1	304 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 9,85 (s ancho, 1H), 7,37-7,33 (m, 2H), 7,18-7,13 (m, 2H), 6. 52 (d, J = 7,4 Hz, 1H), 5,14-5,05 (m, 1H), 4,50 (quin, J = 6. 8 Hz, 1H), 4,31 (s, 1H), 2,84-2,78 (m, 2H), 1,97-1,91 (m, 2H), 1,70-1,54 (m, 2H), 1,36 (t, J = 6. 7 Hz, 3H).

	133 ---- 1	290 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 9,83 (s ancho, 1H), 9,68 (s ancho, 1H), 7,14 (dd, J = 7,4. 1,6 Hz, 1H), 7,07-7,03 (m, 1H), 6. 81-6. 74 (m, 2H), 6. 42 (d, J = 7,0 Hz, 1H), 4,92-4,85 (m, 1H), 4,60 (quin, J = 6. 8 Hz, 1H), 4,31 (d, J = 2,3 Hz, 1H), 1,35 (d, J = 7,0 Hz, 3H), 1,27-1,22 (m, 6H).
	134 ---- 1	296 (M+H)+ ¹ H-RMN (300 MHz, DMSO-d ₆): δ ppm 10,03 (s ancho, 1H), 7,48-7,39 (m, 2H), 7,23-7,20 (m, 1H), 6. 60 (d, J = 5,1 Hz, 1H) 4,58-4,53 (m, 1H), 4,38 (s, 1H), 3,66 (q, J = 5,1 Hz, 2H), 1,39 (d, J = 5,1 Hz, 3H), 0,99 (t, J = 5,1 Hz, 3H).

 <chem>CC[C@H](C)N1C(=O)NC(=NC1)NC[C@H](c2ccc(F)cc2)C</chem>	135 ---- 1	306 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 9,95 (s ancho, 1H), 7,36 (dd, J = 9,0, 5,5 Hz, 2H), 7,18-7,14 (m, 2H), 6. 54 (d, J = 7,0 Hz, 1H) 4,66 (s ancho, 1H), 4,54-4,49 (m, 1H), 4,34 (s, 1H), 1,97-1,86 (m, 1H), 1,65-1,55 (m, 1H), 1,38 (d, J = 6. 8 Hz, 3H), 1,23 (d, J = 6. 8 Hz, 3H), 0,70 (t, J = 6. 8 Hz, 3H).
 <chem>CCCN1C(=O)NC(=NC1)NC[C@H](c2ccc(F)cc2)C</chem>	136 ---- 1	292 (M+H)+ ¹ H-RMN (400 MHz, DMSO-d ₆): δ ppm 9,95 (s ancho, 1H), 7,36 (dd, J = 9,0, 5,5 Hz, 2H), 7,18-7,14 (m, 2H), 6. 54 (d, J = 7,0 Hz, 1H) 4,56-4,49 (m, 1H), 4,35 (d, J = 2,3 Hz, 1H), 3,57-3,53 (m, 2H), 1,44-1,36 (m, 5H), 0,77 (t, J = 7,4 Hz, 3H).

	137 ---- 65	327 (M+H)+ ¹H-RMN (400 MHz, DMSO-d₆): δ ppm 10,36 (s ancho, 1H), 8,09 (q, J = 8,0 Hz, 1H), 7,39- 7,35 (m, 4H), 7,30-7,22 (m, 3H), 6. 87 (m, 1H), 4,61 (quin, J = 6. 8 Hz, 1H), 4,49 (s, 1H), 1,44 (d, J = 6. 8 Hz, 3H).
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Ejemplo 73. Ensayo de inhibición de miosina

Se valoraron agentes de moléculas pequeñas en cuanto a su capacidad para inhibir la actividad enzimática de miosina cardíaca bovina usando un ensayo bioquímico que acopla la liberación de ADP (difosfato de adenosina) de miosina cardíaca a un sistema de acoplamiento enzimático que consiste en piruvato quinasa y lactato deshidrogenasa (PK/LDH) y verificando la disminución de absorbancia de NADH (a 340 nm) en función del tiempo. PK convierte ADP en ATP (trifosfato de adenosina) convirtiendo PEP (fosfoenolpiruvato) en piruvato. El piruvato es seguidamente convertido en lactato por LDH convirtiendo NADH (nicotinamida-adenina-dinucleótido) en NAD (nicotinamida-adenina- dinucleótido oxidado). La fuente la miosina cardíaca fue de corazón bovino en la forma de miofibrillas descortezadas. Antes de ensayar los agentes de moléculas pequeñas, las miofibrillas bovinas fueron valoradas en cuanto a su respuesta a calcio y la concentración de calcio que consigue una activación 50% (pCa₅₀) o 75% (pCa₇₅) del sistema de miofibrillas que fue escogida como la condición final para valorar la actividad inhibidora de los agentes de moléculas pequeñas. La actividad enzimática se midió en una solución tamponada que contenía PIPES 12 mM (ácido piperazino-N,N'-bis(2-etanosulfónico)), cloruro de magnesio 2 mM a pH 6,8 (tampón PM 12). Las condiciones finales del ensayo fueron de 1 mg/ml de miofibrillas cardíacas bovinas, PK/LDH 0,4 mM, ATP 50 μm, 0,1 mg/ml de BSA (albúmina de suero bovino), 10 ppm de antiespumante, DTT 1 mM, NADH 0,5 mM, PEP 1,5 mM a la concentración de calcio libre deseada necesaria para conseguir una activación de 50% o 75% de las miofibrillas.

Se creó una serie de diluciones de compuesto en DMSO de forma que la concentración deseada final de compuesto se consiguiera en un volumen de 100 μl con una concentración fija de DMSO de 2% (v/v). Normalmente se añadieron 2 μl de las series de diluciones a placa de 96 pocillos para conseguir una respuesta de dosis de 8 o 12 puntos. A continuación de

la adición de 50 µl de una solución que contenía miofibrillas cardíacas bovinas, PK/LDH y una solución de calcio (la que conseguía la activación deseada), se comenzó la reacción enzimática con la adición de 50 µl de una solución que contenía ATP, PEP y NADH. El progreso de la reacción fue seguido en una placa Molecular Devices M5e a temperatura ambiente usando placas de media área transparente. El lector de placas se configuró para leer la absorbancia a 340 nm en un modo cinético durante 15 minutos. Los datos se registraron como la pendiente de la respuesta de la absorbancia al tiempo. Las pendientes de la respuesta a la absorbancia como una función del tiempo se normalizaron respecto a las pendientes de la placa que contenía DMSO. Seguidamente esta velocidad normalizada se representó gráficamente como una función de la concentración de moléculas pequeñas y los datos fueron ajustados a un ajuste de cuatro parámetros usando el sistema GraphPad Prism. El punto medio de esta representación gráfica es la IC50 y la concentración a la que se inhibe un cincuenta por ciento de la respuesta total. Cualquier agente que no consiga una inhibición de cincuenta por ciento a la concentración más elevada ensayada fue expresado como IC50 mayor que la concentración más elevada ensayada (es decir, IC50 > 25 µM).

Tabla 2. Actividad de inhibición de miosina de compuestos ensayados^a

Compuesto nº	Actividad bioquímica (pCa ₇₅)	Actividad bioquímica (pCa ₅₀)
1	+++	+++
2	++	
3	+++	
4	+++	
5	+++	
6	+++	
7	+++	
8	+++	
9	+++	
10	+++	
11	++	
12	+++	
13	+++	
14	+++	

15	+++	
16	++	
17	+++	
21	+++	
22	++	
24	+++	
25	+	
26	+++	
27	+++	+++
28	+++	
29	+++	
30	+++	
31	+++	
32	+++	
33	+++	
34	+++	
35	+++	+++
36		++
37	++	
38	+++	+++
39	+++	
40	+++	
41	+++	
42	+++	
43	+++	
44	+++	
45	+++	+++
46	++	
47	++	
48	++	++
49	+++	+++
50	+++	
51	++	

52	+++	
53	++	
54	++	++
55	+++	
56	+	
57		++
58	+++	
59	+++	
61	++	
62		+++
63		+++
64		++
65		++
66		++
67		+++
68		+++
69	++	+++
70	++	
71		+++
72	++	
73	++	
74	++	
75	++	
76	++	
77	++	
78	+++	
79	++	
80	+++	
81	++	
82	+++	+++
83	+++	
84	+++	
85	+++	

86	++	
90	++	
91	++	
92	++	++
93	+++	++
94	+++	
95	+++	+++
99	+++	
100	++	
101		++
102		++
103		+++
104		+++
105		+++
106		+++
107		+++
108		+++
109		++
110		++
111		++
112		+++
113		++
114		+++
115		
116		+++
117		+++
118		+++
119		+++
120		+++
121		+++
122		++
123		+++
124		+++

125		+++
126		++
127		+++
128		++
129		++
130		+++
131		+++
132		+++
133		+++
134		+++
135		+++
136		+++
137		+++

^a +++ corresponde a los valores de IC50 por debajo de 1 µM. ++ corresponde a los valores de IC50 de 1 a 15 µM. + corresponde a valores de IC50 por encima de 15 µM.

La selectividad frente a miofibrillas de esqueleto de conejo se valoró como se describió anteriormente con la excepción de que la fuente de miosina fue la de miosina de esqueleto rápida de conejo en forma de miofibrillas. Se determinaron también las respuestas de la dosis frente a miofibrillas de esqueleto de conejo como se describió anteriormente.

Ejemplo 74. Preferencia estereoquímica para la actividad

Se ensayaron parejas coincidentes de estereoisómeros en cuanto a su capacidad para inhibir la actividad de miosina como se describió anteriormente. Los resultados se resumen en la Tabla 3. En todos los casos, el estereoisómero (R) es significativamente menos activo que el estereoisómero (S).

Tabla 3. Actividades relativas de estereoisómeros (S) y (R)^a

Estereoisómero (S)			Estereoisómero (R)		
Comp. nº	IC50 (pCa ₇₅)	IC50 (PCa ₅₀)	Comp. nº	IC50 (pCa ₇₅)	IC50 (pCa ₅₀)
1	0,67 µM	0,56 µM	19R	23,93 µM	51,87 µM
21	0,39 µM		20R	19,64 µM	
59	0,45 µM		60R	>39,2 µM	

^a el ensayo se realizó usando miosina 0,5 µM, por lo tanto, los valores de IC50 por debajo de 1,0 µM son aproximados.

Ejemplo 75. Ensayo de contractilidad de cardiomiocitos

La contractilidad de miocitos ventriculares de ratas adultos se determina mediante detección de contornos con un sistema de contractilidad IonOptix. Se colocan partes alícuotas de miocitos en tampón Tyrode (NaCl 137 mM, KCl 3,7 mM, MgCl₂ 0,5 mM, CaCl₂ 1,5 mM, HEPES 4 mM, glucosa 11 mM) en una cámara de perfusión (Series 20 RC-27NE; Warner Instruments) dejando que se adhieran al cubreobjetos, y seguidamente se sometieron a perfusión con tampón Tyrode a 37 °C. Los miocitos son estimulados con campos A 1 Hz y 10 V. Solo los miocitos con estrías transparentes, estáticos antes de avanzar, con una longitud celular de 120-180 micrómetros, un acortamiento fraccionado basal a 3-8% de la longitud celular y una velocidad de contracción mayor que 100 micrómetros por segundo son usados para los experimentos de la contractilidad. Para determinar la respuesta a compuestos, los miocitos se someten primero a perfusión durante 60 segundos con tampón Tyrode seguido de 5 minutos de compuesto y lavado de 140 segundos con tampón Tyrode. Los datos se registran continuamente usando un software IonOptix. Los datos de contractilidad se analizan usando un software Ionwizard (IonOptix). Para cada célula, se halló la media de 10-20 contractilidades transitorias y se compararon bajo condiciones basales (sin compuesto) y de tratamiento con compuesto. La actividad del compuesto se mide por los efectos sobre el acortamiento fraccional (FS), en que el acortamiento fraccional es la relación de la longitud pico la célula en la contracción dividida por la longitud de la célula basal normalizada a 100% para célula sin tratar.

Tabla 4. Inhibición de la contracción de cardiomiocitos por compuestos seleccionados ^a

ID	Actividad a 0,3 μM	Actividad a 1,0 μM
1	++	+++
2	++	+++
12	n.d.	++
19	n.d.	+
27	++	n.d.
67	n.d.	+++

^a + representa los valores de la inhibición del acortamiento fraccional menores que 33%. ++ representa los valores de la inhibición del acortamiento fraccional de 33% a 66%. +++ representa los valores de la inhibición del acortamiento fraccional mayores que 66%.

Ejemplo 76. Efecto farmacodinámico agudo en rata

Los compuestos representativos fueron ensayados en cuanto a su capacidad para modular la contractilidad cardíaca en una rata como una medida de implicación diana in vivo. El acortamiento fraccional, una medida de la contractilidad, se determinó apreciando el cambio de diámetro del ventrículo izquierdo al final de un sístole/contracción (LVESd) relativo a diástole/relajación (LVEDd) y expresando este cambio como la relación $FS = (LVEDd - LVESd)/LVEDd$. Ratas Sprague-Dawley machos alimentadas fueron ligeramente anestesiados con isoflurano y se midió el acortamiento fraccional de línea de base en la posición paraesternal usando una ecocardiografía transtorácica (TTE). A continuación de esta medición, los animales se recuperaron y recibieron una dosis única de compuesto (4 mg/kg) mediante sonda oral. A las tres horas posteriores a la dosis, se recogieron un segundo y tercero ecocardiogramas bajo anestesia ligera para determinar los efectos de los fármacos sobre la contractilidad. Los efectos se representan en la Tabla 5 como el porcentaje de reducción del acortamiento fraccional de línea de base.

Tabla 5. Inhibición de la contractilidad en rata por compuestos seleccionados^a

15

ID	% Reducción en acortamiento fraccionado 3 h después de la dosis
1	+++
45	+
48	+++
49	+++
69	+
70	++
71	+++

^a + representa un cambio relativo en el acortamiento fraccional menor 15%. ++ representa un cambio relativo en el acortamiento fraccional entre 15-30%. +++ representa un cambio relativo en el acortamiento fraccional mayor que 30%.

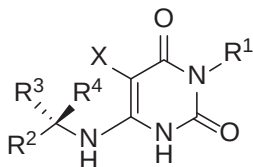
Aunque la invención que antecede ha sido descrita en algún detalle a modo de ilustración y ejemplo para fines de claridad y comprensión, un experto en la técnica apreciará que se pueden practicar ciertos cambios sin modificaciones del alcance de las reivindicaciones anejas. Además, cada referencia proporcionada en la presente memoria descriptiva se incorpora como referencia en su totalidad hasta el mismo alcance que si cada referencia fuera individualmente incorporada como referencia. Cuando exista un conflicto entre la presente

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solicitud y una referencia proporcionada en la presente memoria descriptiva, debe predominar la presente solicitud.

REIVINDICACIONES

1. Un compuesto que tiene la fórmula:



o una sal farmacéuticamente aceptable del mismo, en el cual

- 5 R^1 es un miembro seleccionado entre el grupo que consiste en alquilo C_1-C_8 , cicloalquilo C_3-C_8 , cicloalquil C_3-C_8 -alquilo C_1-C_4 , heterocicloalquilo de 4 a 7 miembros, fenilo, fenil-alquilo C_1-C_4 , heteroarilo de 5 a 6 miembros y heteroaril de 5 a 6 miembros-alquilo C_1-C_4 , en que cada R^1 está opcionalmente sustituido con 1-3 R^a ;
- R^2 es un miembro seleccionado entre el grupo que consiste en fenilo, fenil-alquilo C_1-C_4 ,
10 heteroarilo de 5 a 6 miembros y heteroaril de 5 a 6 miembros-alquilo C_1-C_4 , en que cada R^2 está opcionalmente sustituido con uno 1-5 R^b ;
- R^3 es un miembro seleccionado entre el grupo que consiste en alquilo C_1-C_4 , cicloalquilo C_3-C_4 y heterocicloalquilo de 4 a 7 miembros, en cada R^3 está opcionalmente sustituido con 1-3 R^c ;
- 15 R^4 es H;
- X es un miembro seleccionado entre el grupo que consiste en H y F;
- cada R^a se selecciona independiente entre el grupo que consiste en halo, CN, hidroxilo, alquilo C_1-C_4 , haloalquilo C_1-C_4 , alcoxi C_1-C_4 , fenilo, fenil-alquilo C_1-C_4 , fenil-alcoxi C_1-C_4 , fenoxi, $-COR^{a1}$, $-CO_2R^{a1}$, $-SO_2R^{a1}$, $-SO_2NR^{a1}R^{a2}$ y $-CONR^{a1}R^{a2}$, en que cada R^{a1} y R^{a2} se selecciona
20 independientemente entre el grupo que consiste en H, alquilo C_1-C_4 y fenilo, u opcionalmente R^{a1} y R^{a2} , cuando están unidos a un átomo de nitrógeno, están combinados para formar un anillo de 4 a 6 miembros;
- cada R^b se selecciona independientemente entre el grupo que consiste en halo, CN, hidroxilo, alquilo C_1-C_4 , haloalquilo C_1-C_4 , alcoxi C_1-C_4 , fenoxi, fenil-alcoxi C_1-C_4 , metilenodioxo, difluorometilenodioxo, $-COR^{b1}$, $-CO_2R^{b1}$, $-SO_2R^{b1}$, $-SO_2NR^{b1}R^{b2}$, $CONR^{b1}R^{b2}$, $NR^{b1}R^{b2}$, heteroarilo de 5 a 6 miembros y heterociclilo de 5 a 6 miembros opcionalmente sustituido con oxo, en que cada R^{b1} y R^{b2} se selecciona independientemente entre el grupo que consiste en H y alquilo C_1-C_4 u opcionalmente R^{b1} y R^{b2} , cuando están unidos a un átomo de nitrógeno, están combinados para formar un anillo de 4 a 6 miembros; y
25
- 30 cada R^c se selecciona independientemente entre el grupo que consiste en halo, hidroxilo y alcoxi C_1-C_2 .

2. Un compuesto de la reivindicación 1, o una sal farmacéuticamente aceptable del

mismo, en el cual,

R^1 es un miembro seleccionado entre el grupo que consiste en alquilo C_1-C_8 , cicloalquilo C_3-C_8 , heterocicloalquilo de 4 a 7 miembros, fenilo y heteroarilo de 5 a 6 miembros, en que cada R^1 está opcionalmente sustituido con 1-3 R^a ;

5 R^2 fenilo, que está opcionalmente sustituido con 1-5 R^b ;

R^3 es un miembro seleccionado entre el grupo que consiste en alquilo C_1-C_4 , cicloalquilo C_3-C_4 y heterocicloalquilo de 4 a 7 miembros en cada R^3 está opcionalmente sustituido con 1-2 R^c ;

R^4 es H;

10 X es un miembro seleccionado entre el grupo que consiste en H y F;

cada R^a se selecciona independiente entre el grupo que consiste en halo, CN, alquilo C_1-C_4 , alcoxi C_1-C_4 , $-COR^{a1}$, $-CO_2R^{a1}$, $-SO_2R^{a1}$, $-SO_2NR^{a1}R^{a2}$ y $-CONR^{a1}R^{a2}$, en que cada R^{a1} y R^{a2} se selecciona independientemente entre el grupo que consiste en H y alquilo C_1-C_4 y fenilo, u opcionalmente R^{a1} y R^{a2} , cuando están unidos a un átomo de nitrógeno, están combinados

15 para formar un anillo de 4 a 6 miembros

cada R^b se selecciona independientemente entre el grupo que consiste en halo, CN, alquilo C_1-C_4 , alcoxi C_1-C_4 , $-COR^{b1}$, $-CO_2R^{b1}$, $-SO_2R^{b1}$, $-SO_2NR^{b1}R^{b2}$, $CONR^{b1}R^{b2}$, $NR^{b1}R^{b2}$, heteroarilo de 5 a 6 miembros y heterociclilo de 5 a 6 miembros opcionalmente sustituido con oxo, en que cada R^{b1} y R^{b2} se selecciona independientemente entre el grupo que consiste en H y

20 alquilo C_1-C_4 u opcionalmente R^{b1} y R^{b2} , cuando están unidos a un átomo de nitrógeno, están combinados para formar un anillo de 4 a 6 miembros; y

cada R^c se selecciona independientemente entre el grupo que consiste en halo y alcoxi C_1-C_2 .

25 3. Un compuesto de las reivindicaciones 1 ó 2, o una sal farmacéuticamente aceptable del mismo, en el que X es H.

4. Un compuesto de las reivindicaciones 1 ó 2, o una sal farmacéuticamente aceptable del mismo, en el que R^1 se selecciona entre el grupo que consiste en alquilo C_3-C_4 , cicloalquilo C_3-C_5 y heterocicloalquilo de 4 a 6 miembros, en que cada R^1 está opcionalmente sustituido con 1-2 R^a .

30 5. Un compuesto de las reivindicaciones 1 ó 2, o una sal farmacéuticamente aceptable del mismo, en el que R^1 se selecciona entre el grupo que consiste en fenilo y heteroarilo de 5 a 6 miembros, en que cada R^1 está opcionalmente sustituido con 1-3 R^a .

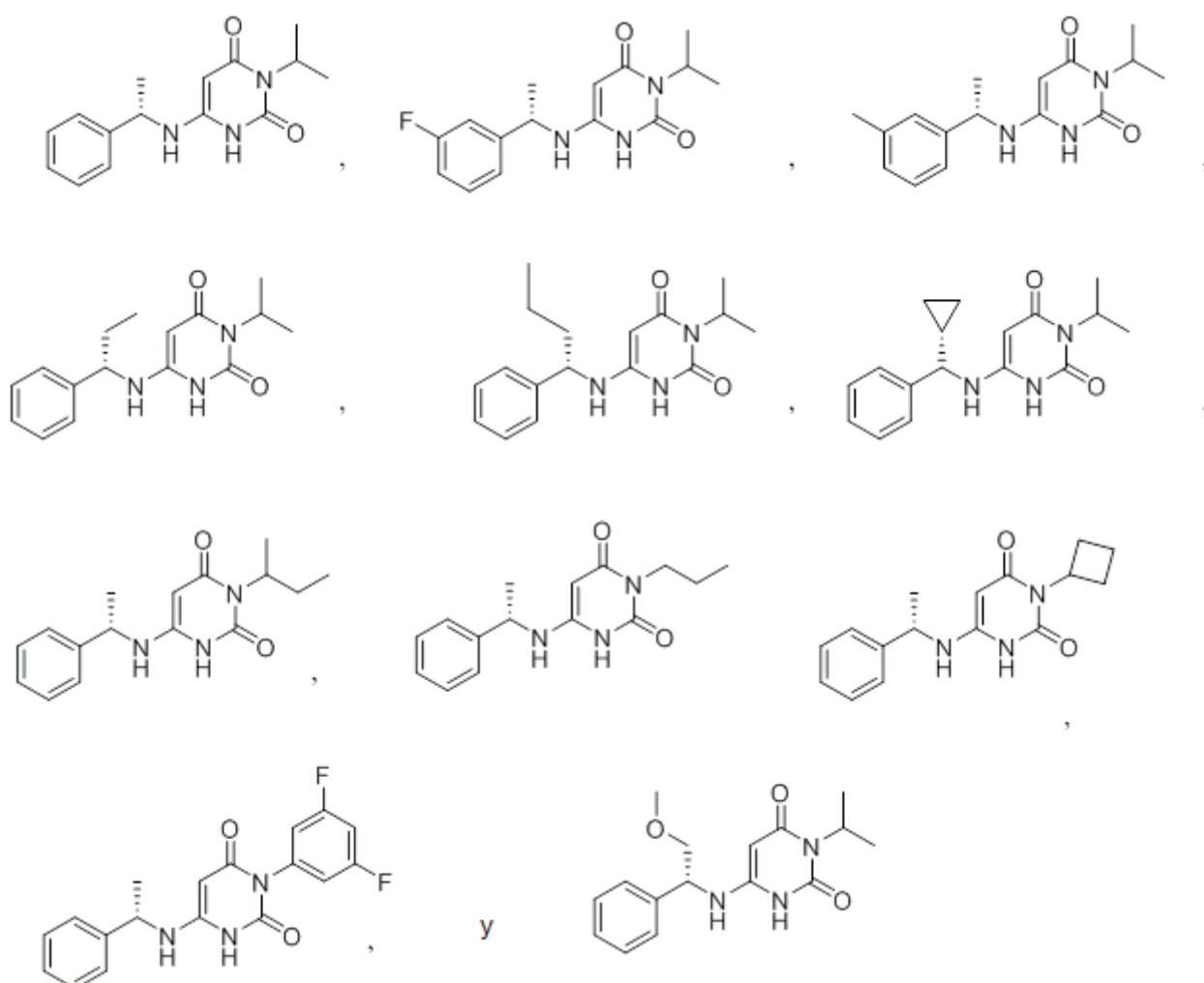
35 6. Un compuesto de las reivindicaciones 1 ó 2, o una sal farmacéuticamente aceptable del mismo, en el que R^1 se selecciona entre el grupo que consiste en alquilo C_3-C_4 , cicloalquilo C_3-C_5 y heterocicloalquilo de 4 a 6 miembros.

7. Un compuesto de las reivindicaciones 1 ó 2, o una sal farmacéuticamente aceptable del mismo, en el que R^1 es heterocicloalquilo de 4 a 6 miembros, opcionalmente sustituido con 1-2 R^a seleccionado entre el grupo que consiste en alquilo C_1-C_4 , alcoxi C_1-C_4 , $-COR^{a1}$, $-CO_2R^{a1}$, $-SO_2R^{a1}$, $-SO_2NR^{a1}R^{a2}$ y $-CONR^{a1}R^{a2}$, en que cada R^{a1} y R^{a2} se selecciona independientemente entre el grupo que consiste en H y alquilo C_1-C_4 .
8. Un compuesto de las reivindicaciones 1 ó 2, o una sal farmacéuticamente aceptable del mismo, en el que R^1 se selecciona entre el grupo que consiste en ciclobutilo, isopropilo, isobutilo, 1-metoxipropan-2-ilo, ciclopentilo, ciclohexilo, 4-tetrahidropiranilo, 1-(metilsulfonil)piperidin-4-ilo, 1-(metoxycarbonil)piperidin-4-ilo, 4,4-difluorociclohexilo, fenilo, 2-piridilo, 3-piridilo, 3-isoxazolilo, 5-isoxazolilo y 1-metil-3-pirazolilo.
9. Un compuesto de las reivindicaciones 1 ó 2, o una sal farmacéuticamente aceptable del mismo, en el que R^2 está opcionalmente sustituido con 1-2 R^b .
10. Un compuesto de las reivindicaciones 1 ó 2, o una sal farmacéuticamente aceptable del mismo, en el que R^2 se selecciona entre el grupo que consiste fenilo, 3-metilfenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2,5-difluorofenilo, 3,5-difluorofenilo, 3-clorofenilo, 3-metoxifenilo, 3-(3-oxazolidin-2-onil)fenilo, 3-(2-metil-1-imidazol)fenilo, 3-(1-pirazolil)fenilo, y 3-(1,2,4-triazol-1-il)fenilo.
11. Un compuesto de las reivindicaciones 1 ó 2, o una sal farmacéuticamente aceptable del mismo, en el que R^3 se selecciona entre el grupo que consiste en alquilo C_1-C_4 , alcoxi C_1-C_4 -alquilo y cicloalquilo C_3-C_4 .
12. Un compuesto de las reivindicaciones 1 ó 2, o una sal farmacéuticamente aceptable del mismo, en el que R^3 se selecciona entre el grupo que consiste en metilo, etilo, propilo, ciclopropilo, ciclobutilo y 2-metoximetilo.
13. Un compuesto de cualquiera de las reivindicaciones 1 a 10, o una sal farmacéuticamente aceptable del mismo, en el que R^3 es metilo.
14. Un compuesto de las reivindicaciones 1 ó 2, o una sal farmacéuticamente aceptable del mismo, en el que R^1 es isopropilo, R^2 está opcionalmente sustituido con 1-2 R^b y R^3 es metilo.
15. Un compuesto de las reivindicaciones 1 ó 2, o una sal farmacéuticamente aceptable del mismo, en el que R^1 es heterocicloalquilo de 4 a 6 miembros, opcionalmente sustituido con 1-2 R^a seleccionado entre el grupo que consiste en alquilo C_1-C_4 , alcoxi C_1-C_4 , $-COR^{a1}$, $-CO_2R^{a1}$, $-SO_2R^{a1}$, $-SO_2NR^{a1}R^{a2}$ y $-CONR^{a1}R^{a2}$, en que cada R^{a1} y R^{a2} se selecciona independiente entre el grupo que consiste en H y alquilo C_1-C_4 ; R^2 está opcionalmente sustituido con 1-2 R^b y R^3 es metilo.
16. Un compuesto de las reivindicaciones 1 ó 2, o una sal farmacéuticamente acep-

table del mismo, en el que R^1 se selecciona entre el grupo que consiste en fenilo y heteroarilo de 5 a 6 miembros, en que cada R^1 está opcionalmente sustituido con 1-3 R^a ; R^2 está opcionalmente sustituido con 1-2 R^b y R^3 es metilo.

17. Una composición farmacéutica que comprende un compuesto de cualquiera de las reivindicaciones 1-16, o una sal farmacéuticamente aceptable del mismo, y un excipiente farmacéuticamente aceptable.

18. Un compuesto de la reivindicación 1, seleccionado entre el grupo que consiste en



o una sal farmacéuticamente aceptable del mismo.

19. Un método para tratar cardiomiopatía hipertrófica (HCM), o un trastorno cardíaco que tiene una característica patofisiológica asociada con HCM, que comprende administrar a un sujeto que lo necesita una cantidad eficaz de un compuesto de cualquiera de las reivindicaciones 1-16 ó 18 o una sal farmacéuticamente aceptable del mismo.

20. Un método para tratar una enfermedad o trastorno seleccionado entre el grupo que consiste en fallo cardíaco diastólico con fracción de eyección conservada, enfermedad

cardíaca isquémica, angina de pecho y cardiomiopatía restrictiva, que comprende administrar a un sujeto que lo necesita una cantidad eficaz de un compuesto de cualquiera de las reivindicaciones 1-16 ó 18 o una sal farmacéuticamente del mismo.

21. Un método para tratar una enfermedad o trastorno caracterizado por hipertrofia ventricular izquierda debida a sobrecarga de volumen o presión, siendo seleccionada dicha enfermedad o trastorno entre el grupo que consiste en regurgitación mitral crónica, estenosis aórtica crónica e hipertensión sistémica crónica, conjuntamente con terapias dirigidas a corregir o aliviar la causa principal de la sobrecarga de volumen o presión, que incluye la reparación/sustitución de válvulas o terapia antihipertensora eficaz, que comprende administrar a un sujeto que lo necesita una cantidad eficaz de un compuesto de cualquiera de las reivindicaciones 1-16 ó 18 o una sal farmacéuticamente aceptable del mismo.

22. Un método para tratar cardiomiopatía hipertrófica (HCM) o un trastorno cardíaco que tiene una característica patofisiológica asociada con HCM, que comprende administrar a un sujeto que lo necesita una cantidad eficaz de un compuesto de cualquiera de las reivindicaciones 1-16 ó 18 o una sal farmacéuticamente aceptable del mismo combinada con terapias que retardan el progreso de un fallo cardíaco mediante una infrarregulación de la estimulación neurohormonal del corazón e intentan prevenir la remodelación cardíaca (por ejemplo, inhibidores de ACE, bloqueadores de receptores de angiotensina (ARB), bloqueadores β , agonistas de receptores de aldosterona o inhibidores de endopeptidasa neural); terapias que mejoran la función cardíaca estimulando la contractilidad cardíaca (por ejemplo, agentes inotrópicos positivos como el agonista β -adrenérgico dobutamina o el inhibidor de fosfodiesterasa milrinona); y terapias que reducen la precarga cardíaca (por ejemplo, diuréticos como furosemida), o la carga posterior (vasodilatadores de cualquier clase que incluyen, pero sin limitación, bloqueadores de canales de calcio, inhibidores de fosfodiesterasa, antagonistas de receptores de endotelina, inhibidores de renina o moduladores de miosina de músculos lisos).



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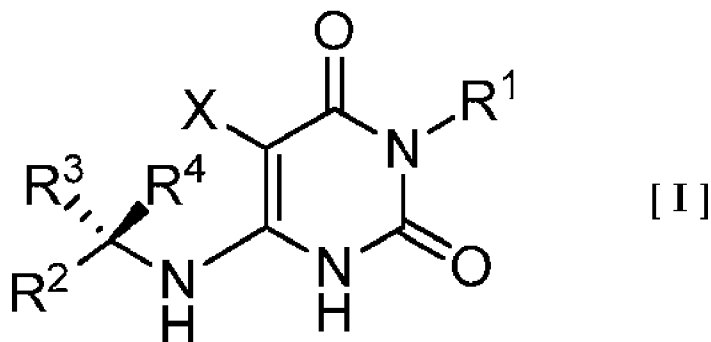
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(54) **Title:** PYRIMIDINEDIONE COMPOUNDS AGAINST CARDIAC CONDITIONS



(57) **Abstract:** Provided are novel pyrimidine dione compounds and pharmaceutically acceptable salts thereof, that are useful for the treatment of hypertrophic cardiomyopathy (HCM) and conditions associated with left ventricular hypertrophy or diastolic dysfunction. The synthesis and characterization of the compounds and pharmaceutically acceptable salts thereof, are described, as well as methods for treating HCM and other forms of heart disease.

PYRIMIDINEDIONE COMPOUNDS AGAINST CARDIAC CONDITIONS

5

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application is an application claiming benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 61/838,088 filed June 21, 2013, and U.S. Provisional Application No. 61/939,655 filed February 13, 2014, and U.S. Provisional Application No. 61/981,366 filed April 18, 2014, each of which is herein incorporated by reference in its entirety.

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STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] NOT APPLICABLE

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BACKGROUND OF THE INVENTION

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[0003] Genetic (heritable) hypertrophic cardiomyopathy (HCM) comprises a group of highly penetrant, monogenic, autosomal dominant myocardial diseases. HCM is caused by one or more of over 1,000 known point mutations in any one of the structural protein genes contributing to the functional unit of myocardium, the sarcomere. About 1 in 500 individuals in the general population are found to have left ventricular hypertrophy unexplained by other known causes (e.g., hypertension or valvular disease), and many of these can be shown to have HCM, once other heritable (e.g., lysosomal storage diseases), metabolic, or infiltrative causes have been excluded.

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[0004] Sarcomere gene mutations that cause HCM are highly penetrant, but there is wide variability in clinical severity and clinical course. Some genotypes are associated with a more malignant course, but there is considerable variability between and even within families carrying the same mutation. Sex differences have also been noted, with male patients generally more severely affected than female patients. While many patients with HCM report

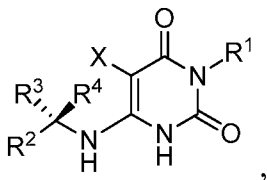
minimal or no symptoms for extended periods of time, HCM is a progressive disease with a significant cumulative burden of morbidity. Symptoms of effort intolerance predominate, and can be exacerbated by exercise and other maneuvers that increase heart rate and/or decrease preload. As with many other disorders, symptoms tend to worsen with age. By far the most prevalent clinical burden for patients with HCM is exertional dyspnea, which limits their activities of daily living and can be debilitating.

[0005] Patients with HCM are often symptomatic in the absence of documented hemodynamic abnormalities like left ventricular outflow tract obstruction (with or without mitral regurgitation). Patients' symptoms of exertional dyspnea can rapidly worsen with the onset of atrial fibrillation, a common complication of HCM that can precipitate acute pulmonary edema that increases the risk of systemic arterial thromboembolic disease, including stroke. Other adverse events associated with HCM include intolerance of hypovolemia or hypervolemia, and syncope. Concomitant coronary artery disease may confer a higher risk of acute coronary syndromes than in patients without HCM. Sudden cardiac death (SCD) in patients with HCM is both uncommon and difficult to predict but is a leading cause of non-traumatic death in young adults. For survivors of SCD, ICD placement is standard practice, and in other HCM patients risk profiling, while imprecise, is used to identify those for whom ICD placement for primary prevention is deemed prudent.

[0006] Medical therapy for HCM is limited to the treatment of symptoms and does not address the fundamental, underlying cause of disease – disruptions in normal sarcomere function. Currently available therapies are variably effective in alleviating symptoms but typically show decreased efficacy with increasing disease duration. Patients are thus empirically managed with beta-blockers, non-dihydropyridine calcium channel blockers, and/or disopyramide. None of these agents carry labeled indications for treating HCM, and essentially no rigorous clinical trial evidence is available to guide their use. Compounding this unfortunate situation is the fact that no new medical therapies for HCM have been identified for many years. For patients with hemodynamically significant outflow tract obstruction (resting gradient >30mmHg), in appropriately selected patients surgical myectomy or alcohol septal ablation is usually required to alleviate the hemodynamic obstruction. Provided are new therapeutic agents and methods that remedy the long-felt need for improved treatment of HCM and related cardiac disorders.

BRIEF SUMMARY OF THE INVENTION

[0007] In one aspect, provided is a compound having the formula:



5 or a pharmaceutically acceptable salt thereof. In some embodiments, the above formula, R^1 is a member selected from C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkyl- C_1 - C_4 alkyl, 4- to 7-membered heterocycloalkyl, phenyl, phenyl- C_1 - C_4 alkyl, 5- to 6-membered heteroaryl and 5- to 6-membered heteroaryl- C_1 - C_4 alkyl, wherein each R^1 is optionally substituted with from 1-3 R^a ; R^2 is a member selected from phenyl, phenyl- C_1 - C_4 alkyl, 5- to 6-membered heteroaryl and 5- to 6-membered heteroaryl- C_1 - C_4 alkyl, wherein each R^2 is optionally substituted with from 1-5 R^b ; R^3 is a member selected from C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, and 4- to 7-membered heterocycloalkyl wherein each R^3 is optionally substituted with from 1-3 R^c ; R^4 is H; X is a member selected from H and halo, and in some embodiments X is selected from H and F. Each R^a , when present, is independently selected from halo, CN, hydroxyl, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, phenyl, phenyl- C_1 - C_4 alkyl, phenyl- C_1 - C_4 alkoxy, phenoxy, $-COR^{a1}$, $-CO_2R^{a1}$, $-SO_2R^{a1}$, $-SO_2NR^{a1}R^{a2}$, and $-CONR^{a1}R^{a2}$, wherein each R^{a1} and R^{a2} is independently selected from H, C_1 - C_4 alkyl and phenyl, or optionally R^{a1} and R^{a2} when attached to a nitrogen atom are combined to form a 4- to 6- membered ring. Similarly, each R^b , when present, is independently selected from halo, CN, hydroxyl, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, phenoxy, phenyl- C_1 - C_4 alkoxy, methylenedioxy, difluoromethylenedioxy, $-COR^{b1}$, $-CO_2R^{b1}$, $-SO_2R^{b1}$, $-SO_2NR^{b1}R^{b2}$, $CONR^{b1}R^{b2}$, $NR^{b1}R^{b2}$, 5- to 6-membered heteroaryl, and 5- to 6-membered heterocyclyl optionally substituted with oxo, wherein each R^{b1} and R^{b2} is independently selected from H and C_1 - C_4 alkyl or optionally R^{b1} and R^{b2} when attached to a nitrogen atom are combined to form a 4- to 6- membered ring; and each R^c , when present, is independently selected from halo, hydroxyl and C_1 - C_2 alkoxy.

[0008] In another aspect, provided is a pharmaceutical composition containing a compound or or pharmaceutically acceptable salt described herein and a pharmaceutically acceptable excipient.

[0009] In another aspect, provided is a method of treating hypertrophic cardiomyopathy (HCM) or a cardiac disorder having one or more pathophysiological features associated with

HCM. The method includes administering to a subject in need thereof an effective amount of a compound or pharmaceutically acceptable salt described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

- 5 [0010] **Figure 1** shows a schematic route for the synthesis of the compounds or pharmaceutically acceptable salts described herein (Figure 1A) and a route for the preparation of chiral amines (Figure 1B).

DETAILED DESCRIPTION OF THE INVENTION

10 I. General

- [0011] A series of pyrimidine dione compounds and pharmaceutically acceptable salts thereof has been found to reduce excess contractility in hypercontractile states and/or promote cardiac relaxation in hearts with diastolic dysfunction by stabilizing the conformation of beta cardiac myosin post-ATP hydrolysis but prior to strongly binding the actin filament and releasing phosphate, thus reducing the proportion of myosin molecules that are available to participate in the “powerstroke” portion of the muscle contraction cycle. As such, the compounds can improve cardiac elasticity, reduce dynamic and/or static left ventricular outflow obstruction, improve diastolic left ventricular relaxation, reduce left ventricular diastolic (filling) pressures, reduce functional mitral regurgitation, and/or reduce left atrial and pulmonary capillary wedge pressures in patients with HCM helping overcome the debilitating exertional dyspnea and/or symptoms referable to left ventricular outflow obstruction (presyncope or syncope) that often accompanies the disease. The compounds can also be used to treat other cardiac disorders.

25 II. Definitions

- [0012] As used herein, the term “alkyl” refers to a straight or branched, saturated, aliphatic radical having the number of carbon atoms indicated. Alkyl can include any number of carbons, such as C₁₋₂, C₁₋₃, C₁₋₄, C₁₋₅, C₁₋₆, C₁₋₇, C₁₋₈, C₂₋₃, C₂₋₄, C₂₋₅, C₂₋₆, C₃₋₄, C₃₋₅, C₃₋₆, C₄₋₅, C₄₋₆ and C₅₋₆. For example, C₁₋₆ alkyl includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, etc. Alkyl can refer to alkyl groups having up to 20 carbons atoms, such as, but not limited to heptyl, octyl, nonyl, decyl, etc. Unless stated otherwise, alkyl groups are unsubstituted. A “substituted alkyl”

group can be substituted with one or more moieties selected from halo, hydroxy, amino, alkylamino, nitro, cyano, and alkoxy.

[0013] As used herein, the term “cycloalkyl” refers to a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing from 3 to 12 ring atoms, or the number of atoms indicated. Cycloalkyl can include any number of carbons, such as C₃₋₆, C₄₋₆, C₅₋₆, C₃₋₈, C₄₋₈, C₅₋₈, and C₆₋₈. Saturated monocyclic cycloalkyl rings include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclooctyl. Saturated bicyclic and polycyclic cycloalkyl rings include, for example, norbornane, [2.2.2] bicyclooctane, decahydronaphthalene and adamantane. Cycloalkyl groups can also be partially unsaturated, having one or more double bonds in the ring. Representative cycloalkyl groups that are partially unsaturated include, but are not limited to, cyclobutene, cyclopentene, cyclohexene, cyclohexadiene (1,3- and 1,4-isomers), cycloheptene, cycloheptadiene, cyclooctene, cyclooctadiene (1,3-, 1,4- and 1,5-isomers), norbornene, and norbornadiene. Unless otherwise stated, cycloalkyl groups are unsubstituted. A “substituted cycloalkyl” group can be substituted with one or more moieties selected from halo, hydroxy, amino, alkylamino, nitro, cyano, and alkoxy.

[0014] As used herein, the term “heterocycloalkyl” refers to a saturated ring system having from 3 to 12 ring members and from 1 to 4 heteroatoms selected from N, O and S.

Additional heteroatoms including, but not limited to, B, Al, Si and P can also be present in a heterocycloalkyl group. The heteroatoms can be oxidized to form moieties such as, but not limited to, -S(O)- and -S(O)₂-. Heterocycloalkyl groups can include any number of ring atoms, such as, 3 to 6, 4 to 6, 5 to 6, or 4 to 7 ring members. Any suitable number of heteroatoms can be included in the heterocycloalkyl groups, such as 1, 2, 3, or 4, or 1 to 2, 1 to 3, 1 to 4, 2 to 3, 2 to 4, or 3 to 4. Examples of heterocycloalkyl groups include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine, azepane, azocane, quinuclidine, pyrazolidine, imidazolidine, piperazine (1,2-, 1,3- and 1,4-isomers), oxirane, oxetane, tetrahydrofuran, oxane (tetrahydropyran), oxepane, thiirane, thietane, thiolane (tetrahydrothiophene), thiane (tetrahydrothiopyran), oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, dioxolane, dithiolane, morpholine, thiomorpholine, dioxane, or dithiane. Heterocycloalkyl groups are unsubstituted, but can be described, in some embodiments as substituted. “Substituted heterocycloalkyl” groups can be substituted with one or more moieties selected from halo, hydroxy, amino, alkylamino, nitro, cyano, and alkoxy.

[0015] As used herein, the term “heteroaryl” refers to a monocyclic or fused bicyclic or tricyclic aromatic ring assembly containing 5 to 16 ring atoms, where from 1 to 5 of the ring atoms are a heteroatom such as N, O or S. Additional heteroatoms including, but not limited to, B, Al, Si and P can also be present in a heteroaryl group. The heteroatoms can be oxidized to form moieties such as, but not limited to, -S(O)- and -S(O)₂-. Heteroaryl groups can include any number of ring atoms, such as, 5 to 6, 5 to 8, 6 to 8, 5 to 9, 5 to 10, 5 to 11, or 5 to 12 ring members. Any suitable number of heteroatoms can be included in the heteroaryl groups, such as 1, 2, 3, 4, or 5, or 1 to 2, 1 to 3, 1 to 4, 1 to 5, 2 to 3, 2 to 4, 2 to 5, 3 to 4, or 3 to 5. Heteroaryl groups can have from 5 to 8 ring members and from 1 to 4 heteroatoms, or from 5 to 8 ring members and from 1 to 3 heteroatoms, or from 5 to 6 ring members and from 1 to 4 heteroatoms, or from 5 to 6 ring members and from 1 to 3 heteroatoms. Examples of heteroaryl groups include, but are not limited to, pyrrole, pyridine, imidazole, pyrazole, triazole, tetrazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole. Heteroaryl groups are unsubstituted, but can be described, in some embodiments as substituted. “Substituted heteroaryl” groups can be substituted with one or more moieties selected from halo, hydroxy, amino, alkylamino, nitro, cyano, and alkoxy.

[0016] As used herein, the term “alkoxy” refers to an alkyl group having an oxygen atom that connects the alkyl group to the point of attachment: *i.e.*, alkyl-O-. As for the alkyl portion, alkoxy groups can have any suitable number of carbon atoms, such as C₁₋₆ or C₁₋₄. Alkoxy groups include, for example, methoxy, ethoxy, propoxy, iso-propoxy, butoxy, 2-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, pentoxy, hexoxy, etc. Alkoxy groups are unsubstituted, but can be described, in some embodiments as substituted. “Substituted alkoxy” groups can be substituted with one or more moieties selected from halo, hydroxy, amino, alkylamino, nitro, cyano, and alkoxy.

[0017] As used herein, the terms “halo” and “halogen” refer to fluorine, chlorine, bromine and iodine.

[0018] As used herein, the term “pharmaceutically acceptable” refers to a substance that is compatible with a compound or salt as described herein, as well as with any other ingredients with which the compound is formulated. Furthermore, a pharmaceutically acceptable substance is not deleterious to the recipient of the substance.

[0019] As used herein, the term “salt” refers to an acid or base salt of a compound described herein. Pharmaceutically acceptable salts can be derived, for example, from mineral acids (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like), organic acids (acetic acid, propionic acid, glutamic acid, citric acid and the like), and quaternary ammonium ions. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, which is incorporated herein by reference. The neutral form of a compound may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner.

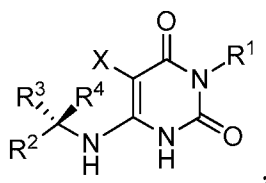
[0020] As used herein, the term “pharmaceutical composition” refers to a product comprising a compound or pharmaceutically acceptable salt described herein, an excipient as defined herein, and other optional ingredients in specified amounts, as well as any product which results directly or indirectly from combination of the specified ingredients in the specified amounts.

[0021] As used herein, the term “excipient” refers to a substance that aids the administration of an active agent to a subject. Pharmaceutical excipients include, but are not limited to, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors and colors. One of skill in the art will recognize that other excipients can be useful.

[0022] As used herein, the terms “treat,” “treating” and “treatment” refer to any indicia of success in the treatment or amelioration of a pathology, injury, condition, or symptom related to hypertrophic cardiomyopathy, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms; making the pathology, injury, condition, or symptom more tolerable to the patient; decreasing the frequency or duration of the pathology, injury, condition, or symptom; or, in some situations, preventing the onset of the pathology, injury, condition, or symptom. Treatment or amelioration can be based on any objective or subjective parameter; including, *e.g.*, the result of a physical examination.

III. Compounds and Pharmaceutically Acceptable Salts Thereof

[0023] In one aspect, provided is a compound having the formula:



or a pharmaceutically acceptable salt thereof.

[0024] In the above formula, R¹ is a member selected from C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl-C₁-C₄ alkyl, 4- to 7-membered heterocycloalkyl, phenyl, phenyl-C₁-C₄ alkyl, 5- to 6-membered heteroaryl and 5- to 6-membered heteroaryl-C₁-C₄ alkyl, wherein each R¹ is optionally substituted with from 1-3 R^a; R² is a member selected from phenyl, phenyl-C₁-C₄ alkyl, 5- to 6-membered heteroaryl and 5- to 6-membered heteroaryl-C₁-C₄ alkyl, wherein each R² is optionally substituted with from 1-5 R^b; R³ is a member selected from C₁-C₄ alkyl, C₃-C₄ cycloalkyl, and 4- to 7-membered heterocycloalkyl wherein each R³ is optionally substituted with from 1-3 R^c; R⁴ is H; X is a member selected from H and halo, and in selected embodiments is selected from H and F. Each R^a, when present, is independently selected from halo, CN, hydroxyl, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, phenyl, phenyl-C₁-C₄ alkyl, phenyl-C₁-C₄ alkoxy, phenoxy, -COR^{a1}, -CO₂R^{a1}, -SO₂R^{a1}, -SO₂NR^{a1}R^{a2}, and -CONR^{a1}R^{a2}, wherein each R^{a1} and R^{a2} is independently selected from H, C₁-C₄ alkyl and phenyl, or optionally R^{a1} and R^{a2} when attached to a nitrogen atom are combined to form a 4- to 6- membered ring. Similarly, each R^b, when present, is independently selected from halo, CN, hydroxyl, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, phenoxy, phenyl-C₁-C₄ alkoxy, methylenedioxy, difluoromethylenedioxy, -COR^{b1}, -CO₂R^{b1}, -SO₂R^{b1}, -SO₂NR^{b1}R^{b2}, CONR^{b1}R^{b2}, NR^{b1}R^{b2}, 5- to 6-membered heteroaryl, and 5- to 6-membered heterocyclyl optionally substituted with oxo, wherein each R^{b1} and R^{b2} is independently selected from H and C₁-C₄ alkyl or optionally R^{b1} and R^{b2} when attached to a nitrogen atom are combined to form a 4- to 6- membered ring; and each R^c, when present, is independently selected from halo, hydroxyl and C₁-C₂ alkoxy.

[0025] In some embodiments, R¹ is selected from C₁-C₈ alkyl, C₃-C₈ cycloalkyl, 4- to 7-membered heterocycloalkyl, phenyl, or 5- to 6-membered heteroaryl, wherein each R¹ is optionally substituted with from 1-3 R^a. R² is phenyl, which is optionally substituted with from 1-5 R^b. R³ is selected from C₁-C₄ alkyl, C₃-C₄ cycloalkyl, or 4- to 7-membered heterocycloalkyl, wherein each R³ is optionally substituted with from 1-2 R^c. R⁴ is H, and X is H or F. In some embodiments, each R^a, when present, is independently halo, CN, C₁-C₄ alkyl, C₁-C₄ alkoxy, -COR^{a1}, -CO₂R^{a1}, -SO₂R^{a1}, -SO₂NR^{a1}R^{a2}, or -CONR^{a1}R^{a2}, wherein each R^{a1} and R^{a2} is independently H or C₁-C₄ alkyl. Alternatively, R^{a1} and R^{a2}, when attached to a

nitrogen atom, are optionally combined to form a 4- to 6- membered ring. Each R^b , when present, is independently halo, CN, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, $-\text{COR}^{b1}$, $-\text{CO}_2\text{R}^{b1}$, $-\text{SO}_2\text{R}^{b1}$, $-\text{SO}_2\text{NR}^{b1}\text{R}^{b2}$, $\text{CONR}^{b1}\text{R}^{b2}$, $\text{NR}^{b1}\text{R}^{b2}$, 5- to 6-membered heteroaryl, or 5- to 6-membered heterocyclyl optionally substituted with oxo, wherein each R^{b1} and R^{b2} is independently H or C_1 - C_4 alkyl. Alternatively, R^{b1} and R^{b2} , when attached to a nitrogen atom, are optionally combined to form a 4- to 6- membered ring. Each R^c , when present, is independently halo or C_1 - C_2 alkoxy.

[0026] In some embodiments, X is H.

[0027] In some embodiments, R^1 is C_3 - C_4 alkyl, C_3 - C_5 cycloalkyl, or 4- to 6-membered heterocycloalkyl, wherein each R^1 is optionally substituted with from 1-2 R^a .

[0028] In some embodiments, R^1 is phenyl or 5- to 6-membered heteroaryl, wherein each R^1 is optionally substituted with from 1-3 R^a .

[0029] In some embodiments, R^1 is C_3 - C_4 alkyl, C_3 - C_5 cycloalkyl, or 4- to 6-membered heterocycloalkyl.

[0030] In some embodiments, R^1 is 4- to 6-membered heterocycloalkyl, optionally substituted with from 1-2 R^a selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy, $-\text{COR}^{a1}$, $-\text{CO}_2\text{R}^{a1}$, $-\text{SO}_2\text{R}^{a1}$, $-\text{SO}_2\text{NR}^{a1}\text{R}^{a2}$, and $-\text{CONR}^{a1}\text{R}^{a2}$, wherein each R^{a1} and R^{a2} is independently H or C_1 - C_4 alkyl.

[0031] In some embodiments, R^1 is cyclobutyl, isopropyl, isobutyl, 1-methoxypropan-2-yl, cyclopentyl, cyclohexyl, 4-tetrahydropyranyl, 1-(methylsulfonyl)piperidin-4-yl, 1-(methoxycarbonyl)piperidin-4-yl, 4,4-difluorocyclohexyl, phenyl, 2-pyridyl, 3-pyridyl, 3-isoxazolyl, 5-isoxazolyl, or 1-methyl-3-pyrazolyl.

[0032] In some embodiments, R^2 is optionally substituted with from 1-2 R^b .

[0033] In some embodiments, R^2 is phenyl, 3-methylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,5-difluorophenyl, 3,5-difluorophenyl, 3-chlorophenyl, 3-methoxyphenyl, 3-(3-oxazolidin-2-onyl)phenyl, 3-(2-methyl-1-imidazolyl)phenyl, 3-(1-pyrazolyl)phenyl, or 3-(1,2,4-triazol-1-yl)phenyl.

[0034] In some embodiments, R^3 is C_1 - C_4 alkyl, C_1 - C_4 alkoxyalkyl, or C_3 - C_4 cycloalkyl.

[0035] In some embodiments, R^3 is methyl, ethyl, propyl, cyclopropyl, cyclobutyl or 2-methoxymethyl.

[0036] In some embodiments, R³ is methyl.

[0037] The compounds or pharmaceutically acceptable salts described herein can have any combination of the R¹, R², R³, R⁴, R^a, R^{a1}, R^{a2}, R^b, R^{b1}, R^{b2}, R^c, and X groups recited above. Selected embodiments recited for R², for example, can be combined with any of the selected
5 embodiments recited for R¹ which, in turn, can be combined with any of the selected
embodiments recited for R³.

[0038] In some embodiments, for example, R¹ is C₃-C₈ alkyl; R³ is C₃-C₄ cycloalkyl or 4-
to 7-membered heterocycloalkyl; and R² is phenyl. In other embodiments, R¹ is 4- to 7-
membered heterocycloalkyl or 5- to 6-membered heteroaryl which is optionally substituted
10 with C₁-C₄ alkyl, -CO₂R^{a1}, -SO₂NR^{a1}R^{a2}, or -SO₂R^{a1}; R³ is C₃-C₄ cycloalkyl or 4- to 7-
membered heterocycloalkyl; and R² is phenyl. In still other embodiments, R¹ is C₃-C₈
cycloalkyl or phenyl, R³ is C₃-C₄ cycloalkyl or 4- to 7-membered heterocycloalkyl; and R² is
phenyl.

[0039] In other embodiments, R¹ is C₃-C₈ alkyl; R³ is C₁-C₄ alkyl; and R² is phenyl. In yet
15 other embodiments, R¹ is 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl
which is optionally substituted with C₁-C₄ alkyl, -CO₂R^{a1}, or -SO₂R^{a1}; R³ is C₁-C₄ alkyl; and
R² is phenyl. In still other embodiments, R¹ is C₃-C₈ cycloalkyl or phenyl; R³ is C₁-C₄ alkyl;
and R² is phenyl.

[0040] In some embodiments, R¹ is C₃-C₈ alkyl; R³ is C₃-C₄ cycloalkyl or 4- to 7-
20 membered heterocycloalkyl; and R² is phenyl substituted with 1-2 C₁-C₄ alkoxy or halo. In
still other embodiments, R¹ is 4- to 7-membered heterocycloalkyl or 5- to 6-membered
heteroaryl which is optionally substituted with C₁-C₄ alkyl, -CO₂R^{a1}, or -SO₂R^{a1}; R³ is C₃-C₄
cycloalkyl or 4- to 7-membered heterocycloalkyl; and R² is phenyl substituted with 1-2 C₁-
C₄ alkoxy or halo. In yet other embodiments, R¹ is C₃-C₈ cycloalkyl or phenyl; R³ is C₃-C₄
25 cycloalkyl or 4- to 7-membered heterocycloalkyl; and R² is phenyl substituted with 1-2 C₁-
C₄ alkoxy or halo.

[0041] In some embodiments, R¹ is C₃-C₈ alkyl; R³ is C₁-C₄ alkyl; and R² is phenyl
substituted with 1-2 C₁-C₄ alkoxy or halo. In other embodiments, R¹ is 4- to 7-membered
heterocycloalkyl or 5- to 6-membered heteroaryl which is optionally substituted with C₁-C₄
30 alkyl, -CO₂R^{a1}, or -SO₂R^{a1}; R³ is C₁-C₄ alkyl; and R² is phenyl substituted with 1-2 C₁-C₄
alkoxy or halo. In other embodiments, R¹ is C₃-C₈ cycloalkyl or phenyl; R³ is C₁-C₄ alkyl;
and R² is phenyl substituted with 1-2 C₁-C₄ alkoxy or halo.

[0042] In some embodiments, R^1 is C₃-C₈ alkyl; R^3 is C₃-C₄ cycloalkyl or 4- to 7-membered heterocycloalkyl; and R^2 is phenyl substituted with 5- to 6-membered heteroaryl or 5- to 6-membered heterocyclyl optionally substituted with oxo. In other embodiments, R^1 is 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl which is optionally substituted with C₁-C₄ alkyl, -CO₂R^{a1}, or -SO₂R^{a1}; R^3 is C₃-C₄ cycloalkyl or 4- to 7-membered heterocycloalkyl; and R^2 is phenyl substituted with 5- to 6-membered heteroaryl or 5- to 6-membered heterocyclyl optionally substituted with oxo. In other embodiments, R^1 is C₃-C₈ cycloalkyl or phenyl, R^3 is C₃-C₄ cycloalkyl or 4- to 7-membered heterocycloalkyl; and R^2 is phenyl substituted with 5- to 6-membered heteroaryl or 5- to 6-membered heterocyclyl optionally substituted with oxo.

[0043] In some embodiments, R^1 is C₃-C₈ alkyl; R^3 is C₁-C₄ alkyl; and R^2 is phenyl substituted with 5- to 6-membered heteroaryl or 5- to 6-membered heterocyclyl optionally substituted with oxo. In other embodiments, R^1 is 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl which is optionally substituted with C₁-C₄ alkyl, -CO₂R^{a1}, or -SO₂R^{a1}; R^3 is C₁-C₄ alkyl; and R^2 is phenyl substituted with 5- to 6-membered heteroaryl or 5- to 6-membered heterocyclyl optionally substituted with oxo. In other embodiments, R^1 is C₃-C₈ cycloalkyl or phenyl; R^3 is C₁-C₄ alkyl; and R^2 is phenyl substituted with 5- to 6-membered heteroaryl or 5- to 6-membered heterocyclyl optionally substituted with oxo.

[0044] In some embodiments, R^1 is C₃-C₈ alkyl; R^3 is C₃-C₄ cycloalkyl or 4- to 7-membered heterocycloalkyl; and R^2 is phenyl substituted with CN, C₁-C₄ alkyl, -COR^{b1}, -CO₂R^{b1}, -SO₂R^{b1}, -SO₂NR^{b1}R^{b2}, CONR^{b1}R^{b2}, or NR^{b1}R^{b2}. In other embodiments, R^1 is 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl which is optionally substituted with C₁-C₄ alkyl, -CO₂R^{a1}, or -SO₂R^{a1}; R^3 is C₃-C₄ cycloalkyl or 4- to 7-membered heterocycloalkyl; and R^2 is phenyl substituted with CN, C₁-C₄ alkyl, -COR^{b1}, -CO₂R^{b1}, -SO₂R^{b1}, CONR^{b1}R^{b2}, or NR^{b1}R^{b2}. In other embodiments, R^1 is C₃-C₈ cycloalkyl or phenyl; R^3 is C₃-C₄ cycloalkyl or 4- to 7-membered heterocycloalkyl; and R^2 is phenyl substituted with CN, C₁-C₄ alkyl, -COR^{b1}, -CO₂R^{b1}, -SO₂R^{b1}, CONR^{b1}R^{b2}, or NR^{b1}R^{b2}.

[0045] In some embodiments, R^1 is C₃-C₈ alkyl; R^3 is C₁-C₄ alkyl; and R^2 is phenyl substituted with CN, C₁-C₄ alkyl, -COR^{b1}, -CO₂R^{b1}, -SO₂R^{b1}, CONR^{b1}R^{b2}, or NR^{b1}R^{b2}. In other embodiments, R^1 is 4- to 7-membered heterocycloalkyl or 5- to 6-membered heteroaryl which is optionally substituted with C₁-C₄ alkyl, -CO₂R^{a1}, or -SO₂R^{a1}; R^3 is C₁-C₄ alkyl; and

R² is phenyl substituted with CN, C₁-C₄ alkyl, -COR^{b1}, -CO₂R^{b1}, -SO₂R^{b1}, CONR^{b1}R^{b2}, or NR^{b1}R^{b2}. In other embodiments, R¹ is C₃-C₈ cycloalkyl or phenyl; R³ is C₁-C₄ alkyl; and R² is phenyl substituted with CN, C₁-C₄ alkyl, -COR^{b1}, -CO₂R^{b1}, -SO₂R^{b1}, CONR^{b1}R^{b2}, NR^{b1}R^{b2}, or -CONR^{a1}R^{a2}.

5 [0046] In some embodiments, R¹ is isopropyl; R² is optionally substituted with 1-2 R^b; and R³ is methyl.

[0047] In some embodiments, R¹ is 4- to 6-membered heterocycloalkyl, optionally substituted

with from 1-2 R^a selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, -COR^{a1}, -CO₂R^{a1}, -SO₂R^{a1}, -SO₂ NR^{a1}R^{a2}, and -CONR^{a1}R^{a2}, wherein each R^{a1} and R^{a2} can independently be H or C₁-C₄ alkyl; 10 R² is optionally substituted with 1-2 R^b; and R³ is methyl.

[0048] In some embodiments, R¹ is phenyl or 5- to 6-membered heteroaryl, wherein each R¹ is optionally substituted with from 1-3 R^a; R² is optionally substituted with from 1-2 R^b; and R³ is methyl.

15 [0049] X can be H in any of the embodiments set forth above. In other embodiments, X can be F in any of the embodiments set forth above. Still further, compounds provided herein with an identified stereochemistry (indicated as R or S, or with dashed or wedge bond designations) will be understood by one of skill in the art to be substantially free of other isomers (e.g., at least 80%, 90%, 95% up to 100% free of the other isomer).

20 [0050] In some embodiments, the compound is selected from:

(S)-3-isopropyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-5-fluoro-3-isopropyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-5-bromo-3-isopropyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;

(S)-6-((1-(3-chlorophenyl)ethyl)amino)-5-fluoro-3-isopropylpyrimidine-2,4(1H,3H)-dione;

25 (S)-6-((1-(3,5-difluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

(S)-6-((cyclopropyl(phenyl)methyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

(S)-6-((cyclopropyl(3-methoxyphenyl)methyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

(S)-6-((cyclobutyl(phenyl)methyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;

30 (S)-6-((1-(3-fluorophenyl)ethyl)amino)-3-(tetrahydro-2H-pyran-4-yl)pyrimidine-2,4(1H,3H)-dione;

- (S)-6-((1-(3-methoxyphenyl)ethyl)amino)-3-(tetrahydro-2H-pyran-4-yl)pyrimidine-2,4(1H,3H)-dione;
- 6-(((S)-1-phenylethyl)amino)-3-(tetrahydrofuran-3-yl)pyrimidine-2,4(1H,3H)-dione;
- (S)-3-(1-(methylsulfonyl)piperidin-4-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- 5 methyl (S)-4-(2,6-dioxo-4-((1-phenylethyl)amino)-3,6-dihydropyrimidin-1(2H)-yl)piperidine-1-carboxylate;
- 3-((R)-sec-butyl)-6-(((S)-1-(3-methoxyphenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-6-((1-phenylethyl)amino)-3-(pyridin-3-yl)pyrimidine-2,4(1H,3H)-dione;
- 10 (S)-3-(isoxazol-3-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-6-((1-(3-(1H-pyrazol-1-yl)phenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
- (S)-3-isopropyl-6-((1-(3-methoxyphenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-3-isopropyl-6-((1-(2-methoxyphenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-3-isopropyl-6-((1-phenylpropyl)amino)pyrimidine-2,4(1H,3H)-dione;
- 15 (S)-3-isopropyl-5-methyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-6-((1-(2-fluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
- (S)-6-((1-(3-fluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
- (S)-6-((1-(3-chlorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
- (S)-6-((1-(4-fluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
- 20 (S)-5-fluoro-3-isopropyl-6-((1-phenylpropyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-5-fluoro-6-((1-(3-fluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
- (S)-5-fluoro-3-isopropyl-6-((1-(3-methoxyphenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-6-((1-(2,5-difluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
- (S)-6-((1-(3-bromophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
- 25 (S)-3-ethyl-6-((1-phenylpropyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-3-cyclopropyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-6-((1-phenylethyl)amino)-3-(pyridin-2-yl)pyrimidine-2,4(1H,3H)-dione;
- (S)-3-(1-methyl-1H-pyrazol-3-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-3-(isoxazol-5-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- 30 (S)-6-((1-(3-(1H-1,2,4-triazol-1-yl)phenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
- (S)-3-isopropyl-6-((1-(3-(2-methyl-1H-imidazol-1-yl)phenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;

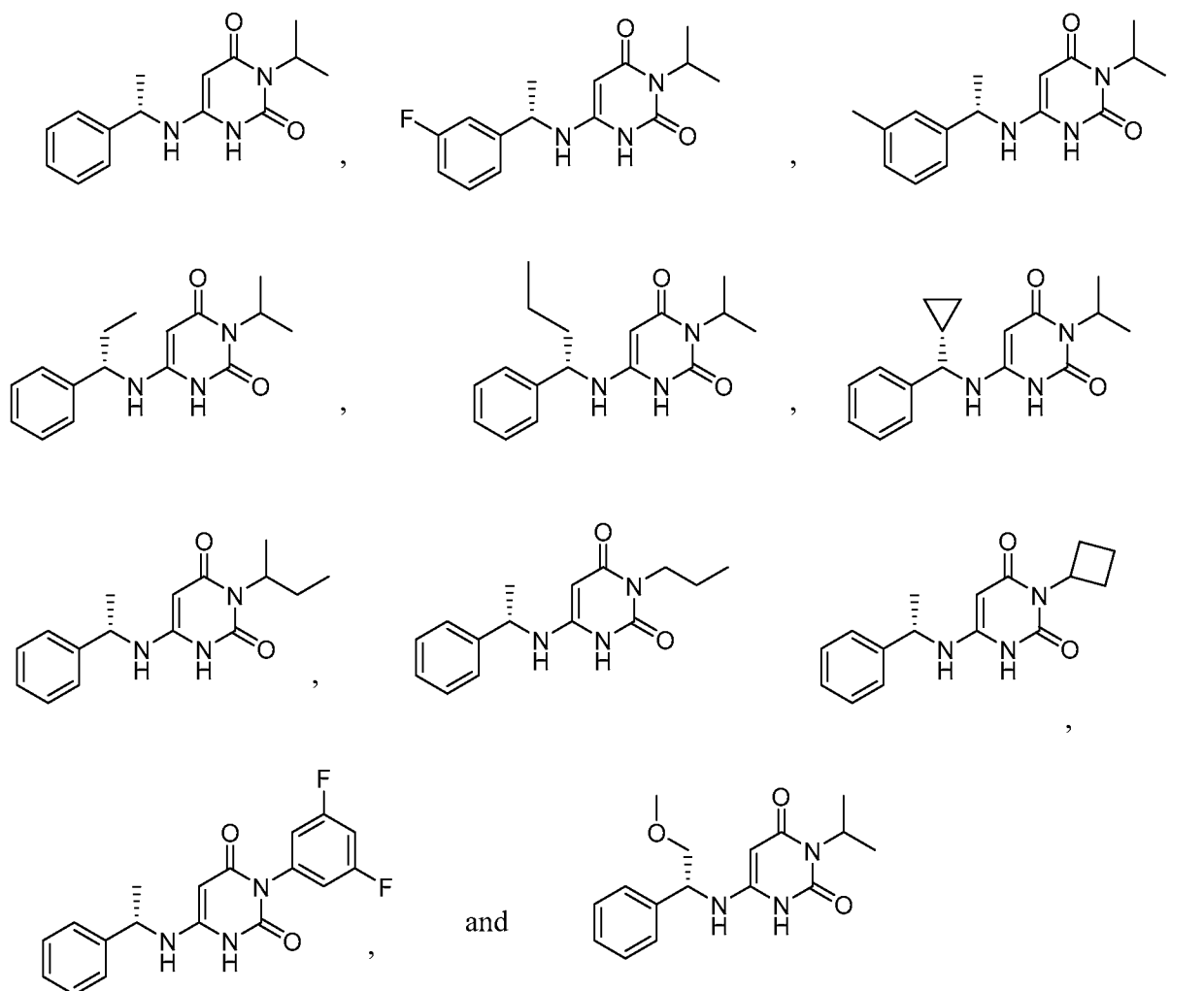
- (S)-3-isopropyl-6-((1-(3-(2-oxooxazolidin-3-yl)phenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-3-cyclohexyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-3-phenyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- 5 (S)-3-ethyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-3-methyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-6-((1-phenylethyl)amino)-3-propylpyrimidine-2,4(1H,3H)-dione;
- (S)-3-(3,5-difluorophenyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-3-isopropyl-6-((1-(m-tolyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- 10 (S)-6-((1-(4-fluorophenyl)propan-2-yl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
- (R)-3-isopropyl-6-((2,2,2-trifluoro-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- 3-((R)-1-(benzyloxy)propan-2-yl)-6-(((S)-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- 3-((R)-1-hydroxypropan-2-yl)-6-(((S)-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- 15 (S)-3-isopropyl-6-((1-(3-(trifluoromethyl)phenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-2-(1-((1-isopropyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)amino)ethyl)benzonitrile
- (S)-3-benzyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-3-(2,6-difluorophenyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-6-((1-(2,6-difluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
- 20 (S)-3-isopropyl-6-((1-(pyridin-4-yl)propan-2-yl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-6-((1-(4-(benzyloxy)phenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
- (S)-6-((1-(4-hydroxyphenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
- (R)-6-((2-(benzyloxy)-1-phenylethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
- (S)-3-(6-methylpyridin-2-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- 25 (S)-3-(2,2-difluoroethyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-6-((1-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-(2,2,2-trifluoroethyl)pyrimidine-2,4(1H,3H)-dione;
- (S)-3-isopropyl-6-((1-(o-tolyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-3-cyclobutyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- 30 (S)-3-isopropyl-6-((1-(2-(trifluoromethyl)phenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-3-(1-methylcyclopropyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- (S)-6-((1-(3-(1H-imidazol-1-yl)phenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
- (S)-6-((1-phenylethyl)amino)-3-(pyridazin-4-yl)pyrimidine-2,4(1H,3H)-dione;

- (S)-4-((1-phenylethyl)amino)-2H-[1,5'-bipyrimidine]-2,6(3H)-dione;
 (S)-6-((1-phenylethyl)amino)-3-(pyrazin-2-yl)pyrimidine-2,4(1H,3H)-dione;
 (S)-3-isopropyl-6-((1-(pyridin-3-yl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
 (S)-3-(1-methyl-1H-pyrazol-4-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
 5 (S)-3-isopropyl-6-((1-phenylbutyl)amino)pyrimidine-2,4(1H,3H)-dione;
 6-(((S)-1-phenylethyl)amino)-3-((R)-tetrahydro-2H-pyran-3-yl)pyrimidine-2,4(1H,3H)-
 dione;
 (S)-3-cyclopentyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
 (S)-3-isopropyl-6-((2-methyl-1-phenylpropyl)amino)pyrimidine-2,4(1H,3H)-dione;
 10 (S)-3-(4,4-difluorocyclohexyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
 (S)-3-(pentan-3-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
 (S)-3-(1-benzoylpiperidin-4-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
 (S)-3-isopropyl-6-((4-phenylbutan-2-yl)amino)pyrimidine-2,4(1H,3H)-dione;
 methyl (S)-2-(2,6-dioxo-4-((1-phenylethyl)amino)-3,6-dihydropyrimidin-1(2H)-yl)acetate
 15 (S)-3-isopropyl-6-((1-phenylpropan-2-yl)amino)pyrimidine-2,4(1H,3H)-dione;
 3-((S)-1-(benzyloxy)propan-2-yl)-6-(((S)-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-
 dione;
 3-((S)-1-hydroxypropan-2-yl)-6-(((S)-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
 (R)-6-((2-hydroxy-1-phenylethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
 20 6-(((S)-1-phenylethyl)amino)-3-((R)-1,1,1-trifluoropropan-2-yl)pyrimidine-2,4(1H,3H)-
 dione;
 6-(((S)-1-phenylethyl)amino)-3-((S)-1,1,1-trifluoropropan-2-yl)pyrimidine-2,4(1H,3H)-
 dione;
 6-(((S)-1-phenylethyl)amino)-3-(4,4,4-trifluorobutan-2-yl)pyrimidine-2,4(1H,3H)-dione;
 25 (S)-6-((1-phenylethyl)amino)-3-(2,2,2-trifluoroethyl)pyrimidine-2,4(1H,3H)-dione;
 (S)-3-(tert-butyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
 (S)-3-(2-methoxyethyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
 6-(((S)-1-phenylpropyl)amino)-3-((S)-1,1,1-trifluoropropan-2-yl)pyrimidine-2,4(1H,3H)-
 dione;
 30 3-((R)-1-cyclopropylethyl)-6-(((S)-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
 3-((S)-1-cyclopropylethyl)-6-(((S)-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
 (S)-6-((cyclobutyl(phenyl)methyl)amino)-3-ethylpyrimidine-2,4(1H,3H)-dione;
 (S)-6-((1-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
 (S)-6-((1-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-ethylpyrimidine-2,4(1H,3H)-dione;

- (S)-6-((1-phenylpropyl)amino)-3-(2,2,2-trifluoroethyl)pyrimidine-2,4(1H,3H)-dione;
(S)-3-(cyclopropylmethyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-6-((cyclopropyl(phenyl)methyl)amino)-3-(2,2,2-trifluoroethyl)pyrimidine-2,4(1H,3H)-
dione;
- 5 (S)-6-((cyclobutyl(phenyl)methyl)amino)-3-(2,2,2-trifluoroethyl)pyrimidine-2,4(1H,3H)-
dione;
(S)-3-(1,3-dihydroxypropan-2-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione;
6-(((S)-1-(4-fluorophenyl)propan-2-yl)amino)-3-((S)-1,1,1-trifluoropropan-2-yl)pyrimidine-
2,4(1H,3H)-dione;
- 10 (S)-6-((1-(3-hydroxyphenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
6-((1-(2-hydroxyphenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-phenylethyl)amino)-3-(1-(trifluoromethyl)cyclopropyl)pyrimidine-2,4(1H,3H)-
dione;
(S)-3-(3,5-difluorophenyl)-6-((1-(4-fluorophenyl)propan-2-yl)amino)pyrimidine-2,4(1H,3H)-
15 dione;
(S)-6-((1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-isopropylpyrimidine-
2,4(1H,3H)-dione;
(S)-6-((1-(2-chlorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
(S)-3-isopropyl-6-((1-(4-methoxyphenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
- 20 (S)-6-((cyclopropyl(phenyl)methyl)amino)-3-ethylpyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(3-chlorophenyl)ethyl)amino)-3-ethylpyrimidine-2,4(1H,3H)-dione;
(S)-3-ethyl-6-((1-(3-(trifluoromethyl)phenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-3-(cyclopropylmethyl)-6-((1-(3-fluorophenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-3-(cyclopropylmethyl)-6-((1-(3-(trifluoromethyl)phenyl)ethyl)amino)pyrimidine-
25 2,4(1H,3H)-dione;
(S)-6-((1-(3-chlorophenyl)ethyl)amino)-3-(cyclopropylmethyl)pyrimidine-2,4(1H,3H)-dione;
(S)-5-chloro-6-((1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-
isopropylpyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(3-fluorophenyl)ethyl)amino)-3-propylpyrimidine-2,4(1H,3H)-dione;
- 30 (S)-6-((1-(3-chlorophenyl)ethyl)amino)-3-propylpyrimidine-2,4(1H,3H)-dione;
(S)-3-propyl-6-((1-(3-(trifluoromethyl)phenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-3-cyclobutyl-6-((1-(4-fluorophenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(2-hydroxyphenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(3,4-difluorophenyl)ethyl)amino)-3-ethylpyrimidine-2,4(1H,3H)-dione;

3-((S)-sec-butyl)-6-(((S)-1-(4-fluorophenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione;
(S)-6-((1-(4-fluorophenyl)ethyl)amino)-3-propylpyrimidine-2,4(1H,3H)-dione; and
(S)-3-(6-fluoropyridin-2-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione, or a
pharmaceutically acceptable salt of any of the above.

5 **[0051]** In some embodiments, the compound is selected from



or a pharmaceutically acceptable salt thereof.

[0052] The compounds or pharmaceutically acceptable salts described herein (**I**) can be prepared via any suitable method. Compounds can be prepared, for example, by the route outlined in Figure 1. As shown in Figure 1A, a pyrimidine trione **v** can be synthesized via condensation of a urea **iii** with a malonate **iv**. The urea **iii** can be prepared via reaction of an amine **i** with an appropriate cyanate **ii**. The pyrimidine trione **v** is derivatized with a suitable leaving group (Lg) to provide intermediate **vi**. The leaving group can be, but is not limited to, a halogen such as a chloride or iodide. A halogenated intermediate **vi** can be prepared

from pyrimidine triones by methods such as those described by Brown (*The Chemistry of Heterocyclic Compounds, The Pyrimidines*, John Wiley & Sons, 2009). Intermediates **vi** can be converted to compounds of formula I via reaction with amines **vii**. Certain chiral amines can be prepared from a ketone or aldehyde **ix** as shown in Figure 1B; a sulfinyl imine **xii** derived from the ketone or aldehyde can be reacted with a Grignard reagent **xiii** to provide a chiral amine **vii**. One of skill in the art will appreciate that the compounds described herein can be prepared via other methods, such as those described by LaRock (*Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, Wiley, 1999).

IV. Compositions

[0053] Also provided is a pharmaceutical composition containing a compound or pharmaceutically acceptable salt described herein and a pharmaceutically acceptable excipient. The compositions may be useful for treating hypertrophic cardiomyopathy in humans and other subjects.

[0054] The pharmaceutical compositions for the administration of the compounds or pharmaceutically acceptable salts described herein may conveniently be presented in unit dosage form and may be prepared by any of the methods known in the art of pharmacy and drug delivery. All methods include the step of bringing the active ingredient into association with a carrier containing one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition, the active agent is generally included in an amount sufficient to produce the desired effect upon myocardial contractility (i.e. to decrease the often supranormal systolic contractility in HCM) and to improve left ventricular relaxation in diastole. Such improved relaxation can alleviate symptoms in hypertrophic cardiomyopathy and other etiologies of diastolic dysfunction. It can also ameliorate the effects of diastolic dysfunction causing impairment of coronary blood flow, improving the latter as an adjunctive agent in angina pectoris and ischemic heart disease. It can also confer benefits on salutary left ventricular remodeling in HCM and other causes of left ventricular hypertrophy due to chronic volume or pressure overload from, e.g., valvular heart disease or systemic hypertension.

[0055] The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions,

dispersible powders or granules, emulsions, hard or soft capsules, syrups, elixirs, solutions, buccal patch, oral gel, chewing gum, chewable tablets, effervescent powder and effervescent tablets. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may

5 contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, antioxidants and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as

10 cellulose, silicon dioxide, aluminum oxide, calcium carbonate, sodium carbonate, glucose, mannitol, sorbitol, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example PVP, cellulose, PEG, starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated,

15 enterically or otherwise, by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated to form osmotic therapeutic tablets for controlled release.

20 **[0056]** Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil. Additionally, emulsions can be prepared with a non-water miscible ingredient such as oils

25 and stabilized with surfactants such as mono-diglycerides, PEG esters and the like.

[0057] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum

30 acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene

oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0058] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0059] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0060] The pharmaceutical compositions described herein may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0061] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. Oral solutions can be prepared in combination with, for example, cyclodextrin, PEG and surfactants.

[0062] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0063] The compounds or pharmaceutically acceptable salts described herein may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols. Additionally, the compounds or pharmaceutically acceptable salts can be administered via ocular delivery by means of solutions or ointments. Still further, transdermal delivery of the subject compounds or pharmaceutically acceptable salts can be accomplished by means of iontophoretic patches and the like. For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds or pharmaceutically acceptable salts described herein are employed. As used herein, topical application is also meant to include the use of mouth washes and gargles.

[0064] The compounds or pharmaceutically acceptable salts described herein may also be coupled to a carrier that is a suitable polymer for targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds or pharmaceutically acceptable salts described herein may be coupled to a carrier that is a biodegradable polymer useful in achieving controlled release of a drug, such as polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

V. Methods of treating cardiac disorders

[0065] The mutations that lead to HCM cause significant perturbations in myosin mechanics. These mutations exert their effects via distinct mechanisms depending on their locations in the myosin gene. The well-studied HCM mutations, R403Q and R453C, are located in different sections of the motor domain and cause distinct mechanistic perturbations that lead to the common outcome of increased force production. Without wishing to be bound by any particular theory, it is believed that the compounds or pharmaceutically acceptable salts described herein can bind directly to the mutant sarcomeric proteins and correct for their aberrant function, either in *cis* (by affecting the same specific function) or in *trans* (by altering a complementary function). As such, they can provide therapeutic benefit for HCM patients by counteracting the hypercontractile and/or impaired relaxation associated with this disease. .

[0066] Also provided is a method of treating hypertrophic cardiomyopathy (HCM) or a cardiac disorder having one or more pathophysiological features associated with HCM. The method includes administering to a subject in need thereof an effective amount of a compound or pharmaceutically acceptable salt described herein.

[0067] The compounds of the invention or their pharmaceutically acceptable salts can alter the natural history of HCM and other diseases rather than merely palliating symptoms. The mechanisms conferring clinical benefit to HCM patients can extend to patients with other forms of heart disease sharing similar pathophysiology, with or without demonstrable genetic influence. For example, an effective treatment for HCM, by improving ventricular relaxation during diastole, can also be effective in a broader population characterized by diastolic dysfunction. The compounds of the invention or their pharmaceutically acceptable salts can specifically target the root causes of the conditions or act upon other downstream pathways. Accordingly, the compounds of the invention or their pharmaceutically acceptable salts can also confer benefit to patients suffering from diastolic heart failure with preserved ejection fraction, ischemic heart disease, angina pectoris, or restrictive cardiomyopathy. Compounds of the invention or their pharmaceutically acceptable salts can also promote salutary ventricular remodeling of left ventricular hypertrophy due to volume or pressure overload; *e.g.*, chronic mitral regurgitation, chronic aortic stenosis, or chronic systemic hypertension; in conjunction with therapies aimed at correcting or alleviating the primary cause of volume or pressure overload (valve repair/replacement, effective

antihypertensive therapy). By reducing left ventricular filling pressures the compounds could reduce the risk of pulmonary edema and respiratory failure. Reducing or eliminating functional mitral regurgitation and/or lowering left atrial pressures may reduce the risk of paroxysmal or permanent atrial fibrillation, and with it reduce the attendant risk of arterial thromboembolic complications including but not limited to cerebral arterial embolic stroke. Reducing or eliminating either dynamic and/or static left ventricular outflow obstruction may reduce the likelihood of requiring septal reduction therapy, either surgical or percutaneous, with their attendant risks of short and long term complications. The compounds or their pharmaceutically acceptable salts may reduce the severity of the chronic ischemic state associated with HCM and thereby reduce the risk of Sudden Cardiac Death (SCD) or its equivalent in patients with implantable cardioverter-defibrillators (frequent and/or repeated ICD discharges) and/or the need for potentially toxic antiarrhythmic medications. The compounds or their pharmaceutically acceptable salts could be valuable in reducing or eliminating the need for concomitant medications with their attendant potential toxicities, drug-drug interactions, and/or side effects. The compounds or their pharmaceutically acceptable salts may reduce interstitial myocardial fibrosis and/or slow the progression, arrest, or reverse left ventricular hypertrophy.

[0068] Depending on the disease to be treated and the subject's condition, the compounds or pharmaceutically acceptable salts described herein may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by implantation (e.g., as when the compound or pharmaceutically acceptable salt is coupled to a stent device), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration.

[0069] In the treatment or prevention of conditions which require improved ventricular relaxation during diastole, an appropriate dosage level will generally be about 0.001 to 100 mg per kg patient body weight per day which can be administered in single or multiple doses. In some embodiments, the dosage level will be about 0.01 to about 25 mg/kg per day; in some embodiments, about 0.05 to about 10 mg/kg per day. A suitable dosage level may be about 0.01 to 25 mg/kg per day, about 0.05 to 10 mg/kg per day, or about 0.1 to 5 mg/kg per day. Within this range the dosage may be 0.005 to 0.05, 0.05 to 0.5 or 0.5 to 5.0 mg/kg per

day. In some embodiments, for oral administration, the compositions are provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds or pharmaceutically acceptable salts may be administered on a regimen of 1 to 4 times per day, in some embodiments, once or twice per day.

[0070] It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound or pharmaceutically acceptable salt employed, the metabolic stability and length of action of that compound or pharmaceutically acceptable salt, the age, body weight, hereditary characteristics, general health, sex and diet of the subject, as well as the mode and time of administration, rate of excretion, drug combination, and the severity of the particular condition for the subject undergoing therapy.

[0071] Compounds and compositions provided herein may be used in combination with other drugs that are used in the treatment, prevention, suppression or amelioration of the diseases or conditions for which compounds and compositions provided herein are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound or composition provided herein. When a compound or composition provided herein is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound or composition provided herein is preferred. Accordingly, the pharmaceutical compositions provided herein include those that also contain one or more other active ingredients or therapeutic agents, in addition to a compound or composition provided herein. Suitable additional active agents include, for example: therapies that retard the progression of heart failure by down-regulating neurohormonal stimulation of the heart and attempt to prevent cardiac remodeling (*e.g.*, ACE inhibitors, angiotensin receptor blockers (ARBs), β -blockers, aldosterone receptor antagonists, or neural endopeptidase inhibitors); therapies that improve cardiac function by stimulating cardiac contractility (*e.g.*, positive inotropic agents, such as the β -adrenergic agonist dobutamine or the phosphodiesterase inhibitor milrinone); and therapies that reduce cardiac preload (*e.g.*, diuretics, such as furosemide) or afterload (vasodilators of any class, including but not limited to calcium channel blockers, phosphodiesterase inhibitors, endothelin receptor antagonists, renin inhibitors, or smooth

muscle myosin modulators). The weight ratio of the compound provided herein to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used.

VI. Examples

5 Abbreviations:

aq: aqueous

BBr₃: boron tribromide

CH₂Cl₂: dichloromethane

CH₃CN: acetonitrile

10 CH₃OH: methanol

DIAD: diisopropyl azodicarboxylate

DIEA: diisopropyl ethylamine

DMF: dimethyl formamide

DMSO: dimethyl sulfoxide

15 equiv.: equivalents

Et₃N: triethylamine

Et₂O: diethyl ether

EtOH: ethanol

FeSO₄: ferrous sulfate

20 h: hour(s)

HCl: hydrogen chloride

H₂O: water

K₂CO₃: potassium carbonate

KHSO₄: potassium bisulfate

25 KNCO: potassium isocyanate

LiBr: lithium bromide

MgSO₄: magnesium sulfate

mL: milliliter

MW: microwave (reaction done in microwave reactor)

30 NaCl: sodium chloride

NaH: sodium hydride

NaHCO₃: sodium bicarbonate

NaOEt: sodium ethoxide

NaOH: sodium hydroxide

NaOMe: sodium methoxide

Na₂SO₄: sodium sulfate

NH₄Cl: ammonium chloride

5 NMP: n-methyl pyrrolidinone

pH: $-\log [H^+]$

POCl₃: phosphoryl trichloride

PPTS: pyridinium p-toluenesulfonate

RP-HPLC: reversed phase high pressure liquid chromatography

10 RT: room temperature

SEMCl: 2-(trimethylsilyl)ethoxymethyl chloride

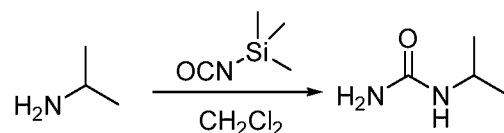
TEBAC: triethylbenzylammonium chloride

TFA: trifluoroacetic acid

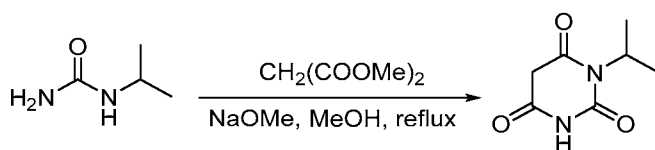
THF: tetrahydrofuran

15 TLC: thin layer chromatography

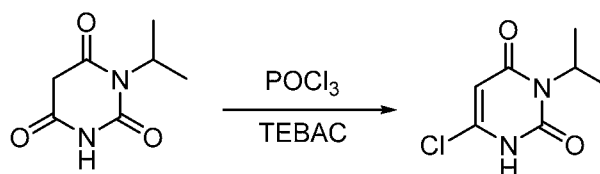
Example 1. Preparation of (S)-3-Isopropyl-6-((1-phenylethyl) amino) pyrimidine-2,4(1H,3H)-dione.



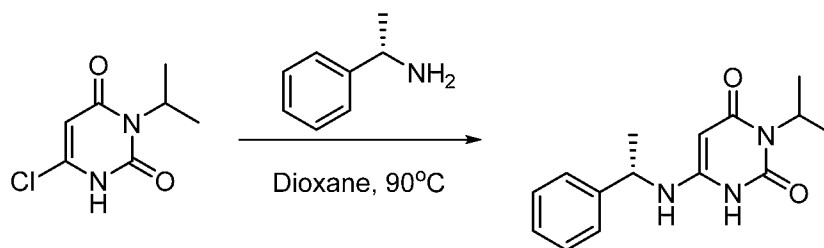
- 20 **[0072] Compound 1.1. Isopropylurea.** To a stirred solution of isopropylamine (15.3 g, 0.258 mol, 1.0 equiv) in CH₂Cl₂ (200 mL) under argon at 0 °C was added dropwise trimethylsilyl isocyanate (30 g, 0.26 mol, 1.0 equiv). The resulting mixture was allowed to reach ambient temperature and stirred overnight. After cooling to 0 °C, CH₃OH (100 mL) was added dropwise. The resulting solution was stirred for 2 hours (h) at room temperature
- 25 and then concentrated under reduced pressure. The crude residue was recrystallized from CH₃OH:Et₂O (1:20) to yield 15.4 g (58%) the title compound as a white solid. LC/MS: m/z (ES⁺) 103 (M+H)⁺.



[0073] Compound 1.2. 1-Isopropyl barbituric acid. To a stirred solution of **1.1** (14.4 g, 0.14 mol, 1.00 equiv) in CH₃OH (500 mL) were added dimethyl malonate (19.55 g, 0.148 mol, 1.05 equiv) and sodium methoxide (18.9 g, 0.35 mol, 2.50 equiv). The resulting mixture was stirred overnight at 65 °C. After cooling to ambient temperature and then to 0 °C, the pH was carefully adjusted to 3 using aqueous concentrated HCl. The resulting mixture was concentrated under reduced pressure. The residue was taken up in EtOH (200 mL) and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography using CH₂Cl₂/CH₃OH (20:1) as eluent to yield 16.8 g (50%) of the title compound as a white solid. . LC/MS: m/z (ES+) 171 (M+H)⁺. ¹H-NMR (300 MHz, d₆-DMSO): δ 11.19 (s, 1H), 4.83 (m, 1H), 3.58 (s, 2H), 1.32 (d, J = 6.0 Hz, 6H).



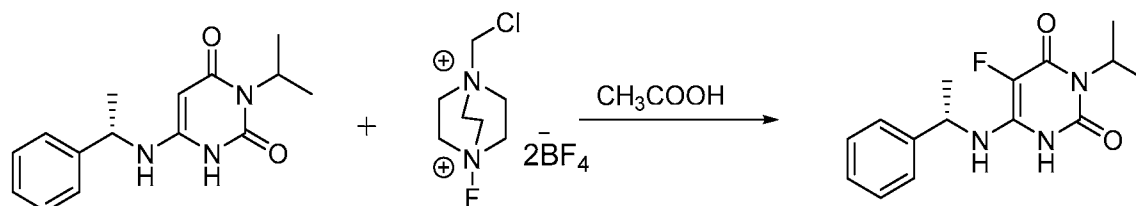
[0074] Compound 1.3. 6-chloro-3-isopropylpyrimidine-2,4(1H,3H)-dione. To a 100-mL round-bottom flask containing compound **1.2** (11.4 g, 66.99 mmol, 1.00 equiv) under argon were added triethylbenzylammonium chloride (21.3 g, 93.51 mmol, 1.40 equiv) and POCl₃ (30 mL). The resulting mixture was stirred overnight at 50 °C. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ (150 mL) followed by slow addition of H₂O (100 mL). The phases were separated and the organic layer was washed with H₂O (100 mL), dried with anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using EtOAc/petroleum ether (1:1) as eluent to yield 5.12 g (40%) of the title compound as a light yellow solid. ¹H-NMR (300 MHz, d₆-DMSO): δ 12.22 (s, 1H), 5.88 (s, 1H), 4.95 (m, 1H), 1.34 (d, J = 6.0 Hz, 6H).



[0075] Compound 1. (S)-3-Isopropyl-6-((1-phenylethyl) amino) pyrimidine-2,4(1H,3H)-dione. To a solution of 6-chloro-3-isopropylpyrimidine-2,4(1H,3H)-dione (**1.3**,

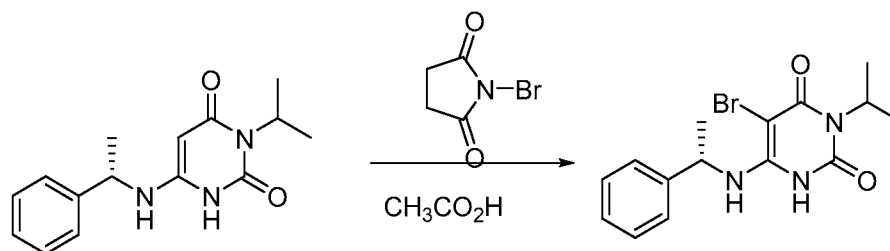
1.0 g, 5.31 mmol) in 1,4-dioxane (20 mL) was added (*S*)- α -methylbenzylamine (Sigma-Aldrich, 1.43 g, 11.7 mmol, 2.2 equiv). The reaction mixture was stirred at 80 °C for 24 h. After cooling to ambient temperature, the mixture was concentrated under reduced pressure. The residual was taken up in EtOAc (70 mL) and washed with aqueous 1N HCl (2 x 50 mL) and brine (40 mL). The organic layer was dried with anhydrous Na₂SO₄ and then concentrated under reduced pressure to half the original volume to yield a precipitate. Hexane (20 mL) was added and the mixture was stirred at room temperature. The resulting solid was collected by filtration, washed with hexane (20 mL), and dried to yield 1.0 g (69%) of the title compound as a white solid. LC/MS: *m/z* (ES⁺) 274 (M+H)⁺. ¹H-NMR (400 MHz, d₆-DMSO): δ 9.77 (s, 1H), 7.32 (m, 4H), 7.24 (m, 1H), 6.50 (d, *J* = 6.8 Hz, 1H), 4.87 (m, 1H), 4.52 (m, 1H), 4.31 (d, *J* = 6.8 Hz, 1H), 1.37 (m, 3H), 1.24 (m, 6H). ¹H NMR (400 MHz, CD₃OD) δ ppm 7.39-7.20 (m, 5H), 5.01 (m, 1H), 4.48 (m, 1H), 1.49 (d, *J* = 6.7 Hz, 3H), 1.36 (m, 6H).

Example 2. Preparation of (*S*)-5-Fluoro-3-isopropyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione (**2**).



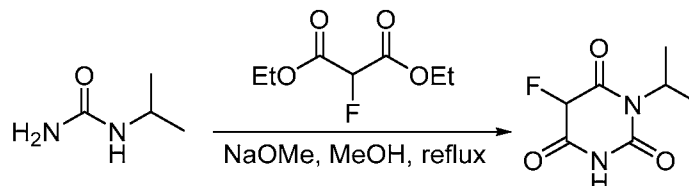
[0076] To a solution of **1** (80 mg, 0.293 mmol) in acetic acid (2.0 mL) was added selectfluor (104 mg, 0.293 mmol, 1.0 equiv.). The mixture was stirred at room temperature for 2 h. It was then concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 0-50% EtOAc in hexanes to give 6 mg (7%) of the title compound as a white solid. LC/MS: *m/z* (ES⁺) 292 (M+H)⁺. ¹H NMR (400 MHz, CD₃OD): δ ppm 7.36-7.24 (m, 5H), 5.04-4.97 (m, 1H), 4.94-4.88 (m, 1H), 1.54 (d, *J* = 8.0 Hz, 3H), 1.39 (m, 6H).

Example 3. Preparation of (S)-5-Bromo-3-isopropyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione (3).

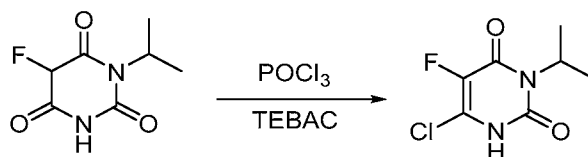


[0077] To a solution of **1** (55 mg, 0.201 mmol) in acetic acid (1.0 mL) was added N-bromosuccinimide (35 mg, 0.196 mmol). The mixture was stirred at room temperature for 1 hour. It was then concentrated under reduced pressure. The residue was purified by a silica gel column, eluted with 0-40% EtOAc in hexanes to give 52 mg (74%) of the title compound as a white solid. LC/MS: m/z (ES⁺) 352, 354 (M+H, bromine pattern)⁺. ¹H-NMR (400 MHz, CDCl₃) δ ppm 8.96 (br s, 1H), 7.43-7.28 (m, 5H), 5.28 (d, J = 7.4 Hz, 1H), 5.14 (m, 1H), 4.87 (m, 1H), 1.62 (d, J = 6.7 Hz, 3H), 1.45-1.39 (m, 6H).

Example 4. Preparation of (S)-6-((1-(3-Chlorophenyl)ethyl)amino)-5-fluoro-3-isopropylpyrimidine-2,4(1H,3H)-dione.

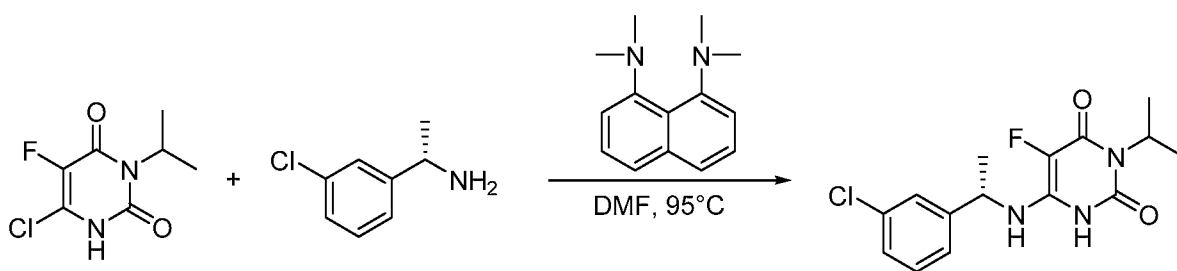


[0078] **Compound 4.1. 5-Fluoro-1-isopropylpyrimidine-2,4,6(1H,3H,5H)-trione.** To a 100 mL round bottom flask containing a solution of **1.1** (1.31 g, 0.013 mol, 1.00 equiv) in CH₃OH (15 mL) were added diethyl fluoromalonate (2.41 g, 0.014 mol, 1.05 equiv) and sodium methoxide (1.74 g, 0.032 mol, 2.50 equiv). The reaction flask was equipped with a reflux condenser and was stirred for 4 h in an oil bath heated at 85 °C. The reaction was cooled to 0 °C and was quenched with careful addition of concentrated HCl, adjusting to pH=2 with the addition of excess concentrated HCl. The reaction mixture was concentrated under reduced pressure and the resulting residue was dried for 18 h under high vacuum to provide 2.65 g of the title compound (98%). ¹H-NMR (400 MHz, CDCl₃): δ ppm 5.53 (d, J = 24.0 Hz, 1H), 4.91 (m, 2H), 1.46 (m, 6H).



[0079] Compound 4.2. 6-Chloro-5-fluoro-3-isopropylpyrimidine-2,4(1H,3H)-dione.

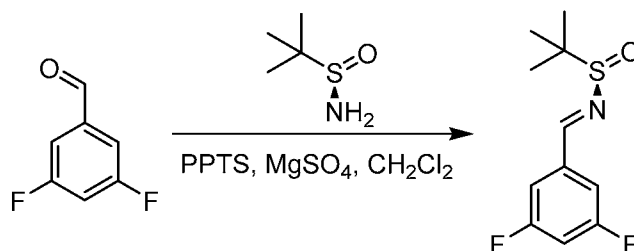
To a 100-mL round-bottom flask equipped with a reflux condensor containing **4.1** (2.65 g, 0.014 mmol, 1.00 equiv) were added triethylbenzylammonium chloride (4.50 g, 0.019 mmol, 1.40 equiv) and POCl₃ (25 mL). The reaction mixture was stirred for 4 h at 50 °C and then was cooled to room temperature. The mixture was concentrated under reduced pressure and the resulting residue was dissolved in CH₂Cl₂ (50 mL). Water (50 mL) was added slowly and the layers were separated. The organic layer was washed a second time with H₂O (100 mL), dried with anhydrous MgSO₄, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, 30% EtOAc in hexanes) to yield 2.67 g (93%) of the title compound as a white solid. ¹H-NMR (400 MHz, CDCl₃): δ ppm 5.19-5.05 (m, 2H), 1.48 (d, J=7.04 Hz, 6H).



[0080] Compound 4. (S)-6-((1-(3-Chlorophenyl)ethyl)amino)-5-fluoro-3-

isopropylpyrimidine-2,4(1H,3H)-dione. To a solution of **4.2** (150 mg, 0.70 mmol, 1 equiv) in DMF (2 mL) contained in a heavy wall pressure vessel were added (S)-3-chloro-α-methylbenzylamine (150 mg, 0.70 mmol, 1.0 equiv) and proton sponge (190 mg, 0.90 mol, 1.25 equiv). The pressure vessel was sealed and the reaction mixture was heated to 95 °C for 3 h behind a blast shield. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by preparative RP-HPLC utilizing a Shimadzu, Prominence LC-20AP system equipped with a Phenomenex Gemini-NX C18 column (eluting with 10-90% CH₃CN/H₂O in 30 min., 20 mL/min (both containing 0.1% TFA)). The fractions containing pure compound were combined and lyophilized to provide 30 mg (13%) of the title compound as a white solid. LC/MS: m/z (ES⁺) 326 (M+H)⁺. ¹H-NMR (400 MHz, CDCl₃) δ ppm 9.47 (br s, 1H), 7.35-7.27 (m, 3H), 7.22-7.16 (m, 1H), 5.12 (m, 1H), 4.89 (m, 1H), 4.69 (d, J = 5.9 Hz, 1H), 1.59 (d, J = 6.7 Hz, 3H), 1.43 (m, 6H).

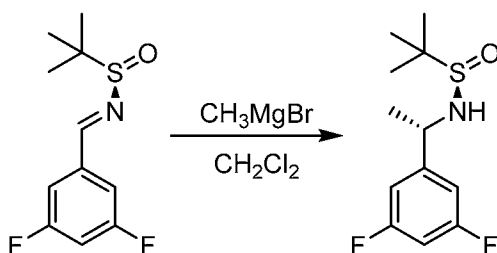
Example 5. Preparation of (S)-6-((1-(3,5-Difluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione.



[0081] Compound 5.1. ((R,E)-N-(3,5-difluorobenzylidene)-2-methylpropane-2-

5 **sulfinamide.** To a solution of 3,5-difluorobenzaldehyde (1.00 g, 7.04 mmol, 1.00 equiv) in CH_2Cl_2 (20 mL) were added pyridinium p-toluenesulfonate (0.089 g, 0.35 mmol, 0.05 equiv), (R)-(+)-2-methylpropane-2-sulfinamide (0.852 g, 7.03 mmol, 1.00 equiv), and MgSO_4 (4.2 g, 35.00 mmol, 5.00 equiv). The resulting mixture was stirred overnight at room temperature. The reaction mixture was filtered and concentrated under reduced pressure. The

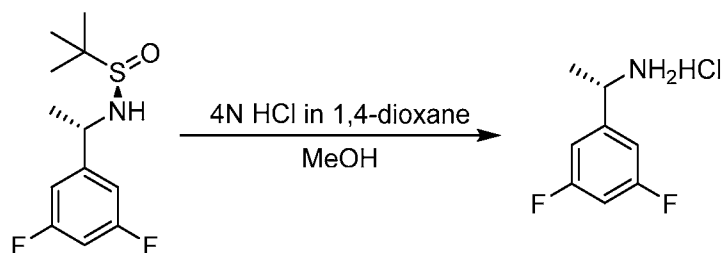
10 resulting residue was purified by flash chromatography (silica gel, 20% EtOAc in petroleum ether) to provide 500 mg (29%) of the title compound as a yellow oil.



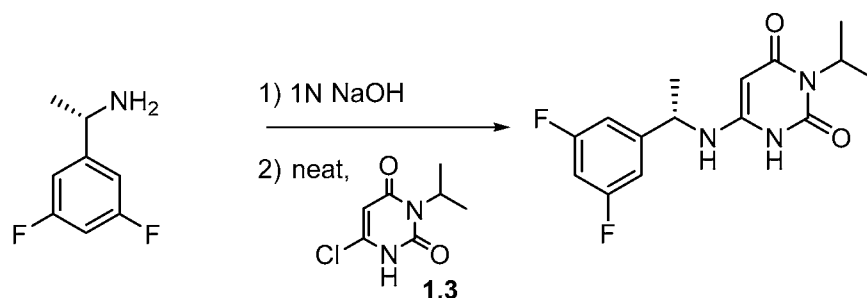
[0082] Compound 5.2. (R)-N-((S)-1-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-

15 **sulfinamide.** Methylmagnesium bromide (5.17 mL, 3M, 2.00 equiv) was added dropwise to a solution of **5.1** (1.9 g, 7.75 mmol, 1.00 equiv) in CH_2Cl_2 (50 mL) under argon at -48°C . The reaction mixture was warmed to room temperature and stirred overnight. The reaction was carefully quenched with a saturated aqueous NH_4Cl solution (20 mL). The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (3 x 50 mL). The

20 combined organic layers were dried over anhydrous MgSO_4 and concentrated under reduced pressure to provide 1.3 g (64%) of the title compound as a yellow oil. ^1H NMR (300 MHz, CDCl_3): δ ppm 6.92-6.81 (m, 2H), 6.75-6.65 (m, 1H), 4.65-4.55, (m, 1H), 3.46-3.42 (m, 1H), 1.53-1.44 (m, 3H), 1.26-1.22 (m, 9H).



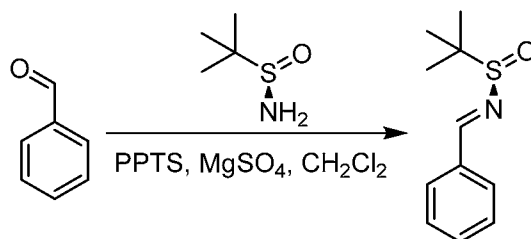
[0083] **Compound 5.3. (S)-1-(3,5-Difluorophenyl)ethan-1-amine hydrochloride.** To a solution of **5.2** (1.3 g, 4.97 mmol, 1.00 equiv) in CH₃OH (10 mL) was added 4N HCl in 1,4-dioxane (2.67 mL, 2.00 equiv). The reaction mixture was stirred for 0.5 h at room temperature and then was concentrated under reduced pressure. The resulting residue was dissolved in CH₃OH (3 mL) and Et₂O (300 mL) was added. The resulting precipitate was isolated by filtration to provide 0.80 g (83%) of the title compound. ¹H NMR (300 MHz, D₂O): δ ppm 6.98-6.83 (m, 3H), 4.45-4.38 (m, 1H), 1.51-1.48 (d, J = 6.9 Hz, 3H).



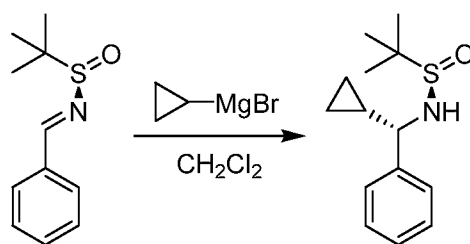
[0084] **Compound 5. (S)-6-((1-(3,5-Difluorophenyl)ethyl)amino)-3-**

isopropylpyrimidine-2,4(1H,3H)-dione. Compound **5.3** (50 mg, 0.32 mmol, 1.00 equiv) was dissolved in 1N NaOH (10 mL), and the resulting mixture was stirred at 25 °C. After 1 h, the mixture was extracted with EtOAc (5 x 10 mL). The combined organic layers were dried with anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue and compound **1.3** (35.6 mg, 0.19 mmol, 0.60 equiv) were combined. The mixture was stirred at 100 °C for 18 h, then was cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by preparative RP-HPLC to provide 28 mg (29%) of the title compound as an off white solid. LC/MS: m/z (ES+) 310 (M+H)⁺. ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 9.83 (s, 1H), 7.06-7.12 (m, 3H), 6.54 (d, J = 6.6 Hz, 1H), 4.91-4.82 (m, 1H), 4.54-4.46 (m, 1H), 4.30 (m, 1H), 1.34 (d, J = 6.6 Hz, 3H), 1.22 (d, J = 6.9 Hz, 6H).

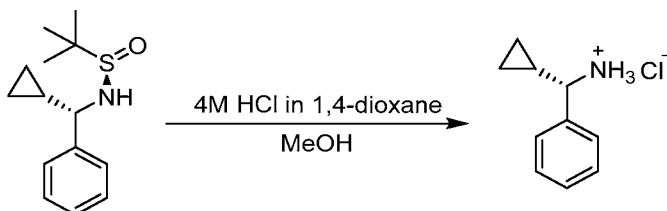
Example 6. Preparation of (S)-6-((Cyclopropyl(phenyl)methyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione.



[0085] **Compound 6.1. (R,E)-N-benzylidene-2-methylpropane-2-sulfonamide.** The title compound was prepared in the same manner as **5.1** except benzaldehyde (5.0 g, 47.12 mmol, 1.00 equiv) was used in place of 3,5-difluorobenzaldehyde to provide 2.8 g (28%) of the title compound. ¹H NMR (300 MHz, d₆-DMSO): δ ppm 8.62 (s, 1H), 7.89-7.87 (m, 2H), 7.55-7.49 (m, 3H), 1.31 (s, 9H).

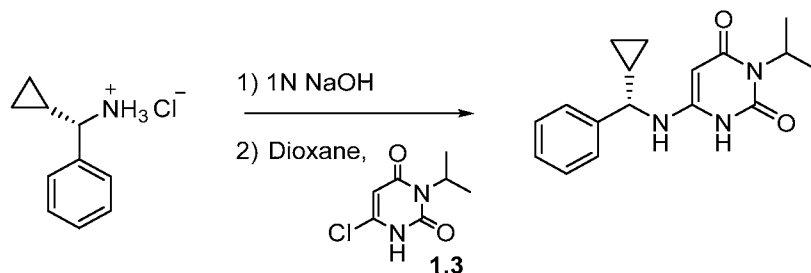


[0086] **Compound 6.2. (S)-N-((S)-Cyclopropyl(phenyl)methyl)-2-methylpropane-2-sulfonamide.** The title compound was prepared using a protocol similar to that used for the preparation of **5.2** except **6.1** (1.0 g, 4.78 mmol, 1.00 equiv) and cyclopropylmagnesium bromide (9.6 mL, 1M, 2.00 equiv) were used in place of **5.1** and methylmagnesium bromide to provide 0.5 g (35%) of the title compound as a yellow oil. ¹H NMR (300 MHz, DMSO-d₆): δ ppm 7.36-7.23 (m, 5H), 3.67-3.51 (m, 2H), 1.31 (m, 10H), 0.85-0.15 (m, 4H).



[0087] **Compound 6.3. (S)-Cyclopropyl(phenyl)methanamine hydrochloride.** The title compound was prepared using a protocol similar to that used for the preparation of **5.3** except **6.2** (500 mg, 1.69 mmol, 1.00 equiv) was used in place of **5.2** to provide 220 mg (88%) of the title compound as a yellow oil. ¹H NMR (300 MHz, d₆-DMSO): δ ppm 7.37-7.31 (m, 5H),

3.53 (d, $J = 10.0$ Hz, 1H), 1.37-1.25 (m, 1H), 0.75-0.55 (m, 1H), 0.53-0.31 (m, 2H), 0.25-0.15 (m, 1H).

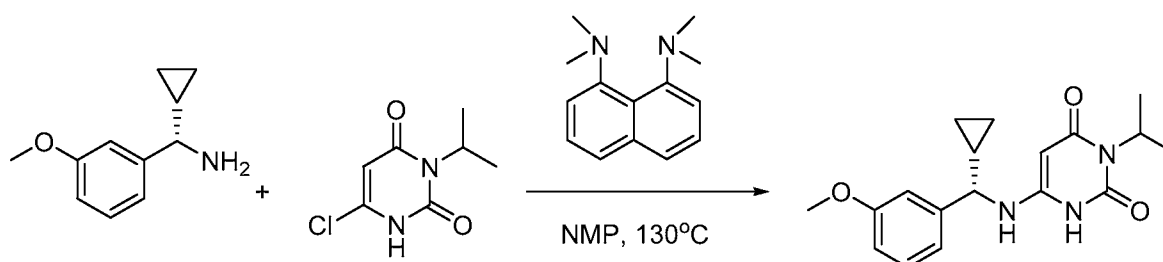


[0088] Compound 6. (S)-6-((Cyclopropyl(phenyl)methyl)amino)-3-

isopropylpyrimidine-2,4(1H,3H)-dione. The title compound was prepared using a procedure similar to that used for the preparation of **5** except **6.3** (200 mg, 1.36 mmol, 1.00 equiv) was used instead of **5.3** and 1,4-dioxane was utilized as a solvent. After concentration under reduced pressure, purification utilizing a chiral HPLC (Phenomenex Lux 5 μ Cellulose-4, 2.12*25, 5 μ m column) with an isocratic mixture of EtOH: Hexane (1: 4) as eluent provided 22 mg (5%) of the title compound as a white solid. LC/MS: m/z (ES⁺) 300 (M+H)⁺. ¹H-NMR (300 MHz, DMSO- d_6) δ ppm 9.82 (s, 1H), 7.39-7.25 (m, 5H), 7.25-7.32 (m, 1H), 6.72 (m, 1H), 4.90 (m, 1H), 4.22 (s, 1H), 3.78 (m, 1H), 1.27 (m, 6H), 1.57 (m, 1H), 0.60 (m, 1H), 0.56-0.32 (m, 2H).

Example 7. Preparation of (S)-6-((cyclopropyl(3-methoxyphenyl)methyl)amino)-3-

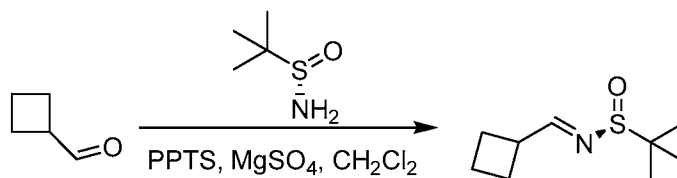
isopropylpyrimidine-2,4(1H,3H)-dione.



[0089] A solution of 6-chloro-3-isopropylpyrimidine-2,4(1H,3H)-dione (**1.3**, 50 mg, 0.265 mmol), (S)-cyclopropyl-(3-methoxyphenyl)methylamine (Sigma-Aldrich, 104 mg, 0.587 mmol), and proton sponge (85 mg, 0.397 mmol) in NMP (0.5 mL) was stirred at 130 °C for 2 h. After cooling to room temperature, the mixture was purified by preparative RP-HPLC (Shimadzu, Prominence LC-20AP system equipped with a Phenomenex Gemini-NX C18 column), eluting with 20-90% CH₃CN in H₂O (both containing 0.1% TFA). The fractions containing pure compound were combined and lyophilized to give 10 mg (11%) of the title compound as a white solid. LC/MS: m/z (ES⁺) 330 (M+H)⁺. ¹H-NMR (400 MHz, CD₃OD): δ

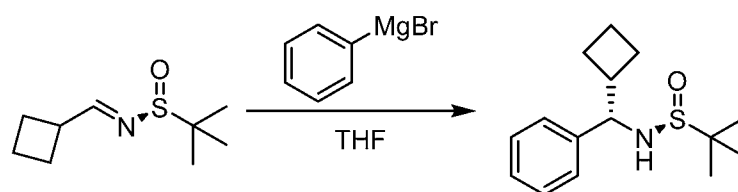
ppm 7.26 (t, J = 7.8 Hz, H), 6.92-6.79 (m, 3H), 5.00 (m, 1H), 3.79 (s, 3H), 3.74 (d, J = 8.6 Hz, 1H), 1.36 (d, J = 7.0 Hz, 6H), 1.23-1.13 (m, 1H), 0.68-0.60 (m, 1H), 0.58-0.50 (m, 1H), 0.50-0.42 (m, 1H), 0.41-0.34 (m, 1H).

Example 8. Preparation of (S)-6-((Cyclobutyl(phenyl)methyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione.



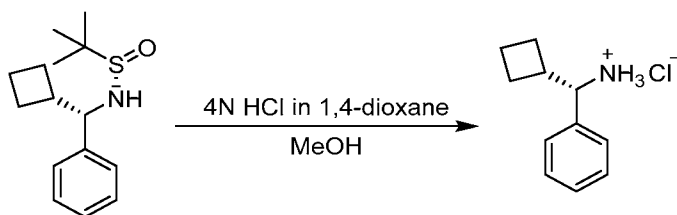
[0090] Compound 8.1. (S,E)-N-(cyclobutylmethylene)-2-methylpropane-2-

sulfonamide. To a solution of cyclobutanecarbaldehyde (1.0 g, 11.89 mmol, 1.00 equiv) in CH₂Cl₂ (10 mL) were added pyridinium p-toluenesulfonate (0.143 g, 0.57 mmol, 0.05 equiv), (S)-(-)-2-methylpropane-2-sulfonamide (1.22 g, 10.07 mmol, 0.85 equiv), and magnesium sulfate (7.14 g, 59.32 mmol, 5.00 equiv). The resulting mixture was stirred overnight at room temperature. The reaction mixture was filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, 30% EtOAc in petroleum ether) to provide 2.0 g (90%) of the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.08 (d, J = 10.8 Hz, 1H), 3.36-3.32 (m, 1H), 2.25-2.16 (m, 4H), 2.03-1.90 (m, 2H), 1.15 (s, 9H).

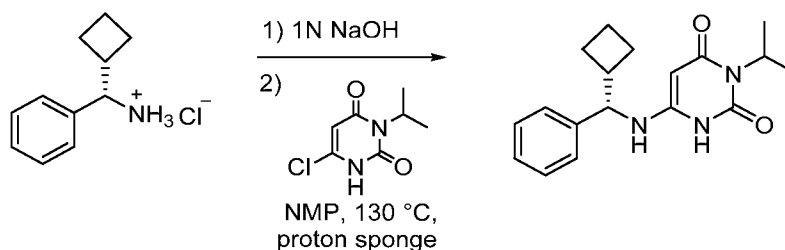


[0091] Compound 8.2. (S)-N-((S)-cyclobutyl(phenyl)methyl)-2-methylpropane-2-

sulfonamide. Phenylmagnesium bromide (3M in Et₂O, 15.3 mL, 2.00 equiv) was added dropwise to a solution of **8.1** (4.3 g, 22.96 mmol, 1.00 equiv) in THF (40 mL). The reaction mixture was heated for 3 h at 65 °C. It was then cooled to room temperature and carefully quenched with a saturated aqueous NH₄Cl solution (30 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL), and the combined organic layers were dried with anhydrous Na₂SO₄ and concentrated under reduced pressure to provide 5.8 g (95%) of the title compound as a white solid. ¹H-NMR (300 MHz, CDCl₃) δ 7.30-7.21 (m, 5H), 4.23 (d, J = 9.6 Hz, 1H), 2.73-2.68 (m, 1H), 1.95-1.60 (m, 6H), 1.14 (s, 9H).



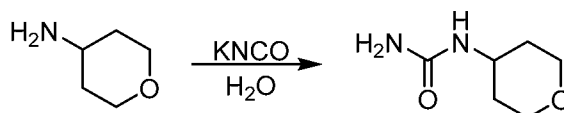
[0092] **Compound 8.3. (S)-Cyclobutyl(phenyl)methanamine hydrochloride.** The title compound was prepared using a procedure similar to that used for the preparation of **5.3** except **8.2** (5.8 g, 0.022 mol, 1.00 equiv) was used in place of **5.2** to provide 3.20 g (91%) of the title compound as a white solid. ¹H NMR (300 MHz, D₂O): δ ppm 7.36-7.28 (m, 5H), 4.18 (m, 1H), 2.87-2.73 (m, 1H), 2.11-2.01 (m, 1H), 1.90-1.69 (m, 5H).



[0093] **Compound 8. (S)-6-((Cyclobutyl(phenyl)methyl)amino)-3-**

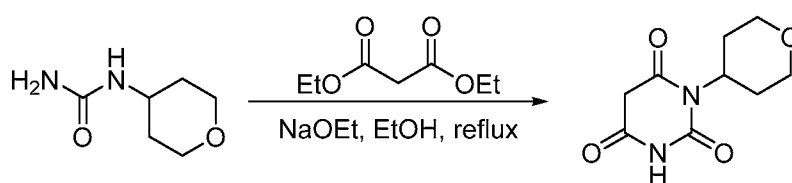
isopropylpyrimidine-2,4(1H,3H)-dione. Compound **8.3** (0.200 g, 1.24 mmol, 1.00 equiv) was dissolved in 1N NaOH (10 mL), and was stirred for 1 h at 25 °C. The reaction mixture was extracted with EtOAc (5 x 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was dissolved in NMP and combined with **1.3** and proton sponge and heated as described for the preparation of **7**. The title compound (35 mg, 9%) was isolated as a white solid. LC/MS: m/z (ES⁺) 314 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD): δ ppm 7.38-7.26 (m, 5H), 5.08-4.97 (m, 1H), 4.25 (d, J = 6.9 Hz, 1H), 2.68-2.58 (m, 1H), 2.19-2.13 (m, 1H), 1.98-1.83 (m, 5H), 1.36 (d, J = 6.9 Hz, 6H).

Example 9. Preparation of (S)-6-((1-phenylethyl)amino)-3-(tetrahydro-2H-pyran-4-yl)pyrimidine-2,4(1H,3H)-dione.



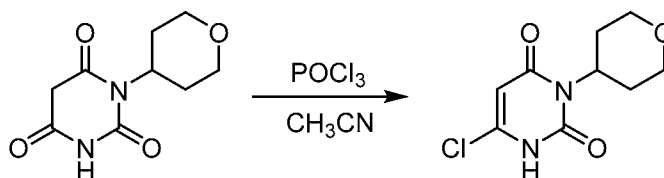
[0094] **Compound 9.1. 1-(tetrahydro-2H-pyran-4-yl)urea.** A mixture of tetrahydro-2H-pyran-4-amine (5.0 g, 49.4 mmol, 1.0 equiv.) and potassium isocyanate (4.0 g, 49.5 mmol, 1.0 equiv.) was refluxed in H₂O (50mL) overnight. The reaction was cooled to room temperature and excess NaCl was added to help saturate the aqueous layer. The precipitate

was isolated by filtration to provide the desired product (1.28g, 8.88 mmol). The aqueous layer was washed with EtOAc (3x 15 mL) and then was concentrated and azeotroped with toluene (3 x 100 mL). The resulting solid was suspended in 1:4 CH₃OH:EtOAc (100 mL) and filtered a total of four times. The combined organics were concentrated under reduced pressure and combined with the isolated precipitate to provide 5.01 g (70%) of the title compound. LC/MS: m/z (ES⁺) 145 (M+H)⁺. ¹H-NMR (400 MHz, DMSO-d₆): δ 6.14 (d, J = 7.5 Hz, 1H), 5.47 (s, 2H), 3.85 (dt, J = 11.6, 3.6 Hz, 2H), 3.65-3.52 (m, 1H), 3.38 (td, J = 11.4, 2.2 Hz, 2H), 1.80-1.72 (m, 2H), 1.42-1.27 (m, 2H).



[0095] Compound 9.2. 1-(tetrahydro-2H-pyran-4-yl)pyrimidine-2,4,6(1H,3H,5H)-trione.

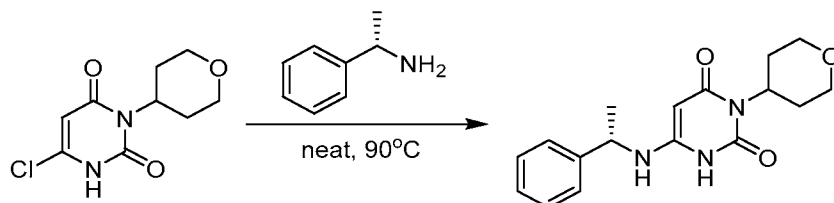
Compound **9.1** (2.8 g, 19.4 mmol) was dissolved in EtOH (30 mL), and diethyl malonate (2.45 mL, 21.4 mmol, 1.1 equiv.), and NaOEt (7.55 mL, 23.3 mmol, 1.2 equiv.) were added. The reaction was stirred at 85 °C overnight, and then was cooled to room temperature. The reaction mixture was diluted with H₂O (5 mL), and excess KHSO₄ was added to saturate the aqueous layer. The reaction mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried with anhydrous MgSO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, 0-25% CH₃OH in CH₂Cl₂) to provide 1.57 g of a mixture containing the title compound which was used without further purification. LC/MS: m/z (ES⁻) 211 (M-H)⁻.



[0096] Compound 9.3. 6-chloro-3-(tetrahydro-2H-pyran-4-yl)pyrimidine-2,4(1H,3H)-dione.

To a solution of **9.2** (1.57 g, 7.4 mmol, 1 equiv.) in CH₃CN (15 mL) was added POCl₃ (0.551 mL, 5.9 mmol, 0.8 equiv.). The reaction mixture was stirred at 80 °C overnight. An additional aliquot of POCl₃ (0.4 equiv.) was added and the reaction mixture was stirred at 80 °C for 3h. Additional aliquots of POCl₃ (0.4 equiv.) were added after 3 h

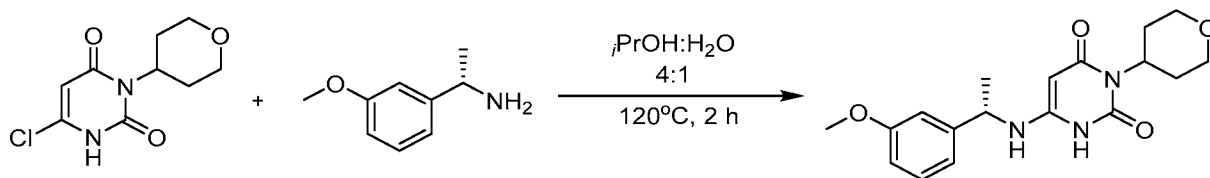
and 5 h of stirring at 80 °C. The reaction mixture was then stirred at 90 °C for 1h. The reaction was cooled to room temperature, concentrated, swirled with Et₂O (15 mL) and decanted. The resulting residue was rinsed with Et₂O (15 mL) and decanted until the Et₂O decanted clear. The resulting residue was carefully suspended in CH₃OH (10 mL), and
 5 filtered. The filtrate was concentrated to obtain a mixture of starting material and the title compound (~85% pure, 1.6 g). LC/MS: m/z (ES-) 229 (M-H)⁻.



[0097] Compound 9. (S)-6-((1-phenylethyl)amino)-3-(tetrahydro-2H-pyran-4-

yl)pyrimidine-2,4(1H,3H)-dione. A mixture of **9.3** (0.15 g, 0.65 mmol, 1 equiv.) and (S)-(-)- α -methylbenzylamine (470 mg, 3.88 mmol, 6.0 equiv.) was stirred overnight at 90 °C. The reaction mixture was cooled to room temperature and the resulting residue was purified by preparative RP-HPLC (0-40% CH₃CN in H₂O in 30 min.), followed by a second purification on a preparatory TLC plate (2000 μ m) (7% CH₃OH in CH₂Cl₂) to provide 23 mg (11%) of
 15 the title compound. LC/MS: m/z (ES+) 316 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆): δ ppm 10.23 (s, 1H), 7.40-7.32 (m, 4H), 7.31-7.17 (m, 1H), 6.93 (s, 1H), 4.84-4.71 (m, 1H), 4.56-4.43 (m, 1H), 4.35 (s, 1H), 3.93-3.78 (m, 2H), 3.28 (t, J = 12.1 Hz, 2H), 2.63-2.39 (m, 2H), 1.40 (d, J = 6.7 Hz, 3H), 1.35-1.16 (m, 2H).

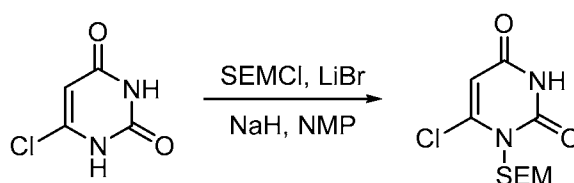
Example 10. Preparation of (S)-6-((1-(3-methoxyphenyl)ethyl)amino)-3-(tetrahydro-2H-pyran-4-yl)pyrimidine-2,4(1H,3H)-dione (**10**).



[0098] To a solution of **9.3** (0.58 g, 0.25 mmol) in a mixture of 2-propanol and H₂O (4:1, 1 mL) was added (S)-1-(3-methoxyphenyl)-ethylamine (0.113 g, 0.75 mmol, 3.0 equiv.). The
 25 reaction mixture was heated to 120 °C for 2 h. After cooling, the reaction mixture was concentrated under reduced pressure, dissolved in CH₃OH and filtered. The filtrate was purified by preparative RP-HPLC (20-100% CH₃CN in H₂O in 40 min. at 25 mL/min.) to

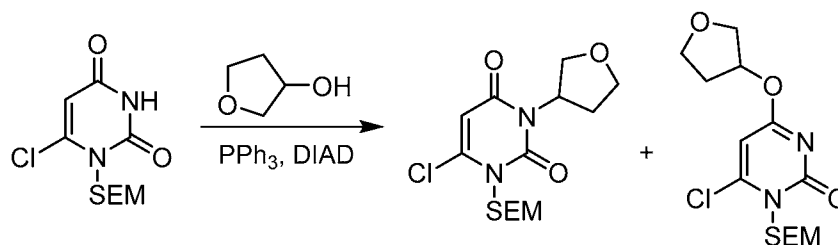
provide 18 mg (21%) of the title compound as an off-white solid. LC/MS: m/z (ES+) 346 (M+H)⁺. ¹H NMR (400 MHz, acetone-d₆) δ 8.90 (s, 1H), 7.15 (dd, J = 8.3, 8.1 Hz, 1H), 6.88 (s, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 6.15 (s, 1H), 4.74 (m, 1H), 4.48 (m, 1H), 4.35 (s, 1H), 3.82 (m, 2H), 3.68 (s, 3H), 3.2 (m, 2H), 2.55 (m, 2H) 1.44 (d, J = 6.6 Hz, 3H), 1.15 (m, 2H).

Example 11. Preparation of 6-(((S)-1-phenylethyl)amino)-3-(tetrahydrofuran-3-yl)pyrimidine-2,4(1H,3H)-dione.



[0099] Compound 11.1. 6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)pyrimidine-

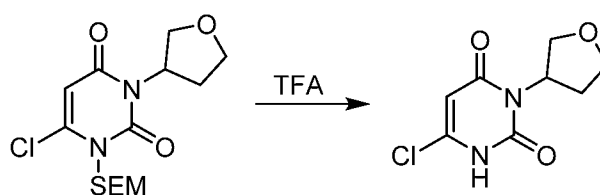
2,4(1H,3H)-dione. To a mixture of 6-chloro-uracil (3.0 g, 20.47 mmol, 1 equiv.) and LiBr (1.78 g, 20.5 mmol, 1.0 equiv.) in NMP (70 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.82 g, 20.5 mmol, 1.0 equiv.). The reaction mixture was stirred at 0 °C for 10 min, and 2-(trimethylsilyl)ethoxymethyl chloride (3.75g, 22.5 mmol, 1.1 equiv.) was slowly added via an addition funnel. The reaction mixture was stirred overnight at room temperature and then diluted with EtOAc (150 mL). The mixture was washed with a saturated aqueous NH₄Cl solution (50 mL), saturated aqueous NaHCO₃ (50 mL), and brine (50 mL). The organic layer was dried with anhydrous Na₂SO₄ and concentrated under reduced pressure to provide 3.2 g (57%) of the title compound as a white solid. LC/MS: m/z (ES+) 299 (M+Na)⁺. ¹H NMR (400 MHz, CDCl₃): δ ppm 9.00-8.80 (br-s, 1H), 5.95 (s, 1H), 5.45 (s, 2H), 3.63 (t, J = 7.0 Hz, 2H), 1.48 (t, J = 7.0 Hz, 2H), 0.01 (s, 9H).



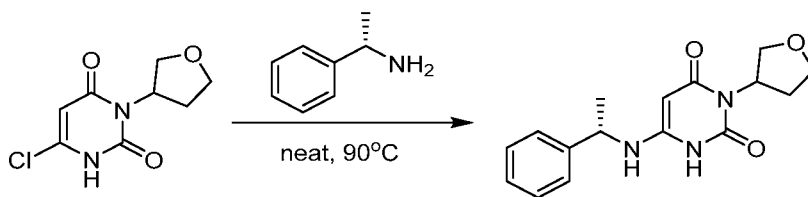
[0100] Compound 11.2. 6-chloro-3-(tetrahydrofuran-3-yl)-1-((2-

(trimethylsilyl)ethoxy)methyl)pyrimidine-2,4(1H,3H)-dione. To a solution of **11.1** (277 mg, 1.0 mmol, 1 equiv.), 3-hydroxytetrahydrofuran (106 mg, 1.2 mmol, 1.2 equiv.), and triphenylphosphine (320 mg, 1.2 mmol, 1.2 equiv.) in THF (7.5 mL) at 0 °C, was added

diisopropyl azodicarboxylate (0.240 g, 1.2 mmol, 1.2 equiv.) dropwise. The reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by preparative RP-HPLC (20-100% CH₃CN in H₂O with 0.1% formic acid buffer in 40 min. at 25 mL/min.) to provide 102 mg (29%) of the title compound. LC/MS: m/z (ES⁺) 347 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) δ 5.92 (s, 1H), 5.58 (m, 1H), 5.41(s, 2H), 4.20 (m, 1H), 4.00-3.85 (m, 3H), 3.65 (t, J = 7.0 Hz, 2H), 2.35-2.20 (m, 1H), 2.20-2.08 (m, 1H), 0.95 (t, 2H), 0.01 (s, 9H); ¹³C NMR (CDCl₃) δ 160.7, 150.7, 145.6, 102.0, 74.8, 68.7, 67.9, 67.5, 51.9, 28.7, 18.0, 0.0.

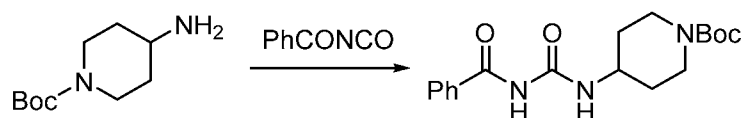


[0101] Compound 11.3. 6-chloro-3-(tetrahydrofuran-3-yl)pyrimidine-2,4(1H,3H)-dione. Compound **11.2** (0.50 g, 1.4 mmol, 1.0 equiv.) was dissolved in trifluoroacetic acid (1 mL). The reaction mixture was stirred at room temperature for 30 minutes and then was concentrated under reduced pressure. The resulting residue was purified by preparative RP-HPLC (10% CH₃CN in H₂O in 40 min. at 25 mL/min.) to provide 300 mg (96%) of the title compound as a white solid. LC/MS: m/z (ES⁺) 217 (M+H)⁺. ¹H NMR (400 MHz, DMSO-d₆): δ ppm 5.90 (s, 1H), 5.35 (m, 1H), 4.00 (m, 1H), 3.85-3.68 (m, 3H), 2.20 (m, 1H), 2.01 (m, 1H).

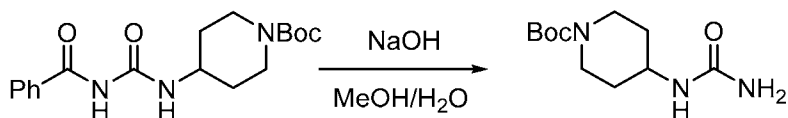


[0102] Compound 11. 6-(((S)-1-phenylethyl)amino)-3-(tetrahydrofuran-3-yl)pyrimidine-2,4(1H,3H)-dione. The title compound was prepared using a procedure similar to that used for the preparation of **9** except **11.3** (22 mg, 0.10 mmol, 1.00 equiv) was used in place of **9.3** to provide 15 mg (50%) of the title compound as a white solid. LC/MS: m/z (ES⁺) 302 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃): δ ppm 10.50 (1H), 7.50-7.20 (m, 5H), 5.90 (m, 1H), 5.60 (m, 1H), 4.78 (m, 1H), 4.45 (s, 1H), 4.20 (m, 1H), 4.05-3.90 (m, 2H), 3.90-3.80 (m, 1H), 2.45-2.10 (m, 2H), 1.55 (d, J = 6.7 Hz, 3H).

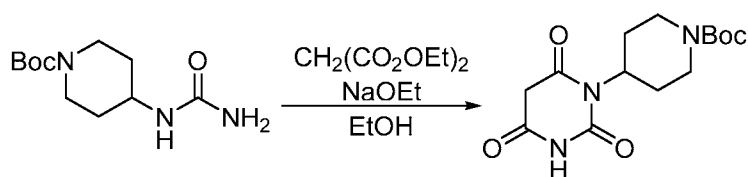
Example 12. Preparation of (*S*)-3-(1-(methylsulfonyl)piperidin-4-yl)-6-(1-phenylethylamino)pyrimidine-2,4(1*H*,3*H*)-dione.



[0103] Compound 12.1. tert-Butyl 4-(3-benzoylureido)piperidine-1-carboxylate. To a solution of benzoylisocyanate (4.8 g, 32.6 mmol) in CH₂Cl₂ (180 mL) at 0 °C was added 4-amino-1-N-boc-piperidine (6.0 g, 30 mmol). The reaction mixture was stirred at room temperature for 4 h and concentrated. The residue was treated with Et₂O (100 mL). The precipitate was filtered and washed with Et₂O to yield 5.70 g (55%) of the title compound as a white solid. LC/MS: *m/z* (ES⁺) 337 (M+H)⁺.

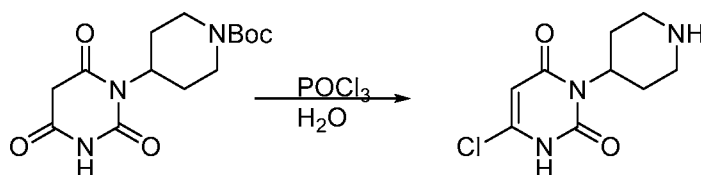


[0104] Compound 12.2. tert-Butyl 4-ureidopiperidine-1-carboxylate. To a mixture of **12.1** (5.60 g, 16.1 mmol) in CH₃OH (70 mL) and H₂O (70 mL) was added sodium hydroxide (11.6 g, 290 mmol) portionwise. The reaction mixture was stirred at room temperature overnight and then refluxed for 1 h. The mixture was cooled to room temperature and concentrated under reduced pressure to remove CH₃OH. The precipitate was filtered, washed with H₂O, and dried to yield 3.2 g (82%) of the title compound as a white solid. LC/MS: *m/z* (ES⁺) 266 (M+Na)⁺.

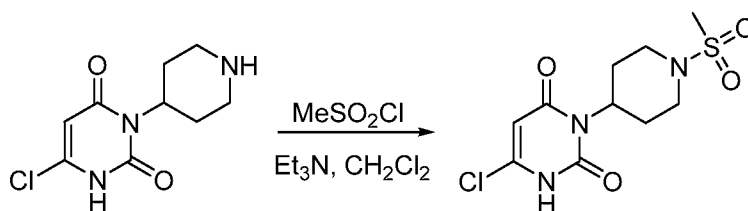


[0105] Compound 12.3. tert-Butyl 4-(2,4,6-trioxo-tetrahydropyrimidin-1(2*H*)-yl)piperidine-1-carboxylate. To a mixture of **12.2** (3.63 g, 14.9 mmol), diethylmalonate (2.6 mL, 16.5 mmol, 1.1 equiv.) and anhydrous ethanol (60 mL) was added NaOEt (21% in EtOH, 6.6 mL, 17.7 mmol, 1.2 equiv.). The mixture was refluxed for 14 h and concentrated. The residue was taken up in H₂O (15 mL) and washed with EtOAc (2 x 30 mL). The aqueous layer was separated and adjusted to pH=5 with concentrated. HCl. The precipitate was

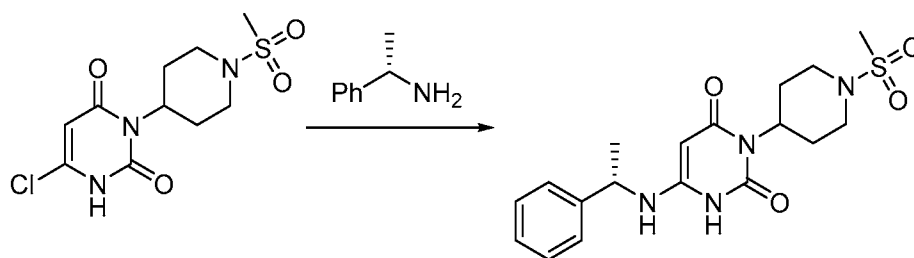
filtered, washed with H₂O and dried to give 3.70 g (80%) of the title compound as an off-white solid. LC/MS: m/z (ES⁺) 334 (M+Na)⁺.



- 5 [0106] **Compound 12.4. 6-chloro-3-(piperidin-4-yl)pyrimidine-2,4(1H,3H)-dione.** To a mixture of **12.3** (2.55 g, 8.19 mmol) and POCl₃ (10 mL, 100.65 mmol) was added H₂O (0.41 mL, 22.78 mmol) dropwise. The mixture was stirred at 120 °C for 30 min and then concentrated. The residue was carefully taken up in ice water (20 g). To the mixture was added K₂CO₃ (~8.0 g) portionwise until the pH was ~7. The precipitate was filtered, washed
10 with H₂O (20 mL) and EtOAc (50 mL). The resulting material was dried to yield 1.45 g (77%) of the title compound as an off-white solid. LC/MS: m/z (ES⁺) 230 (M+H)⁺.



- [0107] **Compound 12.5. 6-chloro-3-(1-(methylsulfonyl)piperidin-4-yl)pyrimidine-2,4(1H,3H)-dione.** To a mixture of **12.4** (380 mg, 1.65 mmol, 1.0 equiv.) and CH₂Cl₂ (8 mL) was added Et₃N (0.70 mL, 4.95 mmol, 3 equiv.) and methanesulfonyl chloride (0.23 mL, 2.5 mmol, 1.5 equiv.). The mixture was stirred at room temperature for 2 h and then quenched with H₂O (3 mL) to yield precipitate. The precipitate was filtered and washed with CH₂Cl₂ (3 x 3 mL). The filtrate was concentrated to ~1.5 mL. Filtration of a second precipitate was
20 followed by washing with H₂O (2 x 1 mL) and CH₂Cl₂ (3 x 2 mL). The precipitates were combined to afford 320 mg (63%) of the title compound as an off-white solid. LC/MS: m/z (ES⁺) 308 (M+H)⁺.

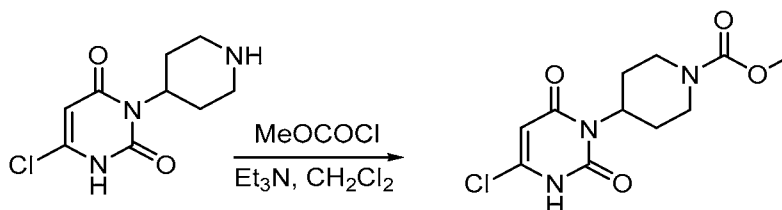


[0108] Compound 12. (S)-3-(1-(methylsulfonyl)piperidin-4-yl)-6-(1-

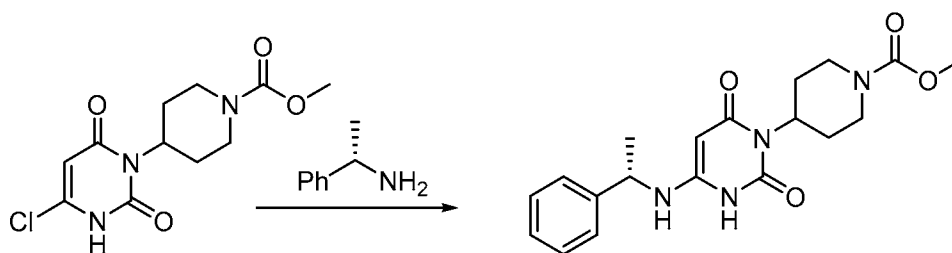
phenylethylamino)pyrimidine-2,4(1H,3H)-dione. A mixture of **12.5** (20 mg, 0.065 mmol) and (S)- α -methylbenzylamine (180 mg, 1.5 mmol, 23 equiv.) was stirred at 125 °C for 1 h.

- 5 The mixture was concentrated under reduced pressure, dissolved in CH₃OH and filtered. The filtrate was purified using preparative RP-HPLC eluting with linear gradient 20% to 100% CH₃CN in H₂O (0.1% formic acid buffer) over 40 min to give 16 mg (63%) of the title compound as an off-white solid. LC/MS: m/z (ES⁺) 393 (M+H)⁺. ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.40 (br s, 1H), 7.35-7.25 (m, 4H), 7.15 (m, 1H), 6.55 (s, 1H), 4.58 (m, 1H), 4.42 (m, 1H), 4.30 (s, 1H), 3.52 (m, 2H), 2.79 (s, 3H), 2.70 -2.62 (m, 2H), 2.50-2.48 (m, 10 2H), 1.48-1.38 (m, 2H), 1.32 (d, J = 6.8 Hz, 3H).

Example 13. Preparation of (S)-methyl 4-(2,6-dioxo-4-(1-phenylethylamino)-2,3-dihydropyrimidin-1(6H)-yl)piperidine-1-carboxylate.



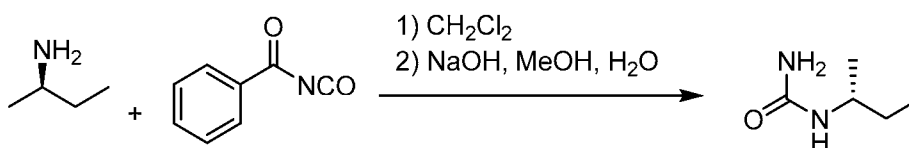
- 15 **[0109] Compound 13.1. Methyl 4-(4-chloro-2,6-dioxo-2,3-dihydropyrimidin-1(6H)-yl)piperidine-1-carboxylate.** To a mixture of **12.4** (115 mg, 0.5 mmol, 1.0 equiv.) and CH₂Cl₂ (2 mL) was added Et₃N (0.14 mL, 1.5 mmol, 3.0 equiv.), followed by methyl chloroformate (95 mg, 1.0 mmol, 2.0 equiv.). The mixture was stirred at room temperature for 1 h, diluted with CH₂Cl₂ (8 mL), washed with a saturated aqueous NaHCO₃ solution (1 20 mL), H₂O (1 mL), brine (1 mL), dried with anhydrous Na₂SO₄ and concentrated to yield 105 mg (73%) of an off-white solid. LC/MS: m/z (ES⁺) 288 (M+H)⁺.



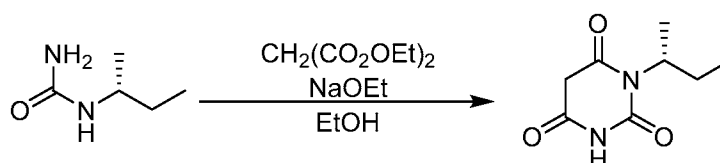
[0110] Compound 13. (S)-methyl 4-(2,6-dioxo-4-(1-phenylethylamino)-2,3-

dihydropyrimidin-1(6H)-yl)piperidine-1-carboxylate. A mixture of **13.1** (58 mg, 0.20 mmol) and (S)-α-methylbenzylamine (240 mg, 1.5 mmol) was stirred at 120 °C for 0.5 h. The title compound was prepared using a procedure similar to that used for the preparation of **9** to provide 40 mg (63%) of the title compound as an off-white solid. LC/MS: m/z (ES⁺) 373 (M+H)⁺. ¹H-NMR (400 MHz, CDCl₃): δ ppm 9.85 (s, 1H), 7.29-7.15 (m, 5H), 5.75 (br s, 1), 4.80 (m, 1H), 4.60 (s, 1H), 4.35 (m, 1H), 4.20 - 4.00 (m, 2H), 3.58 (s, 3H), 2.80 - 2.70 (m, 2H), 2.46 (m, 2H), 1.50 (m, 2H), 1.38 (d, J = 6.7 Hz, 3H).

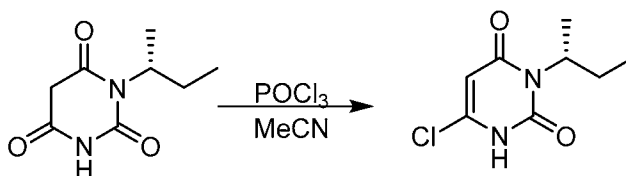
Example 14. Preparation of 3-(R)-sec-butyl-6-((S)-1-(3-methoxyphenyl)ethylamino)pyrimidine-2,4(1H,3H)-dione.



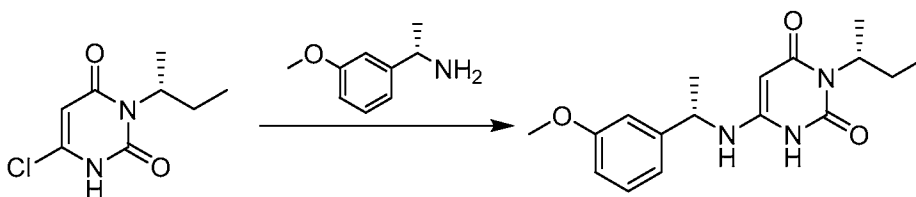
[0111] Compound 14.1. (R)-1-sec-butylurea. Benzoyl isocyanate (5.36 g, 36.5 mmol, 1.05 equiv.) was dissolved in CH₂Cl₂ (20 mL) and cooled to 0 °C in an ice bath. (R)-butan-2-amine (2.54 g, 34.7 mmol, 1 equiv.) in CH₂Cl₂ (10 mL) was carefully added while stirring. The mixture was allowed to stir for 3 h at room temperature. After the reaction was deemed complete, the mixture was concentrated. The residue was suspended in Et₂O (20 mL) and filtered. The solid was taken up in a 1:1 mixture of CH₃OH and H₂O (200 mL) followed by the addition of NaOH (6.9 g, 174 mmol, 5 equiv.). The reaction was stirred overnight at room temperature. The CH₃OH was evaporated from the solution and the resulting precipitate (1.66g, 39%) was collected. LC/MS: m/z (ES⁺) 117 (M+H)⁺.



[0112] **Compound 14.2. (R)-1-sec-butylpyrimidine-2,4,6(1H,3H,5H)-trione.** Compound 14.1 (1.66 g, 14.3 mmol, 1.0 equiv.) was dissolved in EtOH (10 mL), and diethyl malonate (1.8 mL, 15.7 mmol, 1.1 equiv.), and NaOEt (5.6 mL, 17.1 mmol, 1.2 equiv.) were added. The reaction was stirred at 80 °C for 2 h and then cooled to room temperature. Water (20 mL) was added and then EtOH was removed by evaporation. KHSO₄ (excess) was added to saturate the aqueous layer which was then extracted with EtOAc. The combined organics were dried with anhydrous MgSO₄ and concentrated to yield 1.6 g (61%) of the title compound as a crude residue which was used without further purification. LC/MS: m/z (ES-) 183 (M-H)⁻.



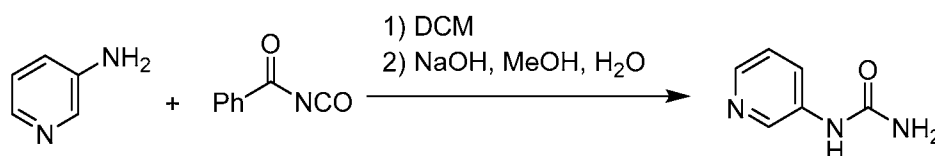
[0113] **Compound 14.3. (R)-3-sec-butyl-6-chloropyrimidine-2,4(1H,3H)-dione.** A mixture of 14.2 (1.6 g, 8.7 mmol, 1 equiv.) and POCl₃ (648 μL, 7.0 mmol, 0.8 equiv.) in CH₃CN (10 mL) was stirred at 90 °C for 2 h. Additional POCl₃ (0.8 equiv.) was added and stirred at 90 °C for 3 h. The reaction was cooled to room temperature, carefully quenched with CH₃OH (10 mL), stirred for 30 minutes and purified with normal phase HPLC 0-25% CH₃OH/CH₂Cl₂ followed by a CH₃OH flush. The product and starting material co-eluted. The mixture was concentrated, the residue was taken up in CH₃CN (10 mL) and POCl₃ (648 μL) was added. The reaction was stirred at 90 °C for 3 h and then cooled to room temperature. The reaction was carefully quenched with CH₃OH (10 mL) and stirred for 30 minutes. The reaction mixture was purified by normal phase HPLC with previous condition, concentrated and dried under vacuum to yield 450 mg (32%) of the title compound as an off-white solid. LC/MS: m/z (ES-) 201 (M-H)⁻.



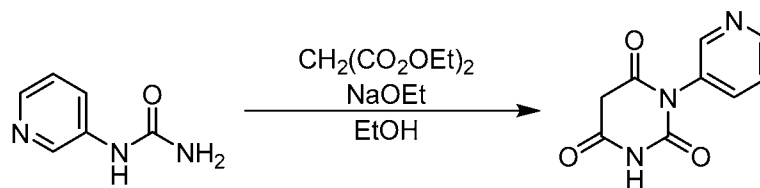
[0114] **Compound 14.3. (R)-3-sec-butyl-6-((S)-1-(3-methoxyphenyl)ethylamino)pyrimidine-2,4(1H,3H)-dione.** A mixture 14.3 (150 mg, 0.74

mmol, 1.0 equiv.) in neat (*S*)-1-(3-methoxyphenyl)ethanamine (400 μ L) was stirred overnight at 90 °C. The reaction was purified using preparative RP-HPLC on an Agilent system with a gradient of 0-40% CH₃CN in H₂O over 45 min to yield 13 mg (6%) of the title compound as an off-white solid. LC/MS: *m/z* (ES⁺) 318 (M+H)⁺. ¹H-NMR (400 MHz, DMSO-*d*₆): δ ppm
 9.79 (s, 1H), 7.28 (t, *J* = 8.1 Hz, 1H), 6.94-6.88 (m, 2H), 6.84 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.51
 (d, *J* = 6.4 Hz, 1H), 4.72-4.59 (m, 1H), 4.47 (m, 1H), 4.35 (s, 1H), 3.76 (s, 3H), 1.98-1.84 (m,
 1H), 1.61 (m, 1H), 1.39 (d, *J* = 6.7 Hz, 3H), 1.25 (d, *J* = 6.9 Hz, 3H), 0.70 (t, *J* = 7.4 Hz, 3H).

Example 15. Preparation of (*S*)-6-(1-phenylethylamino)-3-(pyridin-3-yl)pyrimidine-2,4(1H,3H)-dione.



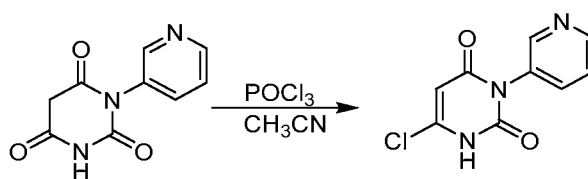
[0115] Compound 15.1. 1-(pyridin-3-yl)urea. Benzoyl isocyanate (3.28 g, 22.3 mmol, 1.05 equiv.) was taken up in CH₂Cl₂ (30 mL) and cooled to -10 °C. Pyridin-3-amine (2 g, 21.2 mmol, 1 equiv.) was added in portions while stirring. The mixture was allowed to stir for 3 h at room temperature. After the reaction was deemed complete, it was concentrated and then taken up in a 1:1 mixture of CH₃OH and H₂O (100 mL) followed by the addition of NaOH (4.25 g, 106.3 mmol, 5 equiv.). The reaction was allowed to stir overnight at room temperature, concentrated to dryness, and then azeotroped three times with toluene. A mixture of 10% CH₃OH in EtOAc (100mL) was added to the solid and stirred for 10 minutes followed by filtration. The solid was suspended and filtered two additional times. The combined filtrates were filtered once more to remove any solids that passed through the filter and concentrated. The residue was triturated with EtOAc (5 mL) and dried under vacuum to yield 3.5 g of crude material (off-white solid) that was utilized without further purification. LC/MS: *m/z* (ES⁺) 138 (M+H)⁺.



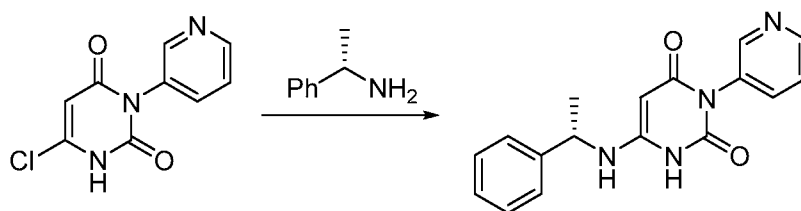
[0116] Compound 15.2. 1-(pyridin-3-yl)pyrimidine-2,4,6(1H,3H,5H)-trione.

Compound **15.1** (3.0 g, 21.8 mmol, 1.0 equiv.) was taken up in EtOH (20 mL), followed by

the addition of diethyl malonate (2.75 mL, 24.1 mmol, 1.1 equiv.), and NaOEt (8.5 mL, 26.3 mmol, 1.2 equiv.). The reaction was stirred at 85°C overnight and then cooled to room temperature. Water (100 mL) was added slowly followed by careful addition of sodium bicarbonate (8 g). The resulting mixture was washed three times with EtOAc. The aqueous layer was concentrated to 50 mL and CH₃OH (150 mL) was added. The precipitate was removed by filtration and the filtrate was concentrated. The resulting residue was purified by flash chromatography (silica gel, 0-25% CH₃OH/CH₂Cl₂) to yield 1.70 g (38%) of the title compound as a light yellowish solid. LC/MS: m/z (ES⁺) 206 (M+H)⁺.



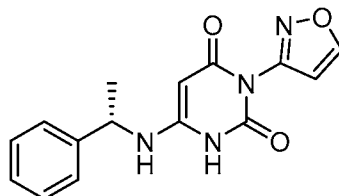
[0117] Compound 15.3. 6-chloro-3-(pyridin-3-yl)pyrimidine-2,4(1H,3H)-dione. A mixture of **15.2** (700 mg, 3.41 mmol, 1.0 equiv.) and POCl₃ (255 μ L, 2.7 mmol, 0.8 equiv.) in CH₃CN (10 mL) was stirred at 90 °C for 2 h. Additional POCl₃ (0.8 equiv) was added and stirring was continued at 90 °C for 2 h. Additional POCl₃ (1.6 equiv.) was added followed by the careful addition of H₂O (150 μ L, 2.5 equiv.) The reaction was stirred overnight at 90 °C. After cooling to room temperature, the mixture was filtered and the solid was carefully washed with CH₃OH (1 mL). Ethyl acetate (20 mL) was added to the filtrate and the resulting precipitate was collected by filtration and dried under vacuum to yield 230 mg (30%) of the title compound as a light yellowish solid. LC/MS: m/z (ES⁺) 224 (M+H)⁺.



[0118] Compound 15. (S)-6-(1-phenylethylamino)-3-(pyridin-3-yl)pyrimidine-2,4(1H,3H)-dione. A mixture of **15.3** (100 mg, 0.45 mmol, 1 equiv.) in neat (S)-(-)- α -methylbenzylamine (500 μ L) was stirred overnight at 100 °C. After cooling, the reaction was purified using preparative RP-HPLC on an Agilent system with a gradient of 0-40% CH₃CN in H₂O over 45 min., followed by a second purification on a preparatory TLC plate (2000 μ m) with 7% CH₃OH /CH₂Cl₂ to yield 39.5 mg (28%) of the title compound. LC/MS: m/z

(ES+) 309 (M+H)⁺. ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 11.15 (s, 1H), 8.49 (dd, J = 4.8, 1.4 Hz, 1H), 8.34 (d, J = 2.4 Hz, 1H), 7.65-7.58 (m, 1H), 7.44 (dd, J = 8.1, 4.8 Hz, 1H), 7.37 (m, 5H), 7.26 (m, 1H), 4.61-4.53 (m, 1H), 4.48 (s, 1H), 1.39 (d, J = 6.8 Hz, 3H).

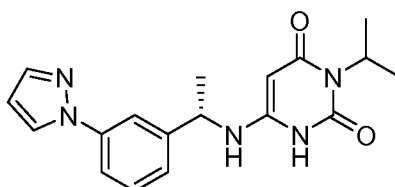
5 Example 16. Preparation of (S)-3-(Isoxazol-3-yl)-6-(1-phenylethylamino)pyrimidine-2,4(1H,3H)-dione (16).



[0119] The title compound was prepared using procedures similar to those used for the preparation of compound **15** except isoxazol-3-amine was used in place of pyridin-3-amine.

10 LC/MS: m/z (ES+) 299 (M+H)⁺. ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 8.96 (s, 1H), 7.38 (d, J = 3.9 Hz, 4H), 7.28 (dd, J = 8.4, 4.3 Hz, 2H), 7.10 (s, 1H), 6.63 (s, 1H), 4.74-4.52 (m, 1H), 4.48 (s, 1H), 1.44 (d, J = 6.6 Hz, 3H).

Example 17. Preparation of (S)-6-((1-(3-(1H-pyrazol-1-yl)phenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione (17).

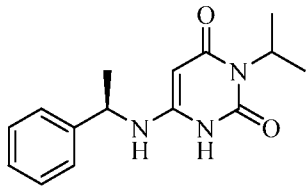
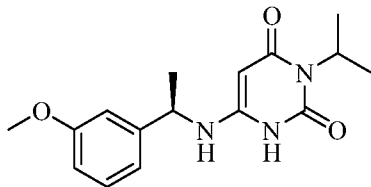
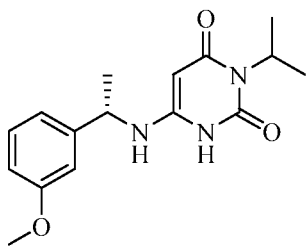
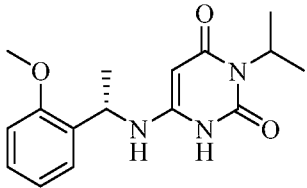
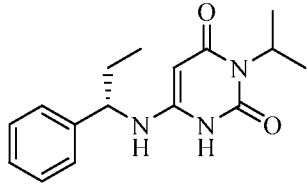


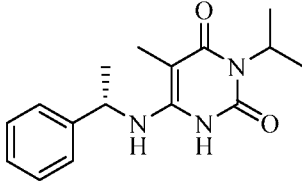
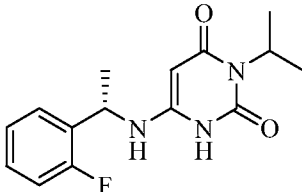
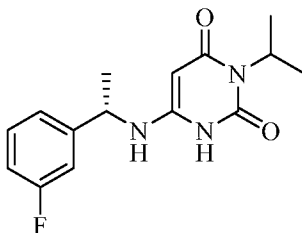
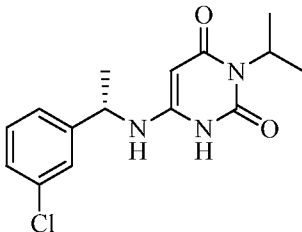
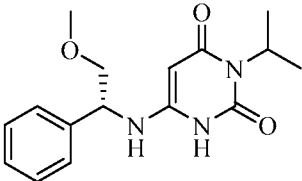
15 [0120] The title compound was prepared by Ullman coupling (P.E. Fanta. "The Ullmann Synthesis of Biaryls". *Synthesis*, 1974, 9-21) of **35** with 1H-pyrazole in the presence of copper iodide, cesium carbonate, and trans-N,N'-dimethylcyclohexane-1,2-diamine. LC/MS: m/z (ES+) 340 (M+H)⁺. ¹H-NMR (400 MHz, CD₃OD): δ ppm 8.26 (s, 1H), 7.70 (m, 2H),
20 7.66 (m, 1H), 7.51 (m, 1H), 7.34 (m, 1H), 6.55 (s, 1H), 5.05 (m, 1H), 4.62 (m, 1H), 1.58 (d, J = 6.8 Hz, 3H), 1.37 (m, 6H).

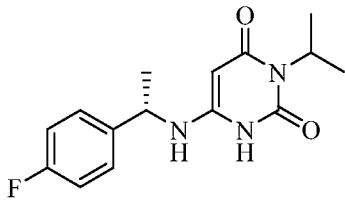
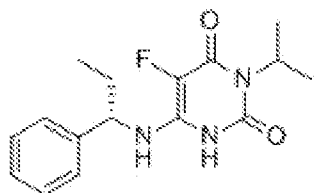
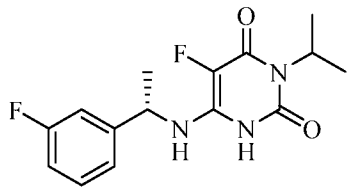
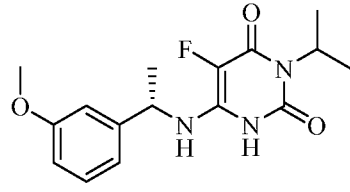
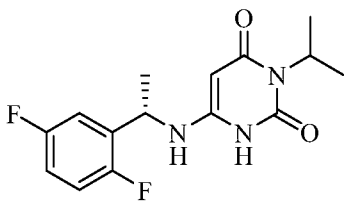
Example 18. Preparation of Additional Pyrimidine Dione Compounds.

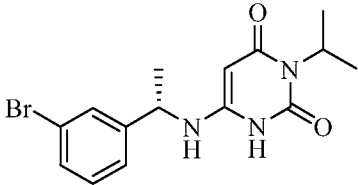
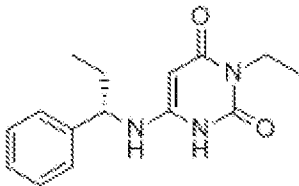
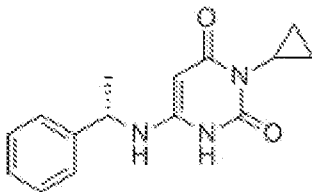
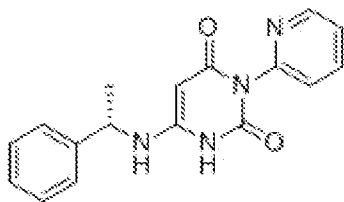
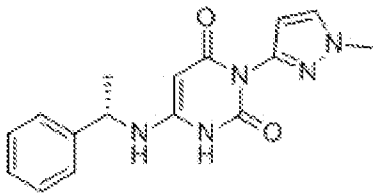
[0121] The compounds in Table 1 were prepared according to the examples as described above.

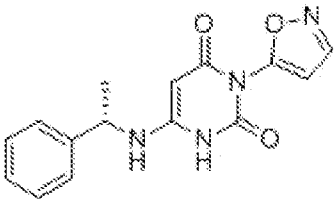
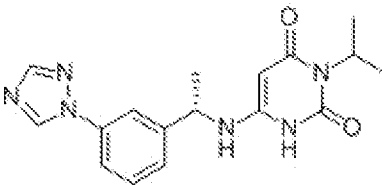
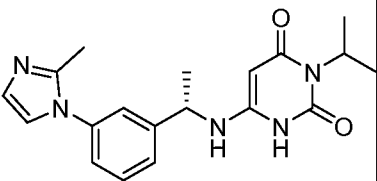
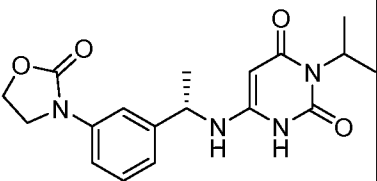
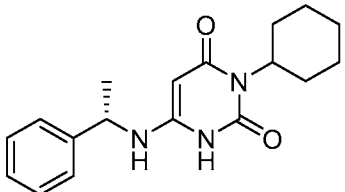
Table 1. Compounds and Analytical Data

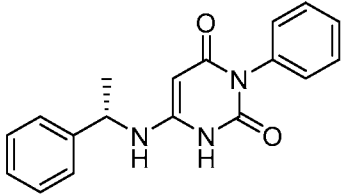
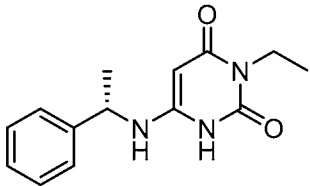
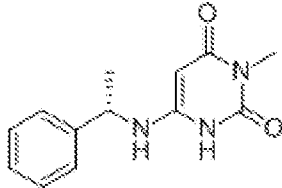
Structure	Compound No. ---- Ref. Example	Observed Mass and/or ¹ H NMR
	19R ---- 1	274 (M+H) ⁺ ¹ H-NMR (400 MHz, CD ₃ OD): δ ppm 7.42 - 7.22 (m, 5H), 5.06 - 4.94 (m, 1H), 4.49 (m, 1H), 1.49 (d, J = 7.0 Hz, 3H), 1.36 (m, 6H).
	20R ---- 1	304 (M+H) ⁺ ¹ H-NMR (400 MHz, CDCl ₃): δ ppm 10.39 (br s, 1H), 7.29 - 7.23 (m, 1H), 6.88 - 6.79 (m, 3H), 5.31 (br s, 1H), 5.09 (m, 1H), 4.78 (br s, 1H), 4.48 - 4.34 (m, 1H), 3.80 (s, 3H), 1.51 (d, J = 7.0 Hz, 3H), 1.44 - 1.38 (m, 6H).
	21 ---- 1	304 (M+H) ⁺ ¹ H-NMR (400 MHz, CD ₃ OD): δ ppm 7.26 (t, J = 7.9 Hz, 1H), 6.92 - 6.85 (m, 2H), 6.85 - 6.80 (m, 1H), 5.01 (m, 1H), 4.45 (d, J = 7.0 Hz, 1H), 3.79 (s, 3H), 1.48 (d, J = 7.0 Hz, 3H), 1.37 (d, J = 7.0 Hz, 6H).
	22 ---- 1	304 (M+H) ⁺ ¹ H-NMR (400 MHz, CD ₃ OD): δ ppm 7.29 - 7.17 (m, 1 H), 7.00 (d, J=7.4 Hz, 1 H), 6.93 (m, 1 H), 5.05 - 4.97 (m, 1 H), 4.83 (s, 1 H), 4.80 - 4.74 (m, 1 H), 3.89 (s, 3 H), 1.45 (d, J=6.7 Hz, 3 H), 1.38 - 1.34 (m, 6 H).
	24 ---- 1	288 (M+H) ⁺ ¹ H-NMR (400 MHz, DMSO-d ₆): δ ppm 9.76 (br s, 1H), 7.41 - 7.13 (m, 5H), 6.50 (d, J = 7.0 Hz, 1H), 4.88 (m, 1H), 4.31 (d, J = 2.4 Hz, 1H), 4.24 (m, 1H), 1.83 - 1.58 (m, 2H), 1.35 - 1.10 (m, 6H), 0.83 (m, 3H).

Structure	Compound No. ---- Ref. Example	Observed Mass and/or ¹ H NMR
	25 ---- 1	288 (M+H) ⁺ ¹ H-NMR (400 MHz, DMSO-d ₆): δ ppm 7.46 - 7.29 (m, 4H), 7.27 - 7.21 (m, 1H), 6.27 (d, J = 9.0 Hz, 1H), 6.08 (br s, 1H), 5.13 (m, 1H), 4.98 (m, 1H), 1.78 (s, 3H), 1.46 (m, 3H), 1.29 (m, 6H).
	26 ---- 1	292 (M+H) ⁺ ¹ H-NMR (400 MHz, CDCl ₃): δ ppm 10.45 (br s, 1H), 7.30 - 7.23 (m, 2H), 7.16 - 7.01 (m, 2H), 5.13 (dt, J = 13.8, 7.0 Hz, 1H), 4.99 (br s, 1H), 4.74 - 4.63 (m, 2H), 1.55 (d, J = 6.7 Hz, 3H), 1.43 (m, 6H).
	27 ---- 1	292 (M+H) ⁺ ¹ H-NMR (400 MHz, CDCl ₃): δ ppm 10.28 (br s, 1H), 7.36 - 7.28 (m, 1H), 7.06 (d, J = 7.8 Hz, 1H), 7.02 - 6.93 (m, 2H), 5.17 - 5.04 (m, 1H), 4.95 - 4.82 (m, 1H), 4.75 - 4.70 (m, 1H), 4.50 - 4.40 (m, 1H), 1.53 (d, J = 7.0 Hz, 3H), 1.46 - 1.37 (m, 6H).
	28 ---- 1	308 (M+H) ⁺ ¹ H NMR (400 MHz, CD ₃ OD): δ ppm 7.39 - 7.31 (m, 2H), 7.29 - 7.23 (m, 2H), 5.01 (m, 1H), 4.50 (q, J = 6.7 Hz, 1H), 1.48 (d, J = 7.0 Hz, 3H), 1.37 (d, J = 7.0 Hz, 6H).
	29 ---- 1	304 (M+H) ⁺ ¹ H NMR (400 MHz, CD ₃ OD): δ ppm 7.38-7.26 (m, 5H), 5.04-4.97 (m, 1H), 4.56 (dd, J = 7.4, 3.9Hz, 1H), 3.67-3.63 (m, 1H), 3.56-3.51 (m, 1H), 3.37 (s, 3H), 1.36 (m, 6H).

Structure	Compound No. --- Ref. Example	Observed Mass and/or ¹ H NMR
	30 --- 1	292 (M+H) ⁺ ¹ H-NMR (400 MHz, CD ₃ OD): δ ppm 7.34 (m, 2H), 7.08 (m, 2H), 5.07 - 4.95 (m, 1H), 4.50 (q, J = 6.8 Hz, 1H), 1.48 (d, J = 6.7 Hz, 3H), 1.37 (m, 6H).
	31 --- 4 & 5	306 (M+H) ⁺ ¹ H-NMR (400 MHz, CDCl ₃): δ ppm 9.70 (br s, 1H), 7.39 - 7.22 (m, 5H), 5.19 - 5.07 (m, 1H), 4.85 (br s, 1H), 4.73 - 4.61 (m, 1H), 1.88 (dq, J = 14.3, 7.0 Hz, 2H), 1.45 (m, 6H), 0.96 (t, J = 7.4 Hz, 3H).
	32 --- 4 & 5	310 (M+H) ⁺ ¹ H-NMR (400 MHz, CDCl ₃): δ ppm 9.89 (br s, 1 H), 7.40 - 7.29 (m, 1 H), 7.13 - 6.95 (m, 3 H), 5.12 (m, 1 H), 5.02 - 4.87 (m, 1 H), 4.82 - 4.69 (m, 1 H), 1.59 (d, J = 6.7 Hz, 3 H), 1.42 (m, 6 H),
	33 --- 4 & 5	322 (M+H) ⁺ ¹ H-NMR (400 MHz, CDCl ₃): δ ppm 9.50 (br s, 1H), 7.30 (dd, J = 9.00, 7.83 Hz, 1H), 6.93-6.90 (m, 3H), 5.19 - 5.04 (m, 1H), 4.88 (m, 1H), 4.75 (m, 1H), 3.79 (s, 3H), 1.59 (d, J = 6.7 Hz, 3H), 1.43 (d, J = 7.0 Hz, 6H).
	34 --- 6	310 (M+H) ⁺ ¹ H-NMR (300 MHz, DMSO-d ₆): δ ppm 9.74 (s, 1H), 7.32 - 7.24 (m, 2H), 7.21 - 7.13 (m, 1H), 6.60 (s, 1H), 4.95 - 4.86 (m, 1H), 4.69 - 4.62 (m, 1H), 4.32 (s, 1H), 1.49 - 1.42 (d, J = 6.6 Hz, 3H), 1.28 - 1.26 (d, J = 6.9 Hz, 6H).

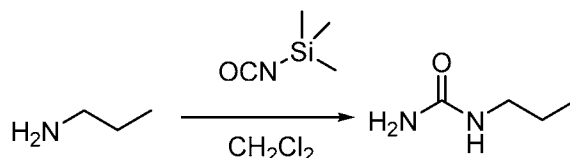
Structure	Compound No. --- Ref. Example	Observed Mass and/or ¹ H NMR
	35 --- 6	352 (M+H) ⁺ ¹ H-NMR (300 MHz, DMSO-d ₆): δ ppm 9.85 (s, 1H), 7.59 (s, 1H), 7.48 (m, 1H), 7.38 - 7.32 (m, 2H), 6.59 (d, J = 5.4 Hz, 1H), 4.95 - 4.88 (m, 1H), 4.57 - 4.50 (m, 1H), 4.36 (s, 1H), 1.41 (d, J = 6.6 Hz, 3H), 1.25 (d, J = 6.9 Hz, 6H).
	36 --- 1 & 5	274 (M+H) ⁺ ¹ H-NMR (300 MHz, DMSO-d ₆): δ ppm 9.96 (br s, 1H), 7.39-7.24 (m, 5H), 6.58 (d, J = 6.6 Hz, 1H), 4.38 (s, 1H), 4.28 (q, J = 6.9 Hz, 1H), 3.65 (q, J = 6.6 Hz, 2H), 1.78-1.66 (m, 2H), 0.99 (t, J = 6.9 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H).
	37 --- 1 & 5	272 (M+H) ⁺ ¹ H-NMR (400 MHz, DMSO-d ₆): δ ppm 9.83 (s, 1H), 7.37 (m, 4H), 7.26 (m, 1H), 6.52 (m, 1H), 4.50 (m, 1H), 4.33 (s, 1H), 2.37 (m, 1H), 1.41 (d, J = 6.8 Hz, 3H), 0.85 (m, 2H), 0.60 (m, 2H).
	38 --- 15	309 (M+H) ⁺ ¹ H-NMR (400 MHz, DMSO-d ₆): δ ppm 10.92 (s, 1H), 8.57 - 8.42 (m, 1H), 7.85 (ddd, J = 7.8, 7.8, 1.7 Hz, 1H), 7.46 - 7.31 (m, 5H), 7.32 - 7.19 (m, 2H), 7.13 (m, 1H), 4.67 - 4.52 (m, 1H), 4.41 (s, 1H), 1.39 (d, J = 6.8 Hz, 3H).
	39 --- 15	312 (M+H) ⁺ ¹ H-NMR (400 MHz, DMSO-d ₆): δ ppm 7.65 (d, J = 2.2 Hz, 1H), 7.41 - 7.35 (m, 5H), 7.32 - 7.24 (m, 1H), 6.77 (d, J = 5.9 Hz, 1H), 6.04 (d, J = 2.1 Hz, 1H), 4.63 - 4.55 (m, 1H), 4.42 (s, 1H), 3.79 (s, 3H), 1.44 (d, J = 6.7 Hz, 3H).

Structure	Compound No. ---- Ref. Example	Observed Mass and/or ¹ H NMR
	40 ---- 15	299 (M+H) ⁺ ¹ H-NMR (400 MHz, DMSO-d ₆): δ ppm 11.07 (s, 1H), 8.93 (s, 1H), 7.43 – 7.31 (m, 4H), 7.31 – 7.04 (m, 2H), 6.59 (s, 1H), 4.62 (m, 1H), 4.43 (s, 1H), 1.40 (d, J = 6.7 Hz, 3H).
	41 ---- 17	341 (M+H) ⁺ ¹ H-NMR (400 MHz, CDCl ₃): δ ppm 10.42 (s, 1H), 8.67 (s, 1H), 8.13 (s, 1H), 7.71 (s, 1H), 7.61 (m, 1H), 7.51 (m, 1H), 7.37 (m, 1H), 5.41 (m, 1H), 5.13 (m, 1H), 4.68 (m, 1H), 4.55 (m, 1H), 1.59 (d, J = 6.8 Hz, 3H), 1.44 (m, 6H).
	42 ---- 17	354 (M+H) ⁺ ¹ H-NMR (400 MHz, DMSO-d ₆): δ ppm 9.85 (s, 1H), 7.52 (m, 1H), 7.39 (m, 2H), 7.34 (m, 2H), 6.94 (m, 1H), 6.60 (m, 1H), 4.90 (m, 1H), 4.62 (m, 1H), 4.38 (s, 1H), 2.26 (s, 3H), 1.44 (d, J = 9.2 Hz, 3H), 1.28 (d, J = 9.2 Hz, 6H).
	43 ---- 17	359 (M+H) ⁺ ¹ H-NMR (400 MHz, DMSO-d ₆): δ ppm 9.84 (s, 1H), 7.62 (s, 1H), 7.42 (m, 2H), 7.12 (d, J = 7.2 Hz, 1H), 6.61 (bs, 1H), 4.91 (m, 1H), 4.69 – 4.43 (m, 3H), 4.34 (s, 1H), 4.09 (m, 2H), 1.42 (d, J = 6.8 Hz, 3H), 1.28 (m, 6H).
	44 ---- 15	314 (M+H) ⁺ ¹ H-NMR (400 MHz, CD ₃ OD): δ ppm 7.28 - 7.13 (m, 5H), 4.52 (m, 1H), 4.39 (m, 2H), 2.22 (m, 2H), 1.69 (m, 2H), 1.54 (m, 1H), 1.44-1.40 (m, 2H), 1.40 (d, J = 6.7 Hz, 3H), 1.30 - 1.20 (m, 2H), 1.20 - 1.08 (m, 1H).

Structure	Compound No. ---- Ref. Example	Observed Mass and/or ¹ H NMR
	45 ---- 15	308 (M+H) ⁺ ¹ H-NMR (400 MHz, CDCl ₃): δ ppm 9.84 (s, 1H), 7.43 - 7.17 (m, 6H), 7.12 (d, J = 7.3 Hz, 2H), 7.05 (d, J = 6.8 Hz, 2H), 5.55 (br s, 1H), 4.68 (s, 1H), 4.25 (m, 1H), 1.18 (d, J = 6.7 Hz, 3H).
	46 ---- 15	260 (M+H) ⁺ ¹ H-NMR (400 MHz, CD ₃ OD): δ ppm 7.37 - 7.30 (m, 4H), 7.10 - 7.06 (m, 1H), 4.55 (s, 1H), 4.51 (q, J = 6.7 Hz, 1H), 3.81 (q, J = 7.0 Hz, 2H), 1.50 (d, J = 7.0 Hz, 3H), 1.11 (t, J = 7.0 Hz, 3H).
	47 ---- 15	246 (M+H) ⁺ ¹ H-NMR (400 MHz, DMSO-d ₆): δ ppm 10.02 (s, 1H), 7.38 - 7.30 (m, 4H), 7.26 - 7.22 (m, 1H), 6.56 (s, 1H), 4.52 (q, J = 6.7 Hz, 1H), 4.39 (s, 1H), 2.97 (s, 3H), 1.40 (d, J = 6.7 Hz, 3H).

Example 48. Preparation of (S)-6-((1-phenylethyl)amino)-3-propylpyrimidine-2,4(1H,3H)-dione.

5

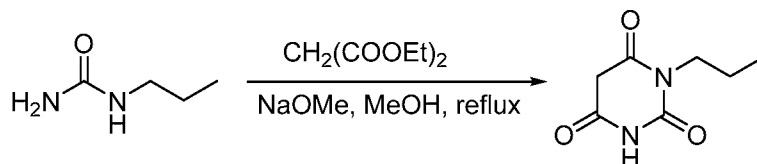


[0122] Compound 48.1. 1-propylurea. To a stirred solution of n-propylamine (2.15 g, 36.5 mmol, 1.00 equiv) in CH₂Cl₂ (35 mL) at 0 °C was added dropwise trimethylsilyl isocyanate (4.94 g (85% purity), 36.5 mmol, 1.00 equiv). The reaction mixture was stirred at room temperature for 72 h and was then cooled to 0 °C. The chilled mixture was quenched

10

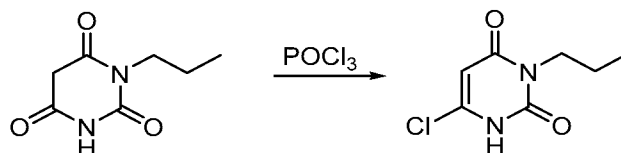
by the dropwise addition of CH₃OH (10 mL) and was concentrated under reduced pressure. The resulting solid was suspended in Et₂O (30 mL) and was filtered. The solid was further washed with Et₂O (30 mL) and dried to afford 2.0 g (38%) of the title compound as a white solid.

5



[0123] **Compound 48.2. 1-propylpyrimidine-2,4,6(1H,3H,5H)-trione.** To **48.1** (600 mg, 5.88 mmol, 1.00 equiv) in CH₃OH (1 mL) was added diethyl malonate (960 mg, 6.0 mmol, 1.02 equiv.) and sodium methoxide (1 mL, 25% NaOCH₃ in CH₃OH by weight). The reaction mixture was heated in the microwave reactor at 130 °C for 1 h. The mixture was cooled and the mixture was carefully adjusted to pH=3 with concentrated HCl. The volatiles were removed and H₂O was added (10 mL). Solid precipitated and was filtered. It was further washed with additional H₂O (10 mL) and dried to afford 560 mg (56%) of title compound as a white solid.

15



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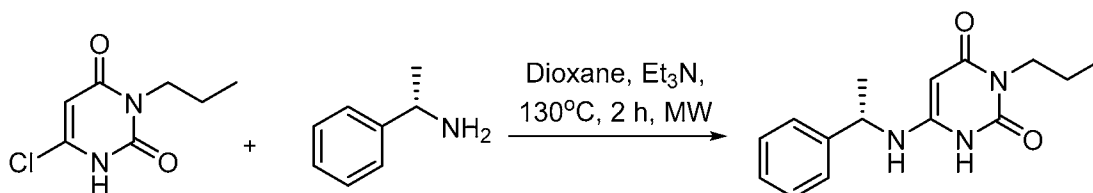
[0124] **Compound 48.3. 6-chloro-3-propylpyrimidine-2,4(1H,3H)-dione.** Compound **48.2** (560 mg, 3.30 mmol) and POCl₃ (2 mL) were added to a heavy wall pressure vessel which was subsequently sealed. The resulting solution was heated to 70 °C and stirred for 50 minutes behind a blast shield. The reaction mixture was cooled and concentrated under reduced pressure. To the resulting residue was added CH₂Cl₂ (30 mL) which was then removed under reduced pressure. The addition and evaporation of CH₂Cl₂ (30 mL) was conducted one additional time and then the resulting residue was diluted with CH₂Cl₂ (50 mL). To the organic layer was carefully added a saturated aqueous NaHCO₃ solution (50 mL). The layers were separated and the organics were further washed with H₂O (30 mL) and brine (30 mL). The organic layer was concentrated and purified by flash column

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chromatography (silica gel, utilizing 10% EtOAc in CH₂Cl₂) to afford 160 mg (26%) of the title compound as a white solid.

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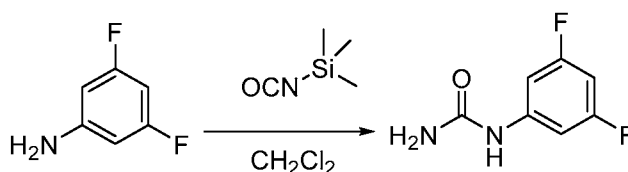


[0125] Compound 48.3. (S)-6-((1-phenylethyl)amino)-3-propylpyrimidine-2,4(1H,3H)-dione. To **48.3** (160 mg, 0.85 mmol, 1.0 equiv.) in 1,4-dioxane (1.5 mL) was added Et₃N

(200 μ L) and (*S*)- α -methylbenzylamine (235 mg, 1.94 mmol, 2.3 equiv.). The mixture was heated in a microwave reactor at 130 °C for 2 h. The mixture was cooled and concentrated. The resulting residue was treated with an 8:3 mixture of H₂O:CH₃CN which resulted in precipitation. The solid was filtered and successively washed with H₂O (10 mL) and EtOAc (10 mL). The solid was dried to give 67 mg (29%) of the title compound as a white solid.

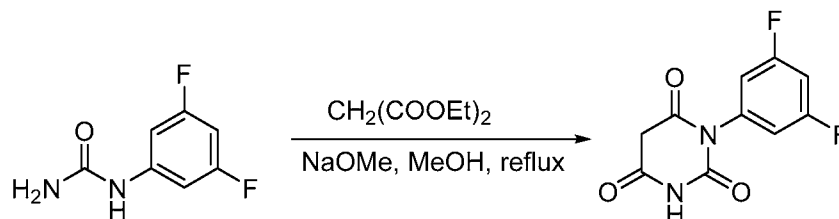
LC/MS: *m/z* (ES+) 274 (M+H)⁺. ¹H-NMR (400 MHz, DMSO-*d*₆): δ ppm 9.92 (br s, 1H), 7.36-7.22 (m, 5H), 6.54 (d, *J* = 7.0 Hz, 1H), 4.50 (quin, *J* = 6.7 Hz, 1H), 4.35 (s, 1H), 3.54 (dd, *J* = 8.0, 6.9 Hz, 2H), 1.42-1.36 (m, 5H), 0.76 (t, *J* = 7.6 Hz, 3H).

Example 49. Preparation of (*S*)-3-(3,5-difluorophenyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione.



[0126] Compound 49.1. 1-(3,5-difluorophenyl)urea. To a stirred solution of 3,5-difluoroaniline (4.0 g, 31 mmol, 1.00 equiv) in CH₂Cl₂ (50 mL) under argon at room temperature was added dropwise trimethylsilyl isocyanate (3.56 g, 30.90 mmol, 1.00 equiv). The reaction mixture was stirred overnight and quenched by the dropwise addition of CH₃OH (50 mL). The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by flash chromatography (silica gel, eluting with CHCl₃/CH₃OH (10:1 to

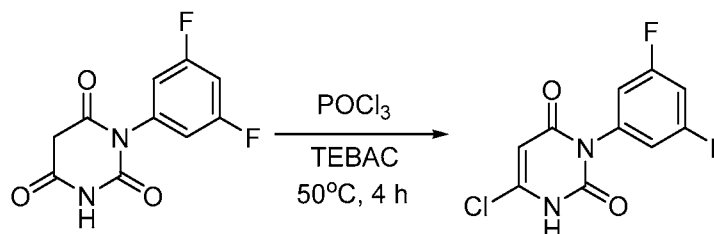
7:1)) to yield 2.0 g (38%) of the title compound as a white solid. $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ ppm 8.96 (s, 1H), 7.16-7.10 (m, 2H), 6.72-6.66 (m, 1H), 6.07 (br s, 2H).



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[0127] **Compound 49.2. 1-(3,5-difluorophenyl)pyrimidine-2,4,6(1H,3H,5H)-trione.** To a stirred solution of **49.1** (1.6 g, 0.0093 mol, 1.1 equiv) in CH_3OH (20 mL) were added diethyl malonate (1.4 g, 0.0087 mol, 1.0 equiv) and sodium methoxide (1.25 g, 0.0231 mol, 2.7 equiv). The resulting mixture was stirred overnight at 65 °C. After cooling to ambient temperature, the pH was carefully adjusted to 5 using aqueous 1N HCl. The resulting solution was extracted with EtOAc (3 x 50 mL). The organic layers were combined and concentrated under reduced pressure. The residue was washed with CH_3OH (50 mL) and the resulting solid was isolated by filtration to give 700 mg (31%) of the title compound as a white solid. $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ ppm 11.66 (s, 1H), 7.43-7.35 (m, 1H), 7.11-7.08 (m, 2H), 3.77 (s, 2H).

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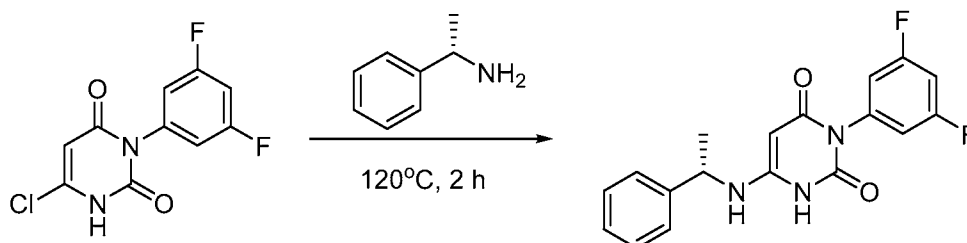
[0128] **Compound 49.3. 6-chloro-3-(3,5-difluorophenyl)pyrimidine-2,4(1H,3H)-dione.**

To a 25-mL round-bottom flask under argon containing **49.2** (740 mg, 3.08 mmol, 1.00 equiv) were added triethylbenzylammonium chloride (840 mg, 1.20 equiv) and POCl_3 (3 mL). The resulting solution was stirred for 4 h at 50 °C. The reaction cooled and quenched by the careful addition of water/ice (20 mL). The pH of the solution was adjusted to 5 with 2N sodium hydroxide. The resulting solution was extracted with EtOAc (2 x 10 mL) and the organic layers were combined. The organic layer was washed with brine (10 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. This resulted in 500

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mg (crude) of the title compound as a white solid. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ ppm 12.60 (br, 1H), 7.38-7.32 (m, 1H), 7.21-7.16 (m, 2H), 6.05 (s, 1H).



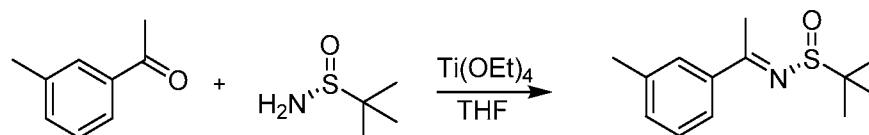
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[0129] Compound 49. (S)-3-(3,5-difluorophenyl)-6-((1-phenylethyl)amino)pyrimidine-

2,4(1H,3H)-dione. To **49.3** (200 mg, 0.77 mmol) was added (*S*)- α -methylbenzylamine (1.5 mL). The resulting solution was stirred for 2 h at 120 °C. The reaction mixture was diluted

with DMF (3 mL) and the crude product (100 mg) was purified by preparative RP-HPLC with the following conditions: XBridge Prep C18 OBD Column, 5 μ m, 19*150mm; mobile phase, H_2O with 0.05%TFA and CH_3CN (40.0% CH_3CN to 90.0% in 10 min). This resulted in 21.6 mg (8%) of the title compound as a white solid. LC/MS: m/z (ES $^+$) 344 ($\text{M}+\text{H}$) $^+$. $^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ ppm 10.25 (br s, 1H), 7.38-7.35 (m, 4H), 7.28-7.21 (m, 2H), 7.03-6.98 (m, 2H), 6.76 (d, J = 6.9 Hz, 1H), 4.59 (quin, J = 6.7 Hz, 1H), 4.50 (d, J = 2.0 Hz, 1H), 1.42 (d, J = 6.7 Hz, 3H).

Example 50. Preparation of (*S*)-3-isopropyl-6-((1-(*m*-tolyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione.

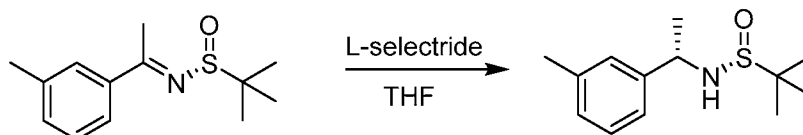


[0130] Compound 50.1. (R,E)-2-methyl-N-(1-(*m*-tolyl)ethylidene)propane-2-

sulfonamide. To a stirred solution of 1-(3-methylphenyl)ethanone (1.61 g, 12.0 mmol, 1.00 equiv.) and (*R*)-(+)-2-methyl-2-propanesulfonamide (1.94 g, 14 mmol, 1.33 equiv.) in THF (50 mL) was added $\text{Ti}(\text{OEt})_4$ (3.19 g, 14 mmol, 1.17 equiv.) dropwise. The reaction mixture was stirred for 16 h at 60 °C, cooled to room temperature, and quenched with a saturated aqueous NaHCO_3 solution (50 mL). The layers were separated and the aqueous layer was

further extracted with EtOAc (2 x 100 mL). The combined organics were concentrated and the resulting residue was purified by flash chromatography (silica gel, eluting with 0-5% CH₃OH in CH₂Cl₂) to afford 1.51 g (53%) of the title compound as a white solid. LC/MS: m/z (ES⁺) 238 (M+H)⁺.

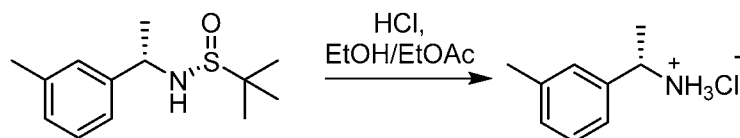
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10 **[0131] Compound 50.2. (R)-2-methyl-N-((S)-1-(m-tolyl)ethyl)propane-2-sulfonamide.**

To a solution of **50.1** (1.51 g, 6.37 mmol) in THF (30 mL) at -78 °C under an N₂ atmosphere was added L-selectride (dropwise, 10 mL, 1.0 M in THF, 10 mmol). The reaction mixture was warmed to 0 °C, stirred for 1 h, and carefully quenched with a saturated aqueous NH₄Cl solution (30 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (2 x 50mL). The combined organics were concentrated and the resulting residue was purified by flash chromatography (silica gel, eluted with 0-5% CH₃OH in CH₂Cl₂) to afford 0.85 g (56%) of the title compound. LC/MS: m/z (ES⁺) 240 (M+H)⁺.

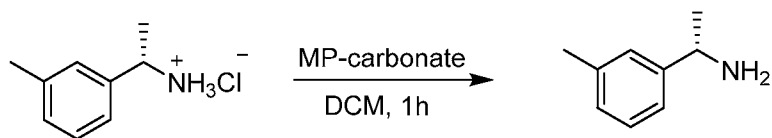
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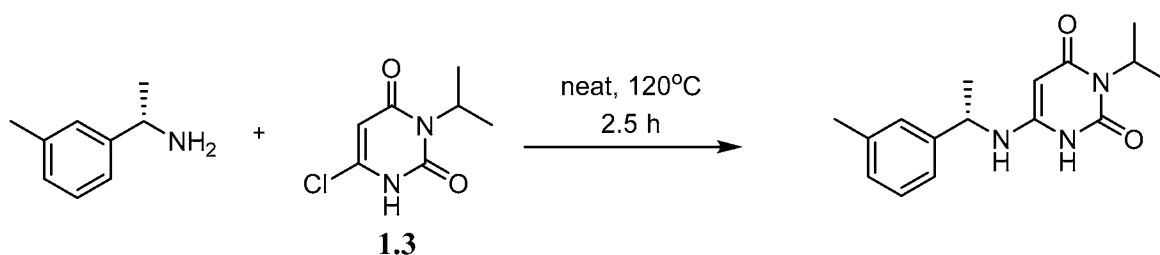
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[0132] Compound 50.3. (S)-1-(m-tolyl)ethan-1-amine hydrochloride. To absolute EtOH (10 mL) was added AcCl (1.5 mL, dropwise). The mixture was stirred for 10 minutes and then was added to **50.2** (0.85 g, 3.56 mmol) in EtOH (3 mL). The reaction mixture was stirred for 2 h at ambient temperature and was concentrated. The resulting solid was suspended in Et₂O and filtered. The solid was washed with additional Et₂O and dried to give 402 mg (66%) of the title compound as white solid. LC/MS: m/z (ES⁺) 136 (M+H)⁺.

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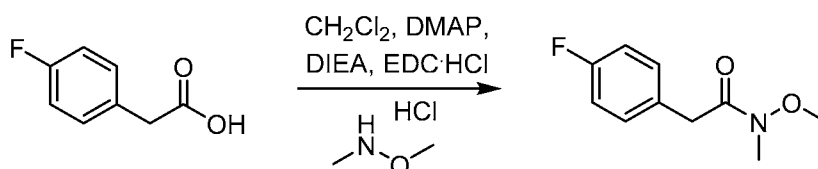
[0133] **Compound 50.4. (S)-1-(m-tolyl)ethan-1-amine.** To a stirred solution of **50.3** (205 mg, 1.20 mmol) in CH₂Cl₂ (10 mL) was added MP-carbonate (1.0g, 3.18 mmol/g). The reaction mixture was stirred at room temperature for 1 h and was then filtered. The solid beads were washed with an additional 10 mL CH₂Cl₂ and the combined filtrates were concentrated to give the title compound which was pushed forward without any purification.



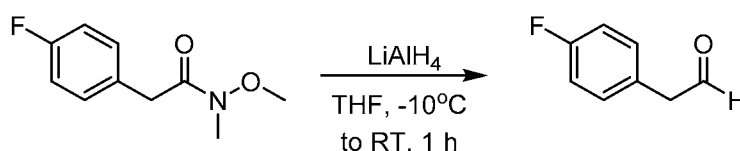
[0134] **Compound 50. (S)-3-isopropyl-6-((1-(m-tolyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione.** To **50.4** (presumed ~1.2 mmol from previous reaction, 2.0 equiv.) in a 0.5 to 2.0 mL microwave tube was added compound **1.3** (110 mg, 0.59 mmol, 1.0 equiv.). The microwave tube was sealed and heated at 120 °C behind a blast shield for 2.5 h. Upon cooling (to ~60 °C), NMP (2.5 mL) was added to the reaction mixture. The mixture was sonicated and heated (to ~60 °C) until the solid completely dissolved. The resulting solution was cooled to 40 °C and a 3:1 mixture of H₂O/CH₃CN (5 mL) was added. A solid precipitated and was collected through filtration. The light beige solid was subsequently washed with H₂O and dried to give 97 mg (57%) of the title compound as a white solid.

LC/MS: m/z (ES⁺) 288 (M+H)⁺. ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.73 (br s, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.12-7.04 (m, 3H), 6.45 (d, J = 8.0 Hz, 1H), 4.90-4.86 (m, 1H), 4.42 (q, J = 6.7 Hz, 1H), 4.31 (d, J = 2.4 Hz, 1H), 2.29 (s, 3H), 1.36 (d, J = 6.7 Hz, 3H), 1.27-1.23 (m, 6H).

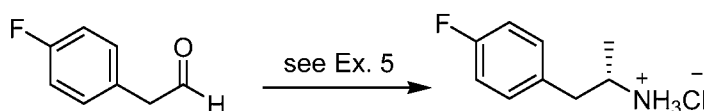
Example 51. Preparation of (S)-6-((1-(4-fluorophenyl)propan-2-yl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione.



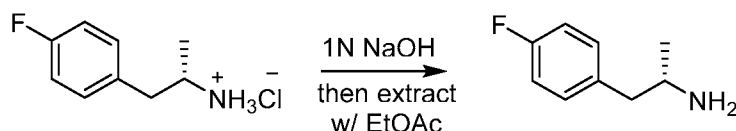
[0135] Compound 51.1. 2-(4-fluorophenyl)-N-methoxy-N-methylacetamide. To a stirred solution of 2-(4-fluorophenyl)acetic acid (15 g, 97.32 mmol, 1.00 equiv) in CH_2Cl_2 (300 mL) was added methoxy(methyl)amine hydrochloride (11.1 g, 113.79 mmol, 1.20 equiv), 4-dimethylaminopyridine (12 g, 98.22 mmol, 1.00 equiv), 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (28.2 g, 147.10 mmol, 1.50 equiv), and DIEA (37.5 g, 290.14 mmol, 3.00 equiv). The resulting solution was stirred at room temperature for 16 h and then diluted with EtOAc (150 mL). The organics were washed with aqueous 1N HCl (2 x 150 mL) and brine (2 x 150 mL). It was then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography (silica gel, eluting with EtOAc/petroleum ether (1:3)). This resulted in 18 g (88%) of the title compound as yellow oil. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ ppm 7.29-7.25 (m, 2H), 7.03-6.99 (m, 2H), 3.75 (s, 2H), 3.65 (s, 3H), 3.21 (s, 3H).



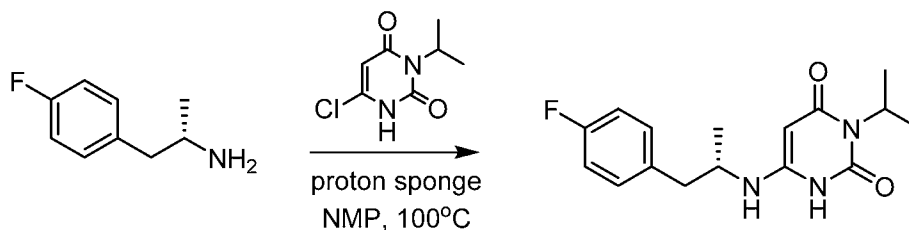
[0136] Compound 51.2. 2-(4-fluorophenyl)acetaldehyde. To a stirred solution of **51.1** (3 g, 15.21 mmol, 1.00 equiv) in THF (60 mL) under argon at -10°C was added LiAlH_4 (1.15 g, 30.30 mmol, 2.00 equiv) in several batches (*CAREFUL... EXOTHERMIC REACTION*). The resulting solution was stirred for 1 h at room temperature before being cooled to -10°C . The reaction was then quenched by the careful addition of a saturated aqueous NH_4Cl solution (50 mL). The resulting solid was filtered and the filtrate was extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give 2.5 g (crude) of the title compound as a yellow oil.



[0137] **Compound 51.3. (*S*)-1-(4-fluorophenyl)propan-2-amine hydrochloride.** The title compound was synthesized according to methods described for the preparation of **5.3**,
 5 utilizing **51.2** in place of 3,5-difluorobenzaldehyde. LC/MS: m/z (ES⁺) 154 (M+H)⁺.

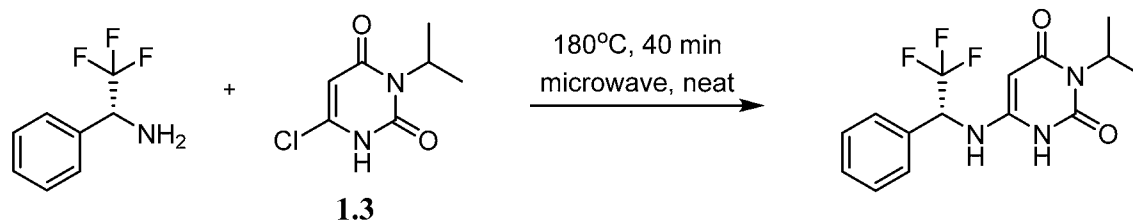


[0138] **Compound 51.4. (*S*)-1-(4-fluorophenyl)propan-2-amine.** To an aqueous solution of 1N NaOH (5 mL) was added **51.3** (300 mg, 1.59 mmol). The resulting mixture
 10 was stirred for one hour at 25 °C. The resulting solution was extracted with EtOAc (2 x 10 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield 160 mg (65%) of the title compound. LC/MS: m/z (ES⁺) 154 (M+H)⁺.



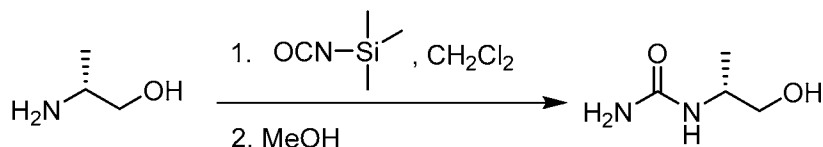
[0139] **Compound 51. (*S*)-6-((1-(4-fluorophenyl)propan-2-yl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione.** To a stirred solution of **51.4** (160 mg, 1.04 mmol, 2.00 equiv) in NMP (0.5 mL) was added **1.3** (99 mg, 0.52 mmol, 1.00 equiv) and proton
 20 sponge (168 mg, 0.78 mmol, 1.50 equiv). The resulting solution was stirred for 5 h at 100 °C in an oil bath. The reaction mixture was concentrated under reduced pressure. The residue (100 mg) was purified by preparative RP-HPLC to afford 30 mg (19%) of the title compound as gray solid. LC/MS: m/z (ES⁺) 306 (M+H)⁺. ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.81 (br s, 1H), 7.27 (dd, J = 8.8, 5.6 Hz, 2H), 7.17-7.12 (m, 2H), 5.89 (d, J = 7.6 Hz, 1H), 5.00-
 25 4.92 (m, 1H), 4.58 (s, 1H), 3.69-3.65 (m, 1H), 2.74 (d, J = 6.4 Hz, 2H), 1.31 (d, J = 6.8 Hz, 6H), 1.08 (d, J = 6.4 Hz, 3H).

Example 52. Preparation of (*R*)-3-isopropyl-6-((2,2,2-trifluoro-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione (**52**).

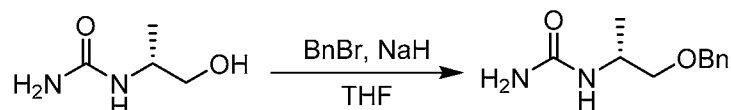


[0140] To a 0.2-0.5 mL microwave vial was added **1.3** (85 mg, 0.45 mmol) and (R)-2,2,2-trifluoro-1-phenylethan-1-amine (200 μ L, excess). The reaction mixture sealed and heated at 180 °C in a microwave reactor for 40 minutes. The reaction mixture was cooled to ambient temperature and then NMP (1 mL) was added to completely dissolve the solid. Next, a 2:1 H₂O/CH₃CN mixture (6 mL) was added which resulted in precipitation. The solid was isolated by filtration, washed with H₂O and dried to give 50 mg (34%) of the title compound as a white solid. LC/MS: m/z (ES⁺) 328 (M+H)⁺. ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.79 (br s, 1H), 7.50-7.40 (m, 5H), 5.66-5.56 (m, 2H), 4.92-4.87 (m, 2H), 1.28-1.25 (m, 6H).

Example 53. Preparation of 3-((R)-1-(benzyloxy)propan-2-yl)-6-(((S)-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione.

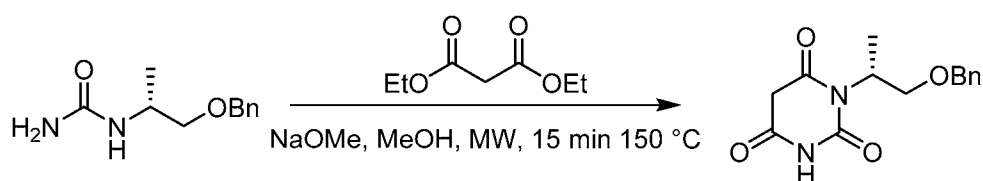


[0141] Compound 53.1. (R)-1-(1-hydroxypropan-2-yl)urea. To a stirred solution of (R)-(-)-2-amino-1-propanol (0.65 g, 8.68 mmol, 1 equiv.) in CH₂Cl₂ (10 mL) under N₂ at 0 °C was added dropwise trimethylsilyl isocyanate (1.00 g, 8.68 mmol, 1.0 equiv.). The reaction mixture was stirred overnight while slowly warming to room temperature. After cooling to 0 °C, CH₃OH (10 mL) was added dropwise. The resulting solution was stirred for 2 h at room temperature and was then concentrated under reduced pressure to provide the title compound (1.02 g, 99%) as a white solid.



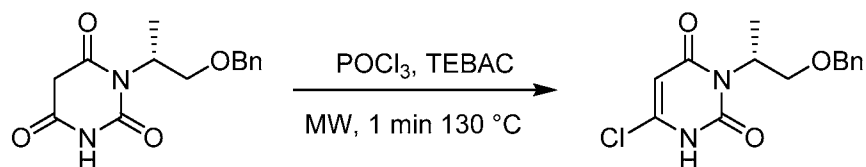
[0142] Compound 53.2. (R)-1-(1-(benzyloxy)propan-2-yl)urea. To a suspension of sodium hydride (0.52 g, 13.2 mmol, 1.5 equiv.) in THF (10 mL) at 0 °C was added **53.1** (1.02

g, 8.67 mmol, 1 equiv.). The reaction mixture was stirred for 20 minutes at 0 °C under N₂ before benzyl bromide (1.03 mL, 8.67 mmol, 1 equiv.) was added. The reaction mixture was stirred overnight while slowly warming to room temperature. The reaction mixture was quenched with H₂O (3 mL) and was extracted into EtOAc (15 mL), dried with anhydrous Na₂SO₄, filtered, and concentrated. The resulting residue was purified by flash chromatography (10% CH₃OH in CH₂Cl₂) to provide 510 mg (28%) of the title compound. LC/MS: m/z (ES⁺) 209 (M+H)⁺. ¹H-NMR (400 MHz, CDCl₃): δ ppm 7.42 - 7.27 (m, 5H), 4.79 (d, J = 6.7 Hz, 1H), 4.52 (d, J = 2.7 Hz, 2H), 3.91 (s, 1H), 3.51 (dd, J = 9.4, 3.9 Hz, 1H), 3.40 (dd, J = 9.2, 5.3 Hz, 1H), 1.19 (d, J = 7.0 Hz, 3H).



[0143] Compound 53.3. (R)-1-(1-(benzyloxy)propan-2-yl)pyrimidine-

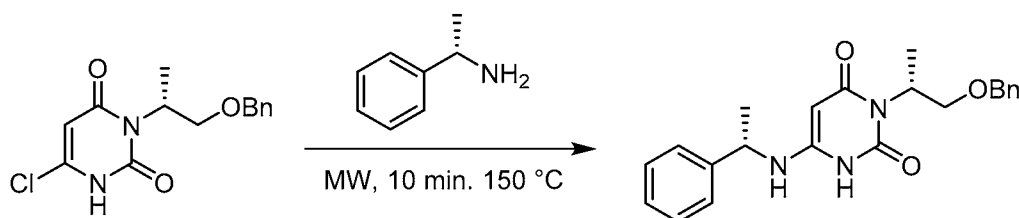
2,4,6(1H,3H,5H)-trione. To a microwave vial containing **53.2** (0.51 g, 2.42 mmol, 1 equiv.) in CH₃OH (10 mL) was added diethyl malonate (2.55 g, 2.55 mmol, 1.05 equiv.) followed by sodium methoxide (25% wt. soln. in CH₃OH, 1.31 g, 6.06 mmol, 2.5 equiv.). The vial was capped and the reaction mixture was heated in a microwave reactor for 15 minutes at 150 °C. After cooling to room temperature, the reaction mixture was quenched with H₂O (2 mL) and the pH was adjusted to 3 with concentrated HCl. The reaction mixture was transferred to a round bottom flask and was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (5% CH₃OH in CH₂Cl₂) to provide 0.62g (92%) of the title compound as a white solid. LC/MS: m/z (ES⁺) 277 (M+H)⁺. ¹H-NMR (400 MHz, CDCl₃): δ ppm 7.99 (s, 1H), 7.38-7.22 (m, 5H), 5.16-5.11 (m, 1H), 4.52 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 4.02 (t, J = 9.8 Hz, 1H), 3.56 (q, J = 1.57 Hz, 2H), 1.37 (d, J = 7.00 Hz, 3H).



[0144] Compound 53.4. (R)-3-(1-(benzyloxy)propan-2-yl)-6-chloropyrimidine-

2,4(1H,3H)-dione. To a microwave vial containing **53.3** (0.25 g, 0.91 mmol, 1 equiv.) was

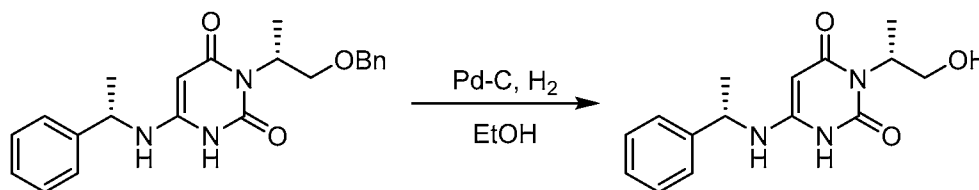
added triethylbenzylammonium chloride (0.28 g, 1.26 mmol, 1.4 equiv.) and POCl₃ (1 mL). The vial was capped and the reaction mixture was heated in a microwave reactor for 1 minute at 130 °C. The reaction mixture was transferred to a round bottom flask and was concentrated under reduced pressure. The resulting residue was dissolved in CH₂Cl₂ (5 mL) and water (2 mL) was carefully added. The mixture was stirred for 10 minutes. The layers were separated and the organic layer was dried with Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, 5% CH₃OH in CH₂Cl₂) to provide 150 mg (55%) of the title compound. LC/MS: m/z (ES+) 295 (M+H)⁺. ¹H-NMR (400 MHz, CDCl₃): δ ppm 10.27 (s, 1H), 7.36-7.20 (m, 5H), 5.32- 5.21 (m, 2H), 4.57 (d, J = 12.0 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 4.10 (dd, J = 10.0, 9.2 Hz, 1H), 1.40 (d, J = 7.0 Hz, 3H).



[0145] Compound 53. 3-((*R*)-1-(benzyloxy)propan-2-yl)-6-(((*S*)-1-

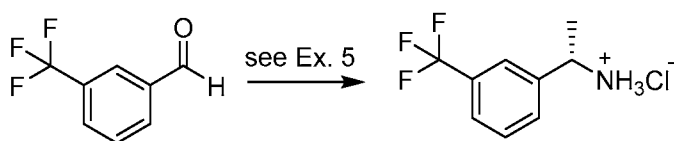
phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione. To a microwave vial containing (*S*)-α-methylbenzylamine (1.5 mL) was added **53.4** (0.12 g, 0.42 mmol). The vial was capped and the reaction mixture was heated in a microwave reactor for 10 minutes at 150 °C. After cooling, the reaction mixture was filtered through a plug of silica gel (10% CH₃OH in CH₂Cl) and the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in CH₂Cl₂ (10 mL) and was washed with 10% HCl (5 mL). The organic layer was dried with anhydrous Na₂SO₄, filtered and concentrated to provide 150 mg (94%) of the title compound. LC/MS: m/z (ES+) 380 (M+H)⁺. ¹H-NMR (400 MHz, CDCl₃): δ ppm 9.96 (br s 1H), 7.35-7.24 (m, 10H), 4.70 (br s, 1H), 4.53-4.41 (m, 4H), 4.03-3.99 (m, 1H), 3.65-3.61 (m, 1H), 1.49 (d, J = 6.7 Hz, 3H), 1.37 (d, J = 7.0 Hz, 3H).

Example 54. Preparation of 3-((*R*)-1-hydroxypropan-2-yl)-6-(((*S*)-1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione (**54**).

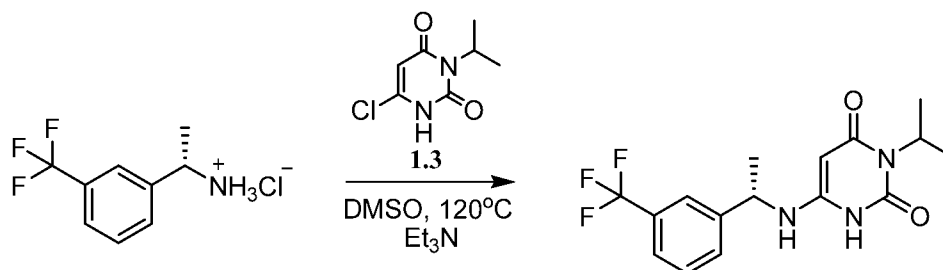


- [0146] To a solution of **53** (0.10 g, 0.26 mmol, 1 equiv.) in EtOH (2 mL) was added palladium on carbon (10 wt. % loading (dry basis), matrix activated carbon, wet support, Degussa type, 0.025 g). The reaction flask was purged with nitrogen and was then fitted with a H_{2(g)} balloon. The reaction mixture was evacuated and then filled with H_{2(g)}. This pump/purge process was repeated three times and the reaction mixture was stirred for 4 h at room temperature. After purging with nitrogen, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was suspended in CH₃CN (2 mL) and the precipitate was isolated by filtration. The precipitate was dissolved in CH₂Cl₂: CH₃OH (1:1, 2 mL) and was filtered through a .2μM PTFE 25mm filter and was concentrated under reduced pressure to provide 27 mg (35%) of the title compound. LC/MS: m/z (ES⁺) 290 (M+H)⁺. ¹H-NMR (400 MHz, CDCl₃): δ ppm 9.67 (s, 1H), 7.35-7.24 (m, 5H), 5.64 (d, J = 5.5 Hz, 1H), 5.08-5.04 (m, 1H), 4.66 (s, 1H), 4.42-4.35 (m, 1H), 4.24 (s, 1H), 4.04-3.91 (m, 1H), 3.78-3.68 (m, 1H), 1.50 (d, J = 6.70 Hz, 3H), 1.35 (d, J = 7.00 Hz, 3H).

Example 55. Preparation of (S)-3-isopropyl-6-((1-(3-(trifluoromethyl)phenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione.



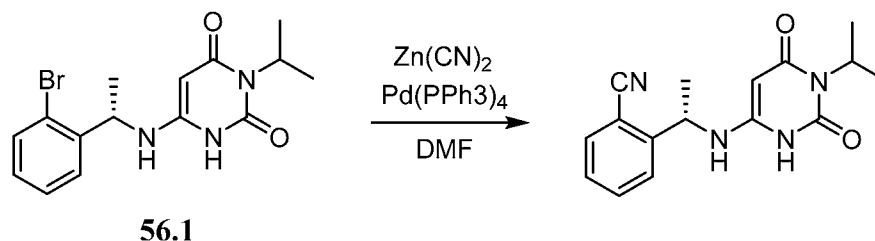
- [0147] **Compound 55.1. (S)-1-(3-(trifluoromethyl)phenyl)ethan-1-amine hydrochloride.** The title compound was synthesized according to methods described for the preparation of **5.3**, utilizing 3-(trifluoromethyl)benzaldehyde in place of 3,5-difluorobenzaldehyde.



[0148] Compound 55. (S)-3-isopropyl-6-((1-(3-(trifluoromethyl)phenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione. To a stirred solution of **55.1** (59.8 mg, 0.27 mmol, 1.00

equiv) in DMSO (1.5 mL) under an inert argon atmosphere was added Et₃N (0.2 mL) and **1.3** (50 mg, 0.27 mmol, 1.00 equiv). The resulting solution was stirred for 6 h at 120 °C in an oil bath. After cooling, the mixture was concentrated under reduced pressure and the resulting residue (75 mg) was purified by preparative RP-HPLC to give 6.5 mg (7%) of the title compound as a white solid. LC/MS: m/z (ES⁺) 342 (M+H)⁺. ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 7.78 (s, 1H), 7.74-7.60 (m, 3H), 7.20 (br, 1H), 6.02 (br, 1H), 4.96 (dt, J = 10.1, 5.1 Hz, 1H), 4.67-4.64 (m, 1H), 4.36 (s, 1H), 1.44 (d, J = 6.8 Hz, 3H), 1.31-1.28 (m, 6H).

Example 56. Preparation of (S)-3-isopropyl-6-((1-(2-cyanophenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione (**56**).



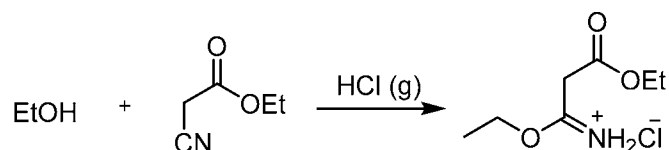
[0149] Intermediate **56.1** was prepared using procedures similar to those for the preparation of compound **35**, utilizing **1.3** and (S)-1-(2-bromophenyl)ethan-1-amine hydrochloride (synthesized from the corresponding 2-bromobenzaldehyde using methods described for example 6.3). To a stirred solution of **56.1** (40 mg, 0.11 mmol, 1.00 equiv,) in DMF (2 mL) was added Zn(CN)₂ (20 mg, 0.17 mmol, 1.50 equiv) and tetrakis(triphenylphosphine) palladium (131 mg, 0.11 mmol, 0.20 equiv). **CAUTION: CYANIDE CONTAINING REACTION.** The resulting solution was stirred under an argon atmosphere at 100 °C in an oil bath for 2 h. Upon cooling, the reaction was quenched with a saturated aqueous FeSO₄ solution (5 mL). The resulting mixture was diluted with EtOAc (20 mL) and washed with a saturated aqueous FeSO₄ solution (2 x 20 mL). The organic layer was dried with anhydrous

Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product (5 mg) was purified by chiral preparative HPLC with the following conditions: Column, Phenomenex Lux-2 5u Cellulose-2, 30*150mm; mobile phase, Hexanes and EtOH (hold 50.0% EtOH in 35 min); resulting in 2.1 mg (6%) of the title compound. LC/MS: m/z (ES⁺) 299 (M+H)⁺.

5 ¹H-NMR (300 MHz, CD₃CN): δ ppm 8.59 (br s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.61-7.56 (m, 1H), 7.48-7.45 (m, 2H), 5.09-4.94 (m, 3H), 1.46 (d, J = 6.6 Hz, 3H), 1.34-1.26 (m, 6H).

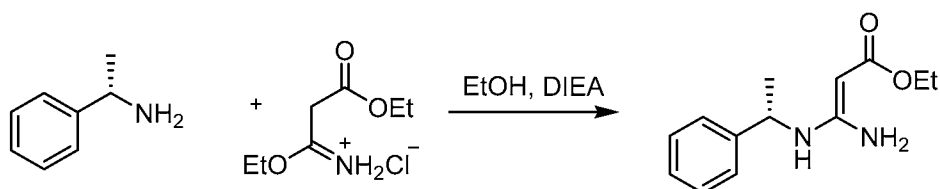
Example 57. Preparation of (*S*)-3-benzyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione.

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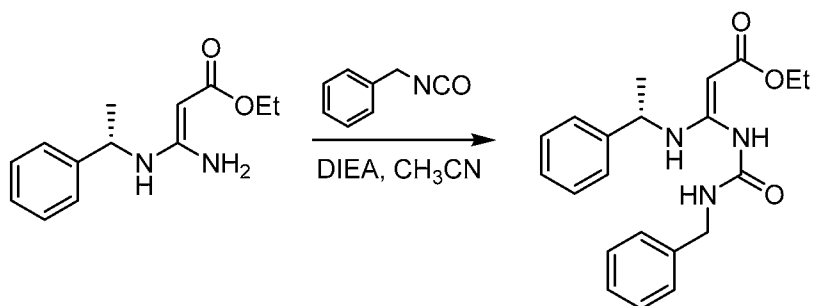
[0150] **Compound 57.1. 3-ethoxy-3-oxo-1-(1-ethoxy)propan-1-iminium chloride.** To a stirred solution of ethyl cyanoacetate (5.0 g, 44 mmol) in anhydrous Et₂O (5 mL) was added absolute EtOH (3 mL). The reaction mixture was cooled to 0 °C and HCl gas was bubbled in for 10 minutes. The reaction mixture was warmed to room temperature and was stirred for 16 h. The white precipitate that formed was filtered and washed with Et₂O (40 mL) and dried to give (6.99 g) the title compound as a white solid. LC/MS: m/z (ES⁺) 160 (M+H)⁺.

20



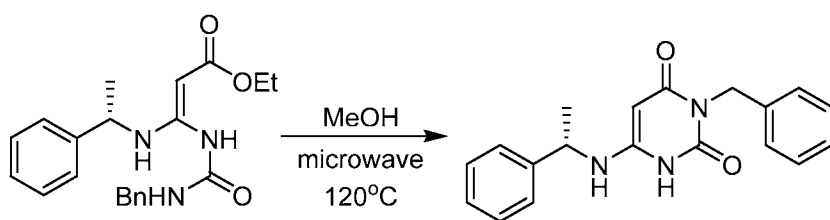
[0151] **Compound 57.2. Ethyl (*S,E/Z*)-3-amino-3-((1-phenylethyl)amino)acrylate.** To a stirred solution of **57.1** (585 mg, 3.0 mmol) in EtOH (15 mL) was added DIEA (0.8 mL), and (*S*)-α-methylbenzylamine (290 mg, 2.4 mmol). The reaction was stirred for 16 h and was concentrated. The crude was purified by flash column chromatography (silica gel, eluting with CH₃OH in CH₂Cl₂ (0 to 10%)) to yield 0.57 g (98%) of the title compound as a clear oil. NMR analysis revealed that the product was a mixture of E/Z isomers. LC/MS: m/z (ES⁺) 235 (M+H)⁺.

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[0152] Compound 57.3. Ethyl (S,Z)-3-(3-benzylureido)-3-((1-phenylethyl)amino)acrylate.

Two reactions were set up in parallel and later combined since both resulted in formation of product (by HPLC). In the first reaction, benzyl isocyanate (150 uL, 1.2 mmol) was added to a stirred solution of **57.2** (143 mg, 0.61 mmol) in CH₃CN (1 mL). After 10 min., DIEA (300 uL) was added. The reaction was stirred for an additional 10 min and was quenched with H₂O (12 mL). Solid precipitated and was removed by filtration. In the second reaction, benzyl isocyanate (150 uL, 1.2 mmol) was added to a stirred solution of **57.2** (143 mg, 0.61 mmol) and DIEA (300 uL) in CH₃CN (1 mL). After 10 min, the reaction mixture was quenched with H₂O (10 mL). The resulting mixture was diluted with EtOAc (40 mL) and the layers were separated. To the organic layer was added the filtrate from first reaction. The layers were separated and the organics were concentrated to give the title compound which was utilized without further purification.

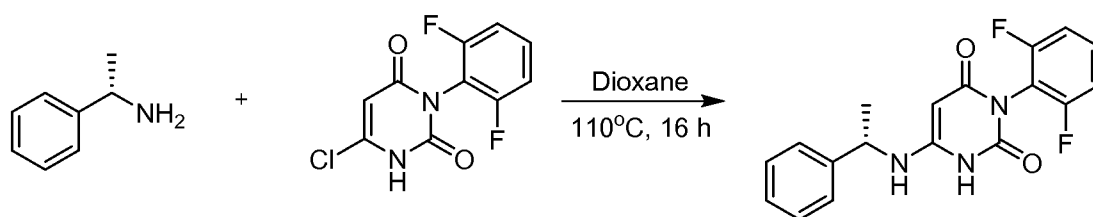


[0153] Compound 57. (S)-3-benzyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione.

Two reactions were conducted and later combined since both resulted in formation of product (by HPLC). The first reaction utilized 1/3 of crude **57.3** in CH₃OH (1 mL). It was heated in a microwave reactor at 120 °C for 10 min. The remaining 2/3 of crude **57.3** in CH₃OH (2 mL) was heated in a microwave reactor at 120 °C for 20 min. After cooling to ambient temperature, the reactions were combined and the CH₃OH was removed under reduced pressure. A 50/50 mixture of CH₃CN/H₂O with 0.1% TFA (5 mL) was added to the

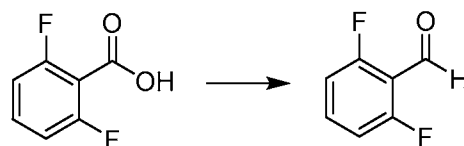
resulting residue. Solid precipitated and was filtered. The resulting brown solid was washed with EtOAc to give 7 mg of the title compound as a white solid. LC/MS: m/z (ES⁺) 322 (M+H)⁺. ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 10.05 (br s, 1H), 7.35-7.31 (m, 4H), 7.26-7.16 (m, 6H), 6.61 (d, J = 7.0 Hz, 1H), 4.79 (s, 2H), 4.52 (quin, J = 6.8 Hz, 1H), 4.42 (d, J = 2.3 Hz, 1H), 1.39 (d, J = 6.7 Hz, 3H).

Example 58. Preparation of (S)-3-(2,6-difluorophenyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione (58).

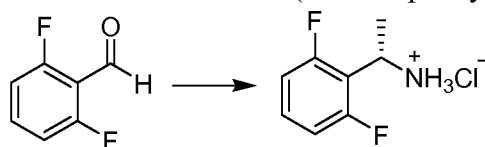


[0154] The title compound was synthesized according to a slightly modified procedure as described in Example 50. Here, 1,4-dioxane was utilized as a solvent and the reaction was heated at 110 °C for 16 h. The resulting mixture was cooled and concentrated under reduced pressure. The crude was purified by preparative RP-HPLC to give 19 mg of the title compound as a white solid. LC/MS: m/z (ES⁺) 344 (M+H)⁺. ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 10.44 (br s, 1H), 7.52-7.42 (m, 2H), 7.39-7.36 (m, 3H), 7.34-7.16 (m, 3H), 6.91 (br s, 1H), 4.65-4.56 (m, 1H), 4.52 (s, 1H), 1.43 (d, J = 6.7 Hz, 3H).

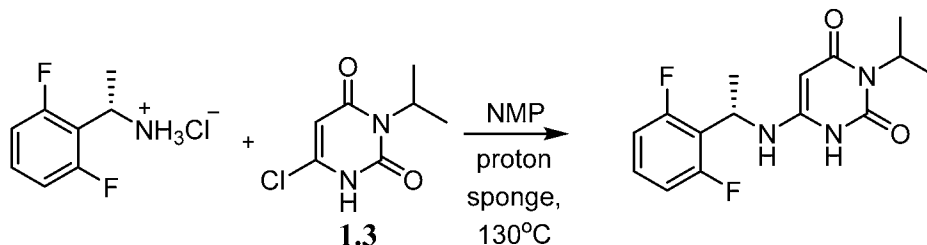
Example 59. Preparation of (S)-6-((1-(2,6-difluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione.



[0155] **Compound 59.1. 2,6-difluorobenzaldehyde.** The title compound was synthesized according to methods described for the preparation of 51.2. Here, commercially available 2,6-difluorobenzoic acid was utilized instead of 2-(4-fluorophenyl)acetic acid.



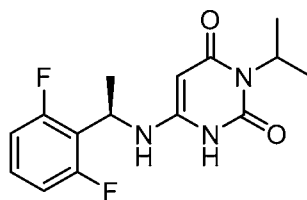
[0156] **Compound 59.2. (S)-1-(2,6-difluorophenyl)ethan-1-amine hydrochloride.** The title compound was synthesized according to methods described for the preparation of **5.3**. Here, **59.1** was utilized instead of 3,5-difluorobenzaldehyde.



[0157] **Compound 59. (S)-6-((1-(2,6-difluorophenyl)ethyl)amino)-3-**

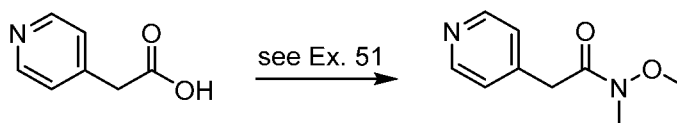
isopropylpyrimidine-2,4(1H,3H)-dione. Reaction of **59.1** with **1.3** was conducted in a similar manner as the procedure described in Example 51. Here though, the reaction mixture was heated at 130 °C for 5 h. Analysis of the reaction mixture via chiral HPLC revealed non-trivial amounts of the enantiomer. Separation of the enantiomers was performed utilizing preparative chiral HPLC with an isocratic mixture of EtOH: Hexane (1:4) as eluent from a Phenomenex Lux-2 5 μ Cellulose-2, 30*150mm column (40 min run). LC/MS: m/z (ES⁺) 310 (M+H)⁺. ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.80 (br s, 1H), 7.45-7.41 (m, 1H), 7.18-7.14 (m, 2H), 6.52 (d, J = 8.0 Hz, 1H), 4.94-4.88 (m, 1H), 4.79 (quint, J = 7.6 Hz, 1H), 4.41 (s, 1H), 1.56 (d, J = 6.8 Hz, 3H), 1.30-1.26 (m, 6H).

Example 60. Preparation of (R)-6-((1-(2,6-difluorophenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione (**60R**).



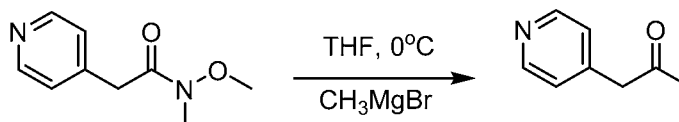
[0158] The title compound was generated as a by-product of the chemistry conducted in Example 59. It was isolated via preparative chiral HPLC with an isocratic mixture of EtOH: Hexane (1: 4) as eluent from a Phenomenex Lux-2 5 μ Cellulose-2, 30*150mm column (40 min run). LC/MS: m/z (ES⁺) 310 (M+H)⁺. ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.98-9.61 (br, 1H), 7.45-7.41 (m, 1H), 7.18-7.14 (m, 2H), 6.52 (d, J = 8.0 Hz, 1H), 4.94-4.88 (m, 1H), 4.79 (quint, J = 7.6 Hz, 1H), 4.41 (s, 1H), 1.56 (d, J = 6.8 Hz, 3H), 1.30-1.26 (m, 6H).

Example 61. Preparation of (S)-3-isopropyl-6-((1-(pyridin-4-yl)propan-2-yl)amino)pyrimidine-2,4(1H,3H)-dione.



[0159] Compound 61.1. N-methoxy-N-methyl-2-(pyridin-4-yl)acetamide. The title compound was synthesized according to methods described for the preparation of **51.1**. Here, commercially available 4-pyridineacetic acid was utilized instead of 2-(4-fluorophenyl)acetic acid.

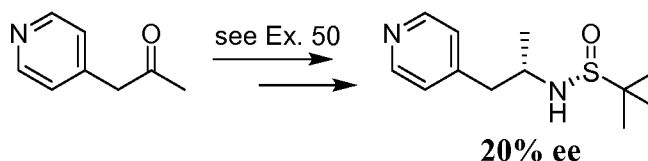
10 acid.



[0160] Compound 61.2. 1-(pyridin-4-yl)propan-2-one. To a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of argon, was added THF (70 mL) and N-methoxy-N-methyl-2-(pyridin-4-yl)acetamide (7.0 g, 0.039 mol, 1.0 equiv). The mixture was cooled to 0 °C and CH₃MgBr (3M in THF, 65 mL, 5.0 equiv) was added dropwise. The resulting solution was warmed to ambient temperature and stirred for 16 h. The reaction mixture was cooled to 0 °C and quenched by the addition of saturated NH₄Cl (aq, 100 mL). The resulting solution was extracted with EtOAc (3x200 mL). The organic layers were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by flash chromatography (silica gel, CH₂Cl₂/CH₃OH (20:1)) to yield 2.7 g (51%) of the title compound as yellow oil. ¹H-NMR (400 MHz, CDCl₃): δ ppm 8.58 (m, 2H), 7.17 (d, J = 0.4 Hz, 2H), 3.75 (s, 2H), 2.24 (s, 3H).

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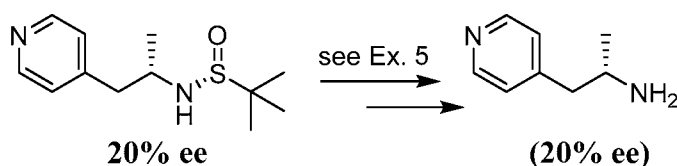
20



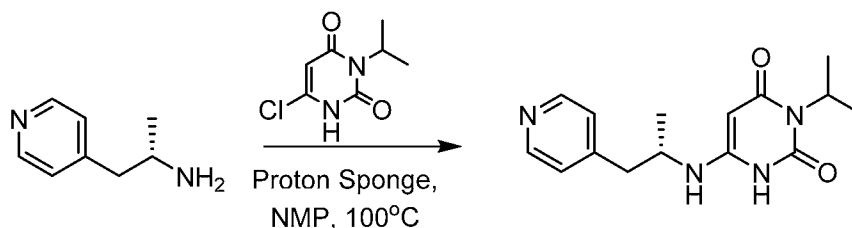
[0161] Compound 61.3. (R)-2-methyl-N-((S)-1-(pyridin-4-yl)propan-2-yl)propane-2-sulfonamide. The title compound was prepared according to procedures described in Example 50 utilizing **61.2** in place of 1-(3-methylphenyl)ethanone. Here, the reduction

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utilizing L-selectride resulted in isolation of the title compound (**61.3**) (20% enantiomeric excess).

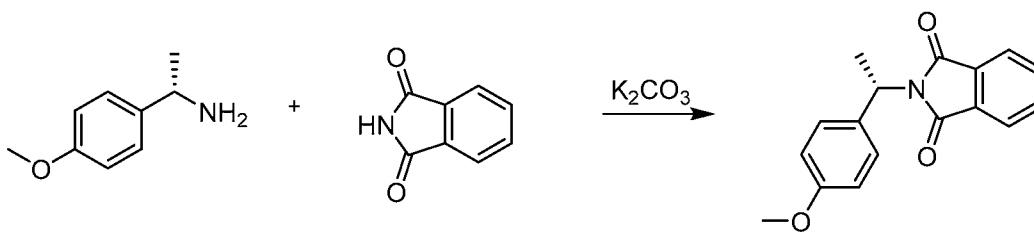


[0162] **Compound 61.4. (S)-1-(pyridin-4-yl)propan-2-amine.** The title compound was prepared utilizing a two-step procedure as described in Example 5. First, sulfonamide **61.3** was converted to the hydrochloride salt by treatment with HCl in 1,4-dioxane (see protocol for Compound **5.3**). Subsequent free-basing of the hydrochloride salt (see protocol for Compound **5**) resulted in the title compound (~20% ee).

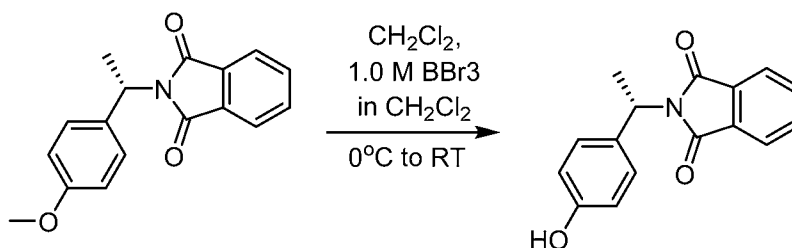


[0163] **Compound 61. (S)-3-isopropyl-6-((1-(pyridin-4-yl)propan-2-yl)amino)pyrimidine-2,4(1H,3H)-dione.** The title compound was prepared according to the protocol described for **51**. Here, the reaction mixture was stirred for at 100 °C for 1 h. The reaction mixture was concentrated under reduced pressure and the residue (100 mg) was purified by Prep-HPLC to give 13.1 mg of the title compound as a mixture of enantiomers. The enantiomers were (13.1 mg) separated by chiral preparative HPLC with a Chiralpak IC, 2*25cm, 5um column, utilizing a isocratic mixture of EtOH: Hexane (1: 3) as eluent (20 min run). This resulted in 8.2 mg (8%) of the title compound as a light yellow solid. LC/MS: m/z (ES+) 289 (M+H)⁺. ¹H-NMR (300 MHz, CD₃OD): δ ppm 8.41 (d, J = 5.7 Hz, 2H), 7.29 (d, J = 6.0 Hz, 2H), 5.06-4.96 (m, 1H), 4.68 (s, 1H), 3.82-3.75 (m, 1H), 2.87-2.83 (m, 2H), 1.36 (d, J = 7.2 Hz, 6H), 1.12 (d, J = 7.2 Hz, 3H).

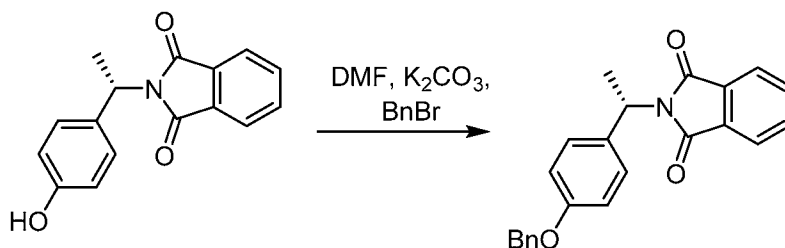
Example 62. Preparation of (S)-6-((1-(4-(benzyloxy)phenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione.



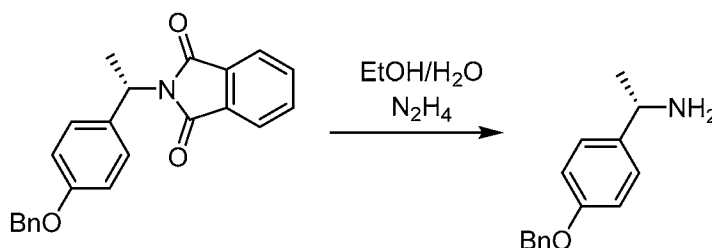
[0164] **Compound 62.1. (S)-2-(1-(4-(methoxy)phenyl)ethyl)isoindoline-1,3-dione.** To phthalimide (1.3 g, 0.0088 mol) in a 2-5 mL microwave vial was added (S)-1-(4-methoxyphenyl)ethan-1-amine (2.20 mL, 0.015 mol) and K_2CO_3 (1.2 g, 0.0087 mol). The reaction mixture capped and heated at 160 °C for 2 minutes. The resulting crude solid was suspended in n-BuOH and was filtered. The filtrate was put aside. The solid was washed with H_2O and the filtrate was discarded. The solid was washed with CH_2Cl_2 and the resulting filtrate was partitioned with H_2O . The organics (n-BuOH and CH_2Cl_2 layer) were combined and concentrated. The crude residue was purified by silica gel column chromatography using CH_2Cl_2 as eluent to yield 1.6 g (64%) of the title compound. LC/MS: m/z (ES⁺) 282 (M+H)⁺.



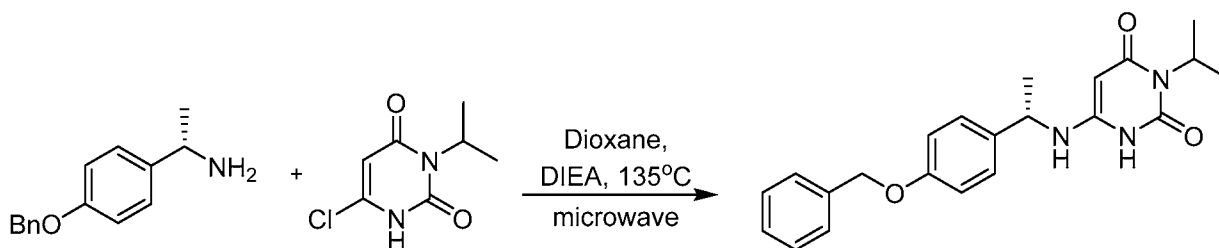
[0165] **Compound 62.2. (S)-2-(1-(4-hydroxyphenyl)ethyl)isoindoline-1,3-dione.** To a stirred solution of **62.1** (640 mg, 2.28 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added BBr_3 (1.0 M in CH_2Cl_2 , 3 mL, dropwise). The reaction was allowed to warm to room temperature over 30 minutes. Significant starting material remained so the reaction was chilled back to 0 °C. Additional BBr_3 (2 mL, 1.0 M in CH_2Cl_2) was added and the reaction was allowed to warm to room temperature over 30 minutes. The reaction mixture was poured over 5% $NaHCO_3$ (aq) in ice. The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 . The combined organics were washed with brine, dried with anhydrous Na_2SO_4 and concentrated to give 500 mg (82%) of the title compound as a white solid. LC/MS: m/z (ES⁺) 268 (M+H)⁺.



[0166] Compound 62.3. (S)-2-(1-(4-(benzyloxy)phenyl)ethyl)isoindoline-1,3-dione. To a stirred solution of **62.2** (500 mg, 1.87 mmol) in DMF (10 mL) was added K_2CO_3 (560 mg, 4.05 mmol, 2.17 equiv.) and benzyl bromide (0.30 mL, 420 mg, 2.45 mmol, 1.3 equiv.). The reaction was stirred at 120 °C for 5 h. The reaction was cooled and filtered. Water was added (20 mL) and EtOAc (60 mL) was utilized to extract product. The organic layer was washed successively with H_2O , 10% Na_2CO_3 (aq), H_2O , and brine (2x). The organics were dried over anhydrous $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography (silica gel, eluting with CH_2Cl_2) to yield 480 mg (72%) of the title compound. LC/MS: m/z (ES⁺) 358 (M+H)⁺.



[0167] Compound 62.4. (S)-1-(4-(benzyloxy)phenyl)ethan-1-amine. To a stirred solution of **62.3** (480 mg, 1.34 mmol) in a 70/30 EtOH/ H_2O mixture (20 mL) was added $N_2H_4 \cdot H_2O$ (1.5 mL). The reaction was stirred for 16 h and concentrated. The resulting material was partitioned between EtOAc and 5% Na_2CO_3 (aq). The layers were separated and the EtOAc layer was washed with brine and concentrated to give 280 mg (92%) of the title compound which was used without further purification. LC/MS: m/z (ES⁺) 228 (M+H)⁺.



[0168] Compound 62. (S)-6-((1-(4-(benzyloxy)phenyl)ethyl)amino)-3-

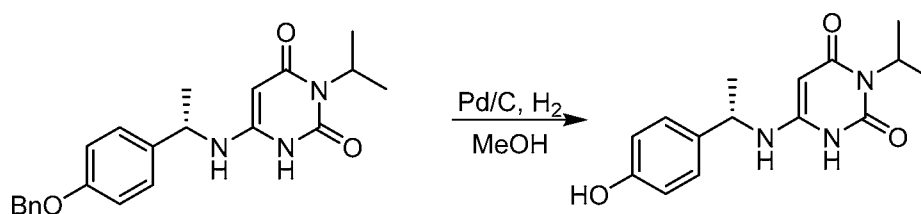
isopropylpyrimidine-2,4(1H,3H)-dione. To a 0.5-2.0 mL microwave vial was added 1,4-dioxane (1 mL), **62.4** (280 mg, 1.23 mmol), **1.3** (250 mg, 1.33 mmol) and DIEA (400 uL).

The reaction mixture was capped, heated at 135 °C in a microwave reactor for 1.5 h, allowed to cool, and then concentrated. The crude reaction mixture was treated with 50/50

CH₃CN/H₂O (0.1% TFA) which led to precipitation. The solid was isolated by filtration and dried to give 45 mg (10%) of a white solid. LC/MS: m/z (ES+) 380 (M+H)⁺. ¹H-NMR (400

MHz, DMSO-d₆): δ ppm 9.73 (br, 1H), 7.43-7.29 (m, 5H), 7.23 (d, J = 14.5 Hz, 2H), 6.97 (d, J = 14.5 Hz, 2H), 6.42 (d, J = 7.0 Hz, 1H), 5.06 (s, 2H), 4.93-4.85 (m, 1H), 4.42 (quin, J = 6.8 Hz, 1H), 4.32 (d, J = 1.6 Hz, 1H), 1.35 (d, J = 6.7 Hz, 3H), (m, 1H) 1.27-1.23 (m, 6H).

Example 63. Preparation of (S)-6-((1-(4-hydroxyphenyl)ethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione (**63**).



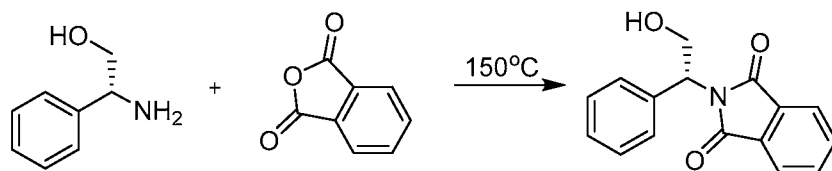
To a stirred solution of **62** (43 mg, 0.11 mmol) in CH₃OH (20 mL) was added palladium on carbon (50 mg, 10 wt. % loading (dry basis), matrix activated carbon, wet

support, Degussa type). The vessel was purged with nitrogen followed by hydrogen. The reaction mixture was stirred under a H₂ atmosphere for 2 h. After purging the system with nitrogen, the mixture was filtered through celite and concentrated. The resulting solid was

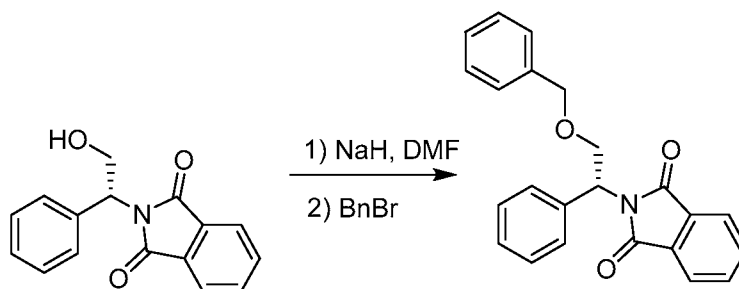
dissolved in 8 mL CH₃CN and then 20 mL H₂O (0.1% TFA) was added. The solution was frozen and lyophilized to give 29 mg (90%) of the title compound as a white solid. LC/MS:

m/z (ES+) 290 (M+H)⁺. ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.70 (br, 1H), 9.32 (s, 1H), 7.10 (d, J = 8.6 Hz, 2H), 6.71 (d, J = 8.6 Hz, 2H), 6.36 (d, J = 7.0 Hz, 1H), 4.92-4.85 (m, 1H), 4.37-4.33 (m, 2H), 1.33 (d, J = 6.7 Hz, 3H), 1.27-1.23 (m, 6H).

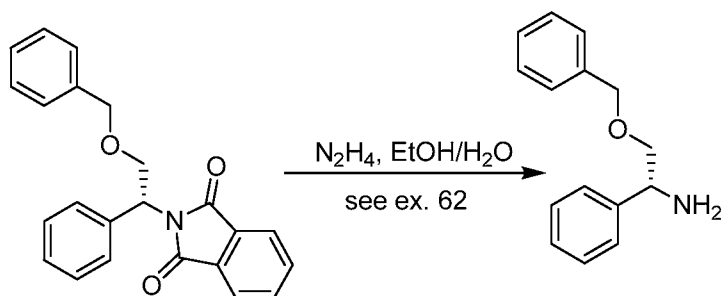
Example 64. Preparation of (R)-6-((2-(benzyloxy)-1-phenylethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione.



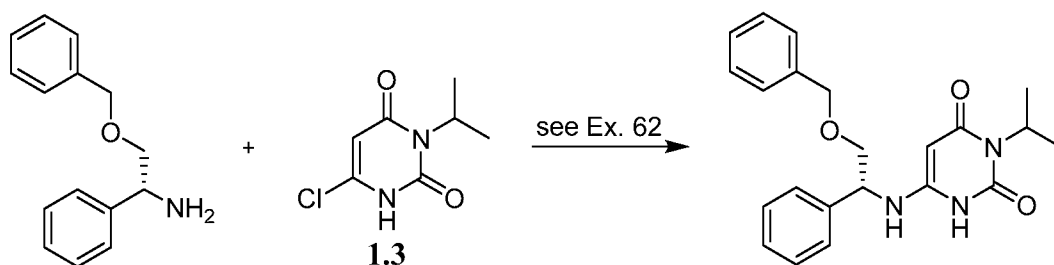
[0170] **Compound 64.1. (R)-2-(2-hydroxy-1-phenylethyl)isoindoline-1,3-dione.** To a 2.0-5.0 mL microwave vial was added (R)-2-amino-2-phenylethan-1-ol (1.53 g, 0.0112 mol) and phthalic anhydride (1.65 g, 0.0112 mol). The reaction mixture was capped and heated to 150 °C for 2 minutes in a microwave reactor. The mixture was cooled and diluted with CH₃CN (2 mL), recapped and heated in the microwave reactor a second time at 140 °C for 20 minutes. The volatiles were removed under reduced pressure and the resulting solid was suspended in EtOAc (50 mL). The organic layer was washed with 5% NaHCO₃ (aq), H₂O, and brine, dried with anhydrous MgSO₄ and concentrated. The crude residue was purified by flash chromatography (silica gel, eluting with CH₃OH in CH₂Cl₂ (0 to 5%) to yield 2.81 g (94%) of the title compound. LC/MS: m/z (ES⁺) 268 (M+H)⁺.



[0171] **Compound 64.2. (R)-2-(2-(benzyloxy)-1-phenylethyl)isoindoline-1,3-dione.** The title compound was made in a similar manner as the procedure described for **62.3**. However, in this case NaH (60% dispersion in mineral oil, 1.2 equiv.) was used in place of K₂CO₃. Specifically, NaH was added at 0 °C and stirred at room temperature for 45 minutes. The reaction was cooled back to 0 °C and then benzyl bromide (1.2 equiv.) was added. A work-up procedure as described for **62.3** followed by flash chromatography (silica gel, eluting with CH₂Cl₂) yielded the title compound in 59% yield. LC/MS: m/z (ES⁺) 358 (M+H)⁺. ¹H-NMR (400 MHz, CDCl₃): δ ppm 7.84-7.79 (m, 2H), 7.72-7.67 (m, 2H), 7.52-7.48 (m, 2H), 7.37-7.20 (m, 8H), 5.62 (dd, J = 10.2, 5.9 Hz, 1H), 4.63 (t, J = 10.2 Hz, 1 H), 4.58 (s, 2H), 4.06-4.01 (m, 1H).

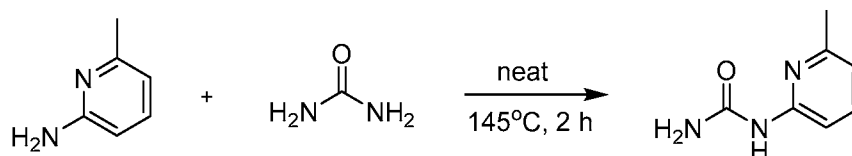


[0172] **Compound 64.3. (*R*)-2-(benzyloxy)-1-phenylethan-1-amine.** The title compound was prepared in a similar manner as the procedure described for **62.4**. LC/MS: m/z (ES⁺) 228 (M+H)⁺. ¹H-NMR (400 MHz, CDCl₃): δ ppm 7.40-7.24 (m, 10H), 4.56 (d, J = 2.0 Hz, 2H), 4.25 (dd, J = 8.8, 3.7 Hz, 1H), 3.65-3.60 (m, 1H), 3.49-3.44 (m, 1H).

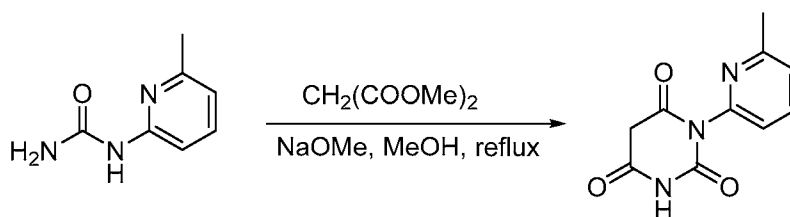


[0173] **Compound 64. (*R*)-6-((2-(benzyloxy)-1-phenylethyl)amino)-3-isopropylpyrimidine-2,4(1H,3H)-dione.** The title compound was prepared in a similar manner as the procedure described for **62**. Here though, the reaction was heated at 140 °C for 1 h. After cooling, the crude reaction mixture was treated with 50/50 CH₃CN/H₂O (0.1% TFA) which led to precipitation. LC/MS: m/z (ES⁺) 380 (M+H)⁺. ¹H-NMR (400 MHz, DMSO-*d*₆): δ ppm 10.01 (br, 1H), 7.36-7.26 (m, 10H), 6.62 (d, J = 6.7 Hz, 1H), 4.93-4.83 (m, 1H), 4.67-4.62 (m, 1H), 4.50 (dd, J = 12.0, 2.0 Hz, 2H), 4.30 (s, 1H), 3.68-3.64 (m, 1H), 3.60-3.55 (m, 1H) 1.27-1.23 (m, 6H).

Example 65. Preparation of (*S*)-3-(6-methylpyridin-2-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione.



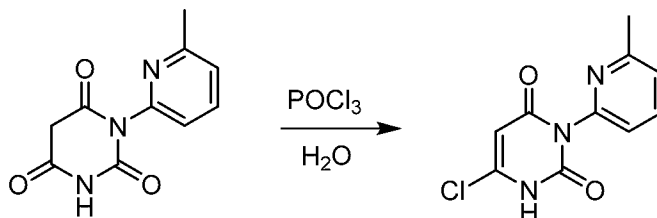
[0174] **Compound 65.1. 1-(6-methylpyridin-2-yl)urea.** To a 25-mL round-bottom flask purged and maintained with an inert atmosphere of argon, was added urea (1.48 g, 24.64 mmol, 1.00 equiv) and 6-methylpyridin-2-amine (3 g, 27.74 mmol, 1.00 equiv). The resulting mixture was stirred for 2 h at 145 °C. After cooling, the crude product (4 g) was purified using CombiFlash: Column, C18 silica gel; utilizing a mobile phase of CH₃CN: H₂O = 0:100 to CH₃CN: H₂O = 50:50 over 40 min. This resulted in the isolation of 1.2 g (32%) of the title compound as a white solid. ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.07 (s, 1H), 7.56-7.52 (m, 1H), 7.18-7.14 (m, 1H), 6.80-6.75 (m, 1H), 2.36 (s, 3H).



[0175] **Compound 65.2. 1-(6-methylpyridin-2-yl)pyrimidine-2,4,6(1H,3H,5H)-trione.**

The title compound was prepared in a similar manner as the procedure described for 1.2.

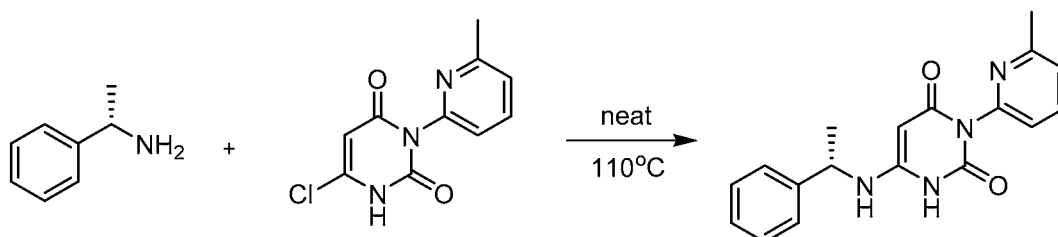
Here though, after stirring overnight at 65 °C, the reaction mixture was concentrated under reduced pressure and the crude product was precipitated from CH₃OH:Et₂O (1:50). The solid was collected by filtration and dissolved in CH₃OH (50 mL). The pH value of the solution was adjusted to 7 with cation ion-exchange resin (Dowex 50WX8-100, 5 g). The solids were filtered and the filtrate was concentrated under reduced pressure resulting in 0.5 g (29%) of the title compound as a white solid. ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.27 (br s, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 3.18 (s, 2H), 2.44 (s, 3H).



[0176] **Compound 65.3. 6-chloro-3-(6-methylpyridin-2-yl)pyrimidine-2,4(1H,3H)-dione.**

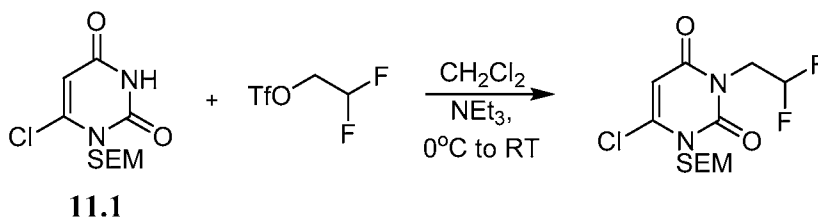
To a stirred solution of 65.2 (500 mg, 2.28 mmol, 1.00 equiv) in POCl₃ (5 mL) at 0 °C was added a drop (~20 μL) of H₂O. The resulting solution was warmed to room temperature,

stirred for 30 min., heated to 70 °C and stirred for 2 h. After cooling, the resulting mixture was concentrated under reduced pressure. The resulting residue was carefully dissolved in 10 mL of ice water. The pH was adjusted to 7 with anion ion-exchange resin (activated 201×4(711) strong base styrene anion exchange resin, 20 g) and the solids were filtered. The filtrate was concentrated under reduced pressure resulting in 0.2 g (37%) of the title compound as a yellow solid.



- [0177] **Compound 65. (S)-3-(6-methylpyridin-2-yl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione.** To a 10-mL round-bottom flask purged and maintained with an inert atmosphere of argon was added (*S*)-α-methylbenzylamine (0.5mL) and **65.3** (200 mg, 0.84 mmol, 1.00 equiv). The resulting solution was stirred for 3 h at 110 °C. After cooling, the resulting mixture was concentrated under vacuum. The residue (100 mg) was purified by preparative RP-HPLC with the following conditions: Column, XBridge Prep C18 OBD Column, 5μm, 19*150mm,; mobile phase, H₂O with 0.05% NH₄(HCO₃) and CH₃CN (15% CH₃CN to 80% in 8 min); This resulted in 28.8 mg (11%) of the title compound as a white solid. LC/MS: m/z (ES⁺) 323 (M+H)⁺. ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 7.76 (t, J = 7.6 Hz, 1H), 7.39- 7.22 (m, 7H), 7.05 (d, J = 7.6 Hz, 1H), 6.82 (br, 1H), 4.63-4.59 (m, 1H), 4.46 (s, 1H), 2.43 (s, 3H), 1.44 (d, J = 6.4 Hz, 3H).

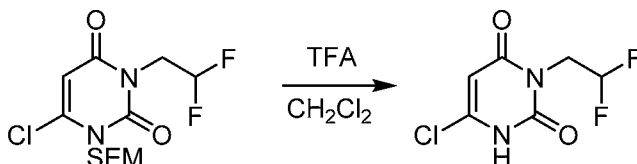
Example 66. Preparation of (*S*)-3-(2,2-difluoroethyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione.



- [0178] **Compound 66.1. 6-chloro-3-(2,2-difluoroethyl)-1-((2-(trimethylsilyl)ethoxy)methyl) pyrimidine-2,4(1H,3H)-dione.** To a stirred solution of **11.1**

(130 mg, 0.47 mmol) and Et₃N (0.2 mL) in CH₂Cl₂ (2 mL) at 0 °C was added 2,2-difluoroethyl trifluoromethanesulfonate (0.10 mL). The reaction was warmed to room temperature and stirred for 30 minutes. The mixture was concentrated to give the title compound in a crude mixture.

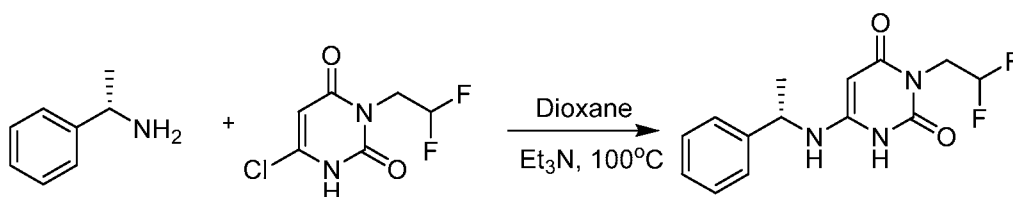
5



[0179] **Compound 66.2. 6-chloro-3-(2,2-difluoroethyl)pyrimidine-2,4(1H,3H)-dione.**

Crude **65.1** was dissolved in CH₂Cl₂/TFA (1:1, 4 mL) and stirred for 3 h and concentrated.

10 The resulting material was treated with 5% NaHCO₃ (aq) until the pH was 7. Ethyl acetate was added to the mixture and the layers were separated. The aqueous layer was concentrated. The resulting solid was suspended in CH₃CN (15 mL) and was removed by filtration. The filtrate was concentrated to give 52 mg of the title compound.



15

[0180] **Compound 66. (S)-3-(2,2-difluoroethyl)-6-((1-phenylethyl)amino)pyrimidine-**

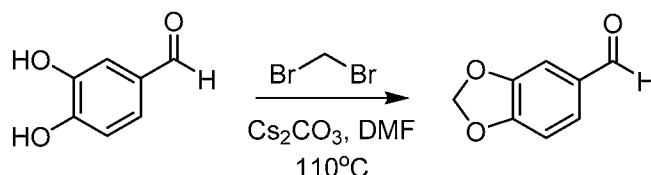
2,4(1H,3H)-dione. To **66.2** (52 mg, 0.25 mmol) in 1,4-dioxane (1.5 mL) was added Et₃N

(100 µL) and (S)-α-methylbenzylamine (188 mg, 1.55 mmol). The reaction mixture was heated in a microwave reactor at 100 °C for 32 minutes, cooled to room temperature, and then

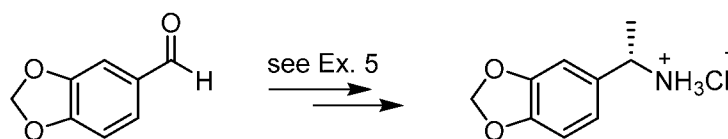
20 concentrated. The resulting residue was dissolved in a 2:3 CH₃CN/H₂O (10 mL) with 2 drops of TFA (~40 µL). The mixture was purified by preparative RP-HPLC to provide 8 mg (11%) of the title compound as a white solid. LC/MS: m/z (ES⁺) 296 (M+H)⁺. ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 10.20 (br s, 1H), 7.37-7.32 (m, 4H), 7.26-7.23 (m, 1H), 6.71 (d, J = 7.0 Hz, 1H), 6.07 (tt, J = 56.0, 4.5 Hz, 1H), 4.54 (quin, J = 6.8 Hz, 1H), 4.43 (d, J = 2.3 Hz,

25 1H), 4.02 (td, J = 14.3, 4.7 Hz, 2H), 1.40 (d, J = 6.7 Hz, 3H).

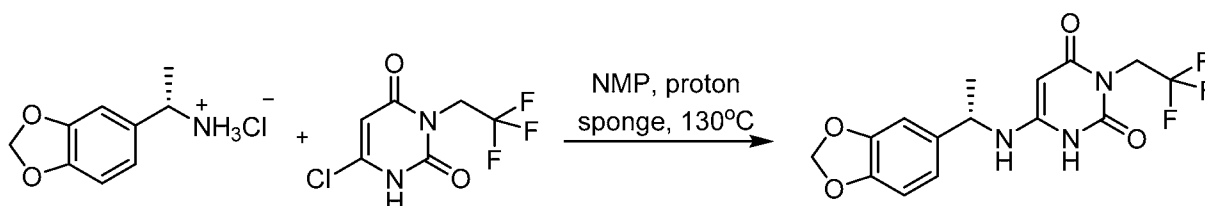
Example 67. Preparation of (S)-6-((1-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-(2,2,2-trifluoroethyl)pyrimidine-2,4(1H,3H)-dione.



[0181] **Compound 67.1. 2H-1,3-benzodioxole-5-carbaldehyde.** To a stirred solution of 3,4-dihydroxybenzaldehyde (10 g, 72.40 mmol, 1.00 equiv) in DMF (150 mL) was added cesium carbonate (35.4 g, 108.31 mmol, 1.50 equiv) and dibromomethane (18.7 g, 107.57 mmol, 1.50 equiv). The resulting solution was stirred for 2 h at 110 °C. The solution was cooled to room temperature and the solid was removed by filtration. The filtrate was diluted with H₂O (300 mL). The resulting solution was extracted with EtOAc (2 x 300 mL). The organic layers were combined, dried over sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, eluted with EtOAc/petroleum ether (1:9) to afford 8 g (74%) of the title compound as a yellow solid. ¹H-NMR (300 MHz, CDCl₃): δ ppm 9.81 (s, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.34 (s, 1H), 6.93 (d, J = 8.1 Hz, 1H), 6.08 (s, 2H).



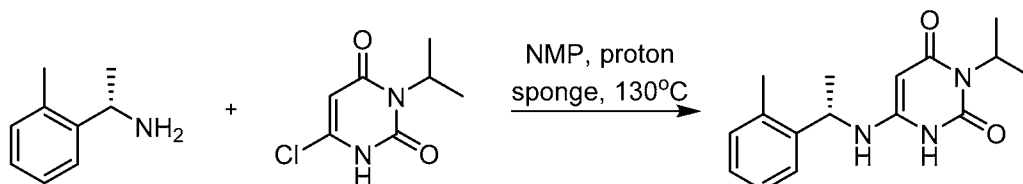
[0182] **Compound 67.2. (S)-1-(benzo[d][1,3]dioxol-5-yl)ethan-1-amine hydrochloride.** The title compound was synthesized according to methods described for the preparation of **5.3**. Here, **67.1** was utilized instead of 3,5-difluorobenzaldehyde. LC/MS: m/z (ES⁺) 166 (M+H)⁺.



[0183] **Compound 67. (S)-6-((1-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-(2,2,2-trifluoroethyl)pyrimidine-2,4(1H,3H)-dione.** The title compound was synthesized according to methods described in Example 59. Here, **67.2** was utilized instead of (S)-1-(2,6-difluorophenyl)ethan-1-amine hydrochloride and 6-chloro-3-(2,2,2-trifluoroethyl)pyrimidine-2,4(1H,3H)-dione was utilized (synthesized according to methods described in Example 1)

instead of **1.3**. LC/MS: m/z (ES⁺) 358 (M+H)⁺. ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 10.27 (br s, 1H), 6.94 (d, J = 1.2 Hz, 1H), 6.89-6.82 (m, 3H), 6.72 (d, J = 6.9 Hz, 1H), 5.99 (s, 2H), 4.48-4.40 (m, 4H), 1.38 (d, J = 6.9 Hz, 3H).

5 Example 68. Preparation of (*S*)-3-isopropyl-6-((1-(*o*-tolyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione (**68**).

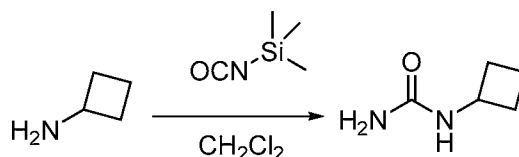


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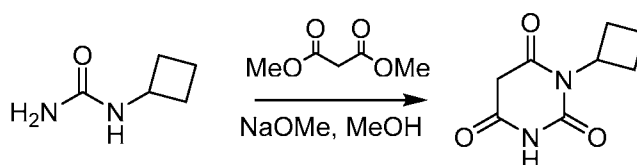
[0184] To a stirred solution of (1*S*)-1-(2-methylphenyl)ethan-1-amine (310 mg, 2.29 mmol, 1.50 equiv) in NMP (1 mL) was added proton sponge (491.4 mg, 2.30 mmol, 1.50 equiv) and **1.3** (288 mg, 1.53 mmol, 1.00 equiv). The resulting solution was stirred for 1 h at 130 °C in an oil bath, cooled to room temperature, and then diluted with DMSO (2 mL). The solids were filtered and the filtrate was purified by Flash-Prep-HPLC with the following conditions: Column: X Bridge C18, 19*150 mm, 5 μ m; Mobile Phase A: H₂O /0.05% TFA, Mobile Phase B: CH₃CN; Flow rate: 20 mL/min; Gradient: 30%B to 70% B in 10 min. This afforded 50 mg of crude product which was subsequently separated by chiral preparative HPLC with the following conditions: Column, Chiralpak IC, 2*25cm, 5 μ m; mobile phase, hexanes and ethanol (9:1, 15 min). This resulted in 35.6 mg (8%) of the title compound as a white solid. LC/MS: m/z (ES⁺) 288 (M+H)⁺. ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 9.76 (br s, 1H), 7.28 (d, J = 7.2 Hz, 1H) 7.24-7.14 (m, 3H), 6.48 (d, J = 6.3 Hz, 1H), 4.95-4.86 (m, 1H), 4.60 (quin, J = 6.9 Hz, 1H), 4.19 (s, 1H), 2.34 (s, 3H), 1.37 (d, J = 6.6 Hz, 3H), 1.27 (d, J = 6.9 Hz, 6H).

25

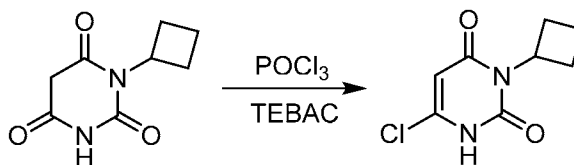
Example 69. Preparation of (*S*)-3-cyclobutyl-6-((1-phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione.



[0185] Compound 69.1. 1-cyclobutylurea. To a stirred solution of cyclobutanamine (40 g, 562.42 mmol, 1.00 equiv) in CH_2Cl_2 (400 mL) at 0°C was added trimethylsilyl isocyanate (64.70 g, 561.60 mmol, 1.00 equiv.) portionwise. The resulting solution was stirred overnight at room temperature and was quenched by the addition of CH_3OH (80 mL). The resulting mixture was stirred for 1 h at room temperature and then concentrated under reduced pressure. The residue was washed with Et_2O (2 x 100 mL) and filtered, which afforded 53 g (83%) of the title compound as a white solid. $^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ ppm 6.17 (d, $J = 9.0\text{Hz}$, 1H), 5.33 (s, 2H), 3.99-3.91 (m, 1H), 2.16-2.07 (m, 2H), 1.81-1.68 (m, 2H), 1.61-1.45 (m, 2H).



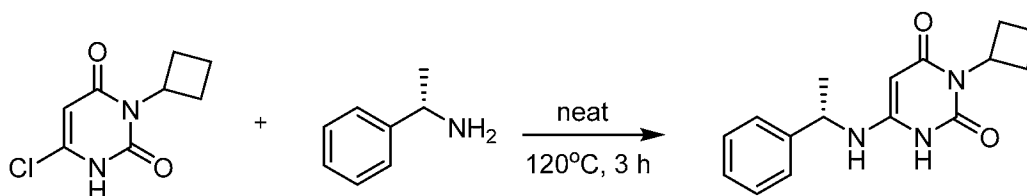
[0186] Compound 69.2. 1-cyclobutylpyrimidine-2,4,6(1H,3H,5H)-trione. To a stirred solution of sodium methoxide (62.43g, 1.156 mol, 2.40 equiv) in CH_3OH (500 mL) was added dimethyl malonate (76.42 g, 0.578 mol, 1.20 equiv) and **69.1** (55 g, 0.48 mol, 1.00 equiv). The resulting solution was heated to 65°C and stirred overnight. The reaction was cooled and quenched by the addition of H_2O (100 mL). The pH of the solution was adjusted to 1 with concentrated HCl . The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography with $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ (20:1) as eluent to afford 60 g (68%) of the title compound as a white solid. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ ppm 11.20 (s, 1H), 4.95-4.86 (m, 1H), 3.56 (s, 2H), 2.72-2.62 (m, 2H), 2.16-2.09 (m, 2H), 1.78-1.60 (m, 2H).



[0187] Compound 69.3. 6-chloro-3-cyclobutylpyrimidine-2,4(1H,3H)-dione. To **69.2** (80 g, 0.44 mol, 1.00 equiv) and triethylbenzylammonium chloride (140.2 g, 0.615 mol, 1.40 equiv) was added (300 mL). The reaction was stirred for 1 h at 65°C and was then concentrated under reduced pressure. The reaction was quenched by the careful addition of 1 L of water/ice and then the pH value of the solution was adjusted to 1 with 2N NaOH (aq). The solid was filtered, washed with CH_3OH (300 mL) and Et_2O (2 x 300 mL), and dried.

This resulted in 78 g (89%) of the title compound as a light yellow solid. $^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ ppm 12.23 (s, 1H), 5.82 (s, 1H), 5.13-5.01 (m, 1H), 2.87-2.73 (m, 2H), 2.13-2.03 (m, 2H), 1.80-1.56 (m, 2H).

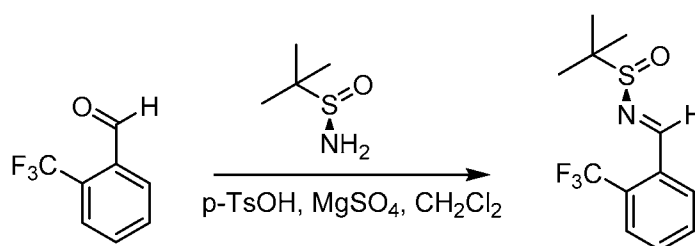
5



[0188] Compound 69. (*S*)-3-cyclobutyl-6-((1-phenylethyl)amino)pyrimidine-

2,4(1H,3H)-dione. To a 500-mL round-bottom flask purged and maintained with an inert atmosphere of argon, was added **69.3** (78 g, 388.79 mmol, 1.00 equiv) and (*S*)- α -methylbenzylamine (150 mL, 2.00 equiv). The reaction mixture was stirred for 3 h at 120 °C. The reaction mixture was cooled to room temperature, diluted with CH_3OH (1 L) and further cooled to 0 °C. The resulting solid was filtered, washed with Et_2O (2 x 300 mL), and dried under vacuum to afford 57.25 g (52%) of the title compound as a white solid. LC/MS: m/z (ES+) 286 ($\text{M}+\text{H}$)⁺. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ ppm 9.94 (br s, 1H), 7.40-7.32 (m, 4H), 7.30-7.26 (m, 1H), 6.40 (br s, 1H), 5.19-5.10 (m, 1H), 4.56-4.49 (m, 1H), 4.35 (s, 1H), 2.91-2.81 (m, 2H), 2.02-1.95 (m, 2H), 1.76-1.58 (m, 2H), 1.42 (d, $J = 6.8\text{Hz}$, 3H).

Example 70. Preparation of (*S*)-3-isopropyl-6-((1-(2-(trifluoromethyl)phenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione.

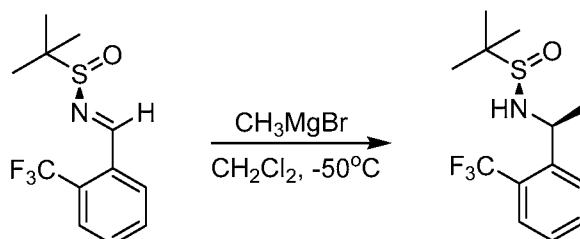


[0189] Compound 70.1. (*R,E*)-2-methyl-N-(2-(trifluoromethyl)benzylidene)propane-2-

sulfonamide. To a 100-mL round-bottom flask purged and maintained with an inert atmosphere of argon, was added CH_2Cl_2 (50 mL), 2-(trifluoromethyl)benzaldehyde (2.01 g, 11.54 mmol, 1.00 equiv), (*R*)-(+)-2-methylpropane-2-sulfonamide (1.68 g, 13.86 mmol, 1.20 equiv), pyridinium *p*-toluenesulfonate (0.145 g, 0.05 equiv) and magnesium sulfate (6.93 g, 5.00 equiv). The resulting solution was stirred for 48 h at 40 °C. The mixture was cooled to room temperature and the solid was filtered. The filtrate was concentrated under reduced

pressure and the resulting residue was purified by flash column chromatography (silica gel, eluting with EtOAc/petroleum ether (1:20)). This resulted in 0.96 g (30%) the title compound as a light yellow solid. LC/MS: m/z (ES+) 278 (M+H)⁺. ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 8.82-8.80 (m, 1H), 8.24 (d, J = 7.2 Hz, 1H), 7.95-7.80 (m, 3H), 1.22 (s, 9H).

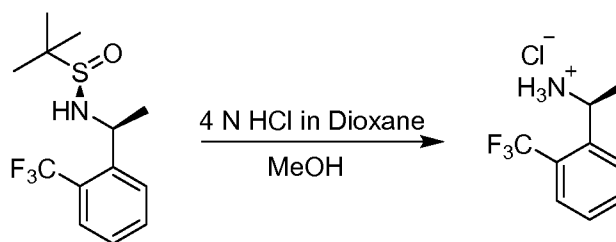
5



[0190] Compound 70.2. (R)-2-methyl-N-((1S)-1-(2-(trifluoromethyl)phenyl)-

ethyl)propane-2-sulfonamide. To a stirred solution of **70.1** (578 mg, 2.08 mmol, 1.00 equiv) in THF (20 mL) at -50 °C was added 3 M methylmagnesium bromide in Et₂O (1.4 mL, 4.20 mmol, 2.0 equiv) dropwise. The resulting solution was stirred at -50 °C for 2.5 h and at room temperature for an additional 10 h. The reaction was quenched by the addition of a saturated aqueous NH₄Cl solution (10 mL) and then concentrated under reduced pressure. The resulting residue was treated with H₂O (50 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The organic layers were combined, dried over Na₂SO₄, and concentrated under reduced pressure. This resulted in 700 mg (60% de) of the title compound as a yellow solid. LC/MS: m/z (ES+) 294 (M+H)⁺. ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 7.77-7.74 (m, 1H), 7.67-7.60 (m, 2H), 7.43-7.38 (m, 1H), 5.53 (d, J = 4.5Hz, 1H), 4.70-4.60 (m, 1H), 1.42 (d, J = 6.6 Hz, 3H), 1.02 (s, 9H).

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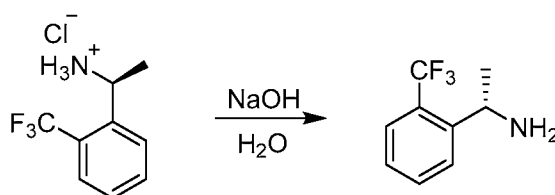


[0191] Compound 70.3. (S)-1-(2-(trifluoromethyl)phenyl)ethan-1-amine

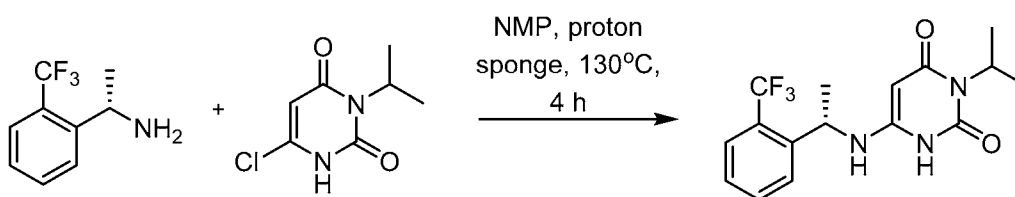
hydrochloride. To a stirred solution of **70.2** (700 mg, 2.39 mmol, 1.00 equiv) in CH₃OH (4 mL) was added 4N HCl in 1,4-dioxane (2 mL) dropwise. The resulting solution was stirred for 1 h at room temperature and then concentrated under reduced pressure. Solid was

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precipitated by the addition of Et₂O (5 mL). The solid was filtered and dried affording the title compound as a white solid (0.32 g, 60%).

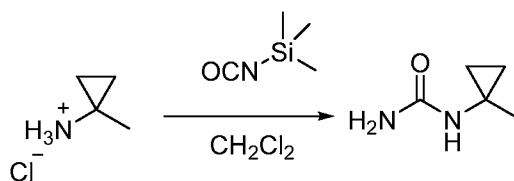


- 5 [0192] **Compound 70.4. (S)-1-(2-(trifluoromethyl)phenyl)ethan-1-amine.** To a 50-mL round-bottom flask was added **70.3** (320 mg, 1.43 mmol, 1.00 equiv) and sodium hydroxide (80 mg, 2.00 mmol, 1.40 equiv) in H₂O (20 mL). The resulting solution was stirred for 1 h at room temperature and was then extracted with EtOAc (20 mL). The organic layer was combined and concentrated under reduced pressure. This afforded 190 mg (70%) of the title compound as light yellow oil.
- 10



- [0193] **Compound 70. (S)-3-isopropyl-6-((1-(2-(trifluoromethyl)phenyl)ethyl)amino)pyrimidine-2,4(1H,3H)-dione.** To a 10-mL round-bottom flask purged and maintained with an inert atmosphere of argon, was added NMP (2 mL), **70.4** (160 mg, 0.85 mmol, 1.00 equiv), **1.3** (160 mg, 0.85 mmol, 1.00 equiv), and proton sponge (273 mg, 1.28 mmol, 1.5 equiv.). The resulting solution was stirred for 4 h at 130 °C. The crude product (200 mg) was purified by chiral preparative HPLC with the following conditions: Column, Phenomenex Lux-2 5u Cellulose-2, 30*150mm; mobile phase, Hex-HPLC and ethanol-HPLC (hold 20% ethanol-HPLC in 14 min); Detector, uv 254/220nm. 160 mg crude product was obtained. The obtained material (60 mg) was further purified using chiral preparative HPLC with following conditions: Column: Phenomenex Lux-2 5μ Cellulose-2 30*150mm; Mobile Phase and Gradient: Hex: EtOH = 80:20; Retention Time (Peak 2) (min):11.106. This resulted in 30 mg of the title compound as a white solid. LC/MS: m/z (ES⁺) 342 (M+H)⁺. ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.84 (br, 1H), 7.78-7.68 (m, 3H), 7.56-7.52 (m, 1H), 6.75 (br s, 1H), 4.93-4.86 (m, 1H), 4.68-4.63 (m, 1H), 4.13 (s, 1H), 1.46 (d, J = 6.8 Hz, 3H), 1.25 (d, J = 7.2 Hz, 6H).
- 15
- 20
- 25

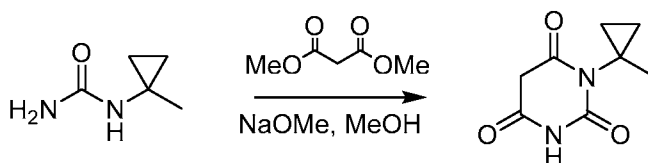
Example 71. Preparation of (*S*)-3-(1-methylcyclopropyl)-6-((1-phenylethyl)amino)pyrimidine-2,4(1*H*,3*H*)-dione.



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[0194] Compound 71.1. 1-(1-methylcyclopropyl)urea. To a stirred solution of 1-methylcyclopropan-1-amine hydrochloride salt (429 mg, 3.99 mmol, 1.00 equiv) and triethylamine (268 mg, 2.65 mmol, 1.00 equiv) in CH₂Cl₂ (6 mL) was added trimethylsilyl isocyanate (366 mg, 3.18 mmol, 1.20 equiv). The resulting mixture was stirred at room temperature overnight and was quenched by the dropwise addition of CH₃OH (2 mL) at 0 °C. The resulting solution warmed to room temperature and stirred for an additional 1 h. The resulting mixture was concentrated under reduced pressure. The crude product was precipitated from CH₃OH:Et₂O (1:40) affording 300 mg (66%) of the title compound as a white solid.

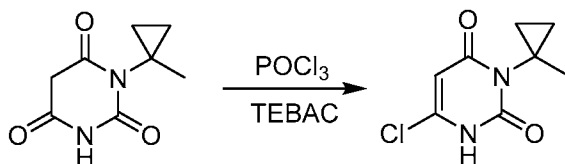
15



[0195] Compound 71.2. 1-(1-methylcyclopropyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione.

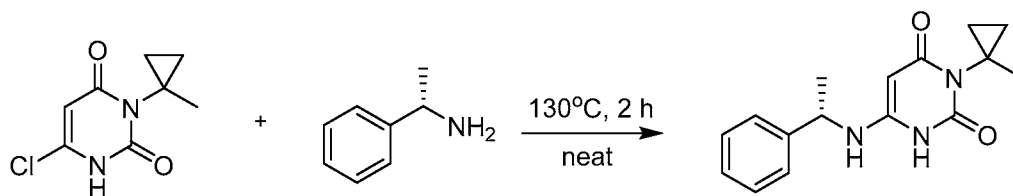
To a stirred solution of **71.1** (320 mg, 2.80 mmol, 1.0 equiv) in CH₃OH (2 mL) was added sodium methoxide (390 mg, 7.2 mmol, 2.5 equiv) and dimethyl malonate (380 mg, 2.88 mmol, 1.0 equiv). The resulting solution was stirred overnight at 65 °C. After cooling, the reaction was quenched by the addition of H₂O (100 mL). The pH of the solution was adjusted to 2 with concentrated HCl and the resulting mixture was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography with EtOAc/petroleum ether (1:3) as eluent. This afforded 100 mg (20%) of the title compound as a white solid. ¹H-NMR (300 MHz, CDCl₃): δ ppm 8.04 (br, 1H), 3.61 (s, 2H), 1.41 (s, 3H), 1.00-, 0.86 (m, 4H).

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[0196] Compound 71.3. 6-chloro-3-(1-methylcyclopropyl)pyrimidine-2,4(1H,3H)-

dione. To **71.2** (100 mg, 0.55 mmol, 1.00 equiv) and triethylbenzylammonium chloride (180 mg, 0.79 mmol, 1.00 equiv) was added POCl₃ (2 mL). The resulting solution was stirred for 3 h at 50 °C and then concentrated under reduced pressure. The residue was carefully quenched by the addition of 10 mL of water/ice and was extracted with EtOAc (2 x 30 mL). The organic layers were combined and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography with CH₂Cl₂/CH₃OH (10:1) as eluent to afford 40 mg (36%) of the title compound as a yellow solid.

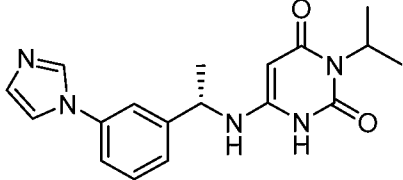
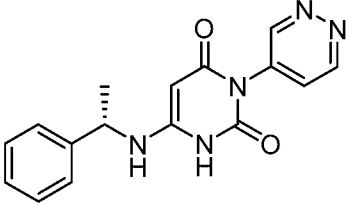
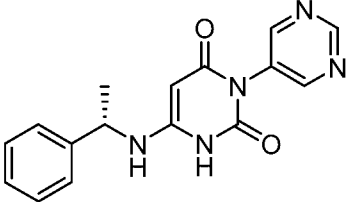
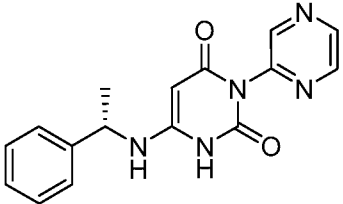


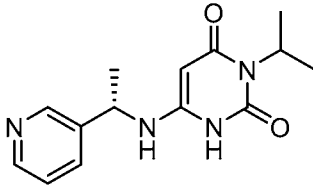
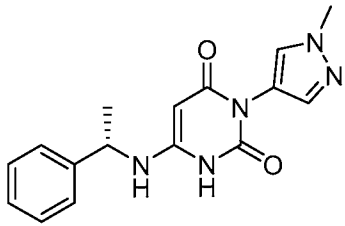
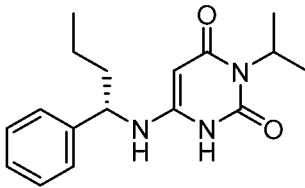
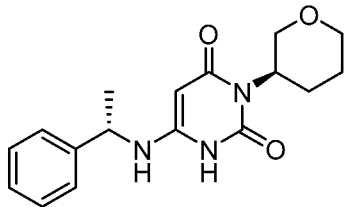
[0197] Compound 71. (S)-3-(1-methylcyclopropyl)-6-((1-

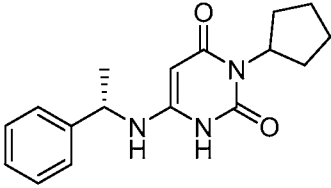
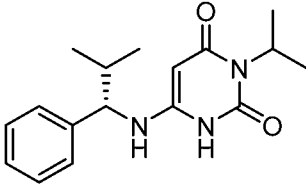
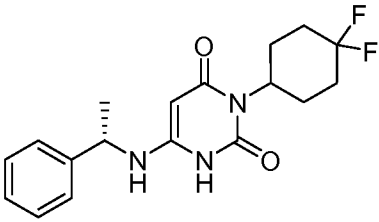
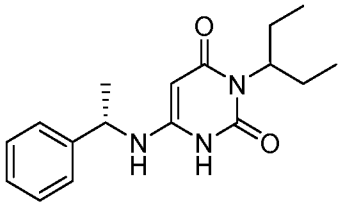
phenylethyl)amino)pyrimidine-2,4(1H,3H)-dione. To **71.3** (40 mg, 0.20 mmol, 1.00 equiv) was added (S)-α-methylbenzylamine (0.5 mL). The reaction mixture was stirred for 2 h at 130 °C and then was concentrated under reduced pressure. The resulting residue was purified by preparative RP-HPLC with the following conditions: Column: X Bridge C18, 19*150 mm, 5 μm; Mobile Phase A: H₂O /0.05% TFA, Mobile Phase B: CH₃CN; Flow rate: 20 mL/min; Gradient: 30% B to 70% B in 10 min. This afforded 15.1 mg (27%) of the title compound as a white solid. LC/MS: m/z (ES⁺) 286 (M+H)⁺. ¹H-NMR (300 MHz, CD₃CN): δ ppm 8.41 (br, 1H), 7.42-7.29 (m, 5H), 5.79 (br, 1H), 4.48-4.44 (m, 1H), 4.30 (s, 1H), 1.47 (d, J = 6.9 Hz, 3H), 1.27 (s, 3H), 0.87-0.77 (m, 4H).

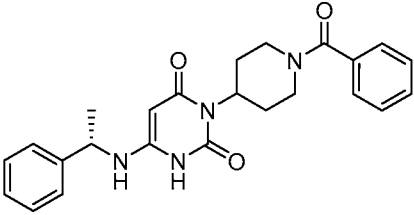
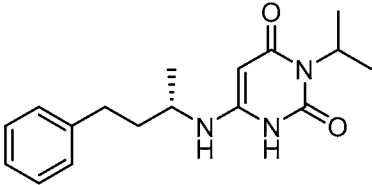
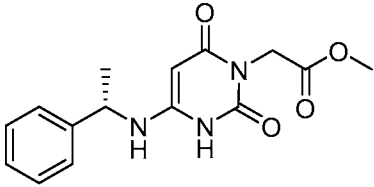
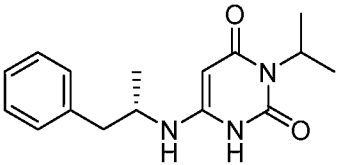
Example 72. Preparation of Additional Pyrimidine Dione Compounds.

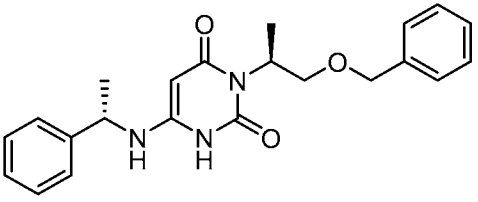
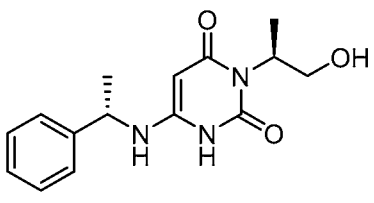
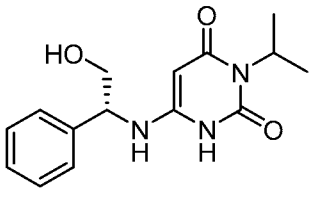
[0198] The compounds in Table 1B were prepared according to the examples as described above (exemplary methods provided as 'Reference. Ex. No.')

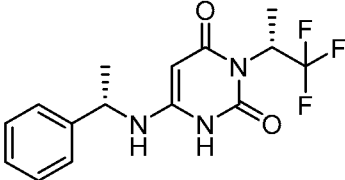
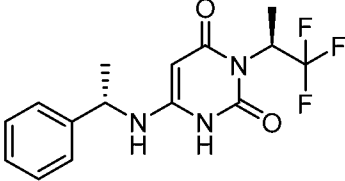
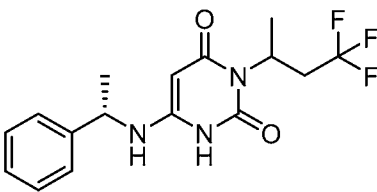
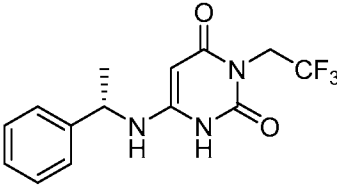
Structure	Compound No. ----- Reference Ex. No.	Observed Mass and/or ¹ H NMR
	72 ----- 17	340 (M+H) ⁺ ¹ H-NMR (300 MHz, DMSO-d ₆): δ ppm 9.89 (br s, 1H), 9.54 (br s, 1H), 8.22 (br s, 1H), 7.82 (br s, 1H), 7.75 (s, 1H), 7.66-7.54 (m, 2H), 7.48 (d, J = 7.5 Hz, 1H), 6.60-6.58 (m, 1H), 4.90-4.83 (m, 1H), 4.55-4.48 (m, 1H), 4.30 (s, 1H), 1.42 (d, J = 6.9 Hz, 3H), 1.27-1.21 (m, 6H).
	73 ----- 15	310 (M+H) ⁺ ¹ H-NMR (400 MHz, DMSO-d ₆): δ ppm 9.20 (m, 1H), 9.04 (br s, 1H), 7.57 (m, 1H), 7.38-7.32 (m, 4H), 7.26-7.21 (m, 1H), 6.76 (m, 1H), 4.69-4.62 (m, 1H), 4.46 (s, 1H), 1.40 (d, J = 6.8 Hz, 3H).
	74 ----- 15	310 (M+H) ⁺ ¹ H-NMR (400 MHz, DMSO-d ₆): δ ppm 8.56 (m, 1H), 8.49 (m, 1H), 8.37 (m, 1H), 7.37-7.31 (m, 4H), 7.26-7.22 (m, 1H), 6.68 (m, 1H), 4.71-4.65 (m, 1H), 4.34 (s, 1H), 1.37 (d, J = 6.8 Hz, 3H).
	75 ----- 15	310 (M+H) ⁺ ¹ H-NMR (400 MHz, DMSO-d ₆): δ ppm 8.60 (m, 1H), 8.57 (m, 1H), 8.49 (br s, 1H), 7.39-7.32 (m, 4H), 7.26-7.22 (m, 1H), 6.68 (m, 1H), 4.69-4.64 (m, 1H), 4.41 (s, 1H), 1.39 (d, J = 6.8 Hz, 3H).

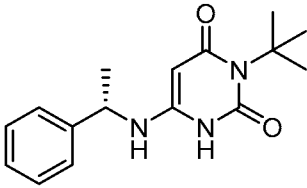
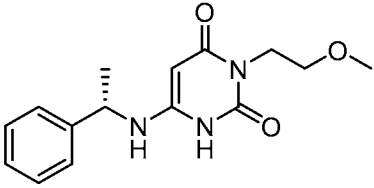
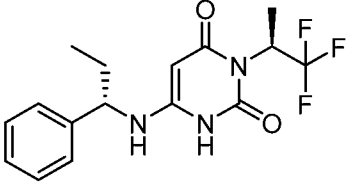
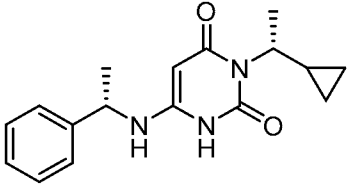
	76 ----- 5 and 58	275 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.70 (br, 1H), 8.60 (d, J = 2.0 Hz, 1H) 8.50 (dd, J = 4.8, 1.6 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.41 (dd, J = 7.6, 4.8 Hz, 1H), 6.67 (br s, 1H), 4.94-4.88 (m, 1H), 4.62-4.58 (m, 1H), 4.38 (s, 1H), 1.45 (d, J = 6.4 Hz, 3H), 1.30-1.28 (m, 6H).
	77 ----- 15	312 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 10.69 (br s, 1H), 7.65 (s, 1H), 7.40-7.20 (m, 7H), 4.52 (quin, J = 6.8 Hz, 1H), 4.40 (s, 1H), 3.30 (br s, 3H), 1.39 (d, J = 7.0 Hz, 3H).
	78 ----- 1	302 (M+H)⁺ ¹H-NMR (400 MHz, CDCl₃): δ ppm 10.58 (br s, 1H), 7.36-7.23 (m, 5H), 5.16 (m, 2H), 4.69 (s, 1H), 4.26 (m, 1H), 1.82-1.71 (m, 2H), 1.44-1.38 (m, 6H), 1.36-1.25 (m, 2H), 0.92 (t, J = 8.0 Hz, 3H).
	79 ----- 11	316 (M+H)⁺ ¹H-NMR (400 MHz, CD₃CN): δ ppm 7.30-7.20 (m, 4H), 7.16-7.11(m, 1H), 6.32 (m, 1H), 4.69-4.62 (m, 1H), 4.43 (quin, J = 6.7 Hz, 1H), 4.29 (s, 1H), 4.00 (t, J = 10.5 Hz, 1H), 3.67-3.59 (m, 1H), 3.44-3.40 (m, 1H), 3.14-3.08 (m, 1H), 2.48-2.38 (m, 1H), 1.56-1.45 (m, 3H), 1.38(d, J = 6.8 Hz, 3H).

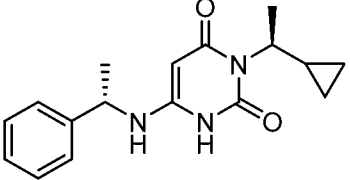
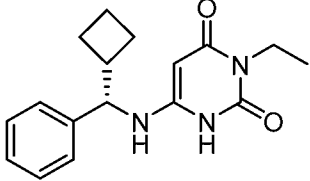
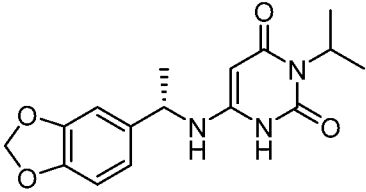
	80 ----- 1	300 (M+H)⁺ ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.82 (br s, 1H), 7.41-7.19 (m, 5H), 6.50 (d, J = 6.7 Hz, 1H), 5.05-5.01 (m, 1H), 4.50-4.46 (m, 1H), 4.34 (s, 1H), 2.01-1.84 (m, 2H), 1.83-1.64 (m, 2H), 1.63-1.51 (m, 2H), 1.49-1.34 (m, 5H).
	81 ----- 5	302 (M+H)⁺ ¹H-NMR (400 MHz, CD₃OD): δ ppm 7.39-7.35 (m, 2H), 7.30-7.28 (m, 3H), 5.06-5.00 (m, 1H), 4.53 (s, 1H), 4.12 (d, J = 7.2 Hz, 1H), 2.10-2.01 (m, 1H), 1.40-1.37 (m, 6H), 1.02 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H).
	82 ----- 7	350 (M+H)⁺ ¹H-NMR (400 MHz, CD₃OD): δ ppm 7.43-7.33 (m, 4H), 7.30-7.26 (m, 1H), 4.82-4.75 (m, 1H), 4.54-4.49 (m, 2H), 2.74-2.65 (m, 2H), 2.15-2.05 (m, 2H), 1.93-1.79 (m, 2H), 1.61-1.57 (m, 2H), 1.51 (d, J = 6.8 Hz, 3H).
	83 ----- 1	302 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.73 (br s, 1H), 7.40 - 7.22 (m, 5H), 6.50 (d, J = 5.1 Hz, 1H), 4.57-4.44 (m, 2H), 4.34 (br s, 1H), 1.90 (ddd, J = 13.3, 9.8, 7.4 Hz, 2H), 1.61- 1.50 (m, 2H), 1.38 (d, J = 6.7 Hz, 3H), 0.74-0.60 (m, 6H).

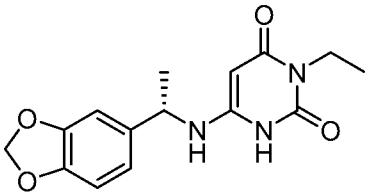
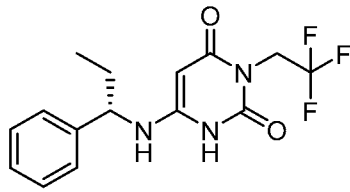
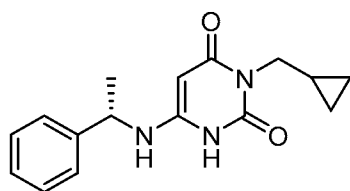
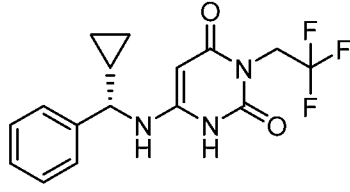
	84 ---- 12	419 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.88 (br s, 1H), 7.45-7.41 (m, 3H), 7.37-7.29 (m, 6H), 7.27-7.22 (m, 1H), 6.54 (d, J = 6.7 Hz, 1H), 4.84-4.79 (m, 1H), 4.52-4.47 (m, 1H), 4.36 (d, J = 2.4 Hz, 1H), 3.57 (m, 2H), 3.05 (m, 2H), 2.38 (m, 2H), 1.50 (m, 2H), 1.38 (d, J = 6.7 Hz, 3H).
	85 ---- 1	302 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.73 (br s, 1H), 7.31-7.22 (m, 2H), 7.21-7.12 (m, 3H), 5.93 (d, J = 8.2 Hz, 1H), 5.00-4.87 (m, 1H), 4.44 (s, 1H), 4.30 (s, 1H), 3.37-3.31 (m, 1H), 2.65-2.53 (m, 2H), 1.70 (dtd, J = 9.0, 6.9, 6.9, 2.0 Hz, 1H), 1.29 (d, J = 7.0 Hz, 6H), 1.11 (d, J = 6.3 Hz, 3H).
	86 ---- 11	304 (M+H)⁺ ¹H-NMR (400 MHz, CD₃OD + CDCl₃): 7.22-7.15 (m, 2H), 7.13-7.07 (m, 3H), 6.28 (d, J = 6.1 Hz, 1H), 4.44 (s, 1H), 4.38 (s, 2H), 4.30-4.23 (m, 1H), 3.55 (s, 3H), 1.35 (d, J = 6.8 Hz, 3H).
	90 ---- 1	288 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.77 (br s, 1H), 7.32-7.26 (m, 2H), 7.23-7.12 (m, 3H), 5.85 (d, J = 7.9 Hz, 1H), 4.97-4.87 (m, 1H), 4.55 (s, 1H), 3.77-3.65 (m, 1H), 2.76-2.68 (m, 2H), 1.27 (d, J = 7.0 Hz, 6H), 1.05 (d, J = 6.7 Hz, 3H).

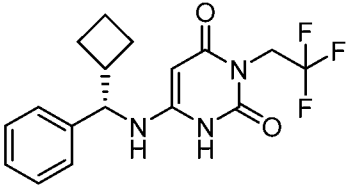
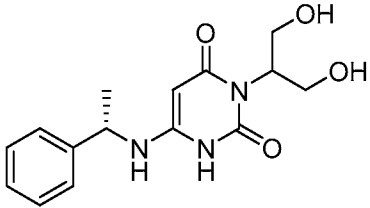
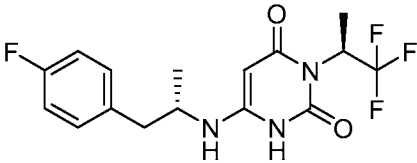
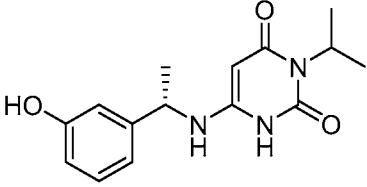
	91 ----- 53	380 (M+H)+ ¹H-NMR (400 MHz, CDCl₃): δ ppm 9.77 (br s, 1H), 7.33-7.23 (m, 10H), 5.23 (br s, 1H), 4.67 (br s, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.44-4.37 (m, 1H), 4.09 (t, J = 9.2 Hz, 1H), 3.63 (dd, J = 9.8, 5.9 Hz, 1H), 1.48 (d, J = 6.7 Hz, 3H), 1.35 (d, J = 7.0 Hz, 3H).
	92 ----- 54	290 (M+H)+ ¹H-NMR (400 MHz, CDCl₃): δ ppm 9.68 (s, 1H), 7.41 - 7.22 (m, 5H), 5.62 (s, 1H), 5.08 (td, J = 7.3, 2.9 Hz, 1H), 4.67 (s, 1H), 4.48 - 4.35 (m, 1H), 3.98 (dd, J = 11.9, 7.6 Hz, 1H), 3.75 (dd, J = 11.7, 3.1 Hz, 1H), 1.52 (d, J = 7.0 Hz, 3H), 1.36 (d, J = 7.0 Hz, 3H).
	93 ----- 1	290 (M+H)+ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 10.01 (d, J = 2.0 Hz, 1H), 7.37-7.23 (m, 5H), 6.61 (d, J = 6.3 Hz, 1H), 5.19 (t, J = 5.1 Hz, 1H), 4.93-4.83 (m, 1H), 4.40- 4.33 (m, 1H), 4.24 (d, J = 2.4 Hz, 1H), 3.66 (dt, J = 11.1, 4.7 Hz, 1H), 3.52- 3.44 (m, 1H), 1.25 (dd, J= 6.9, 2.2 Hz, 6H).

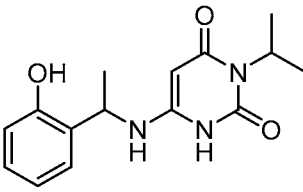
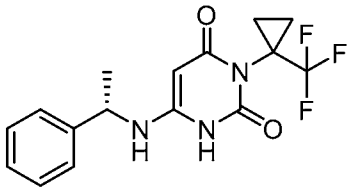
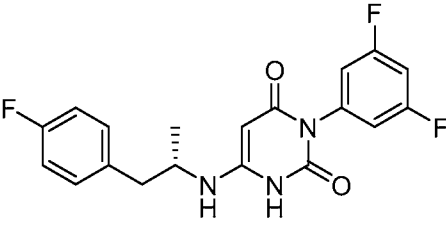
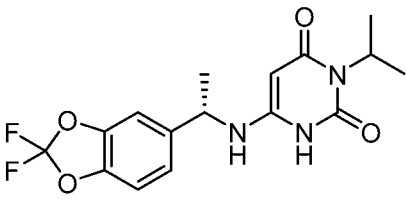
	94 ----- 1 and 50	328 (M+H)⁺ ¹H NMR (400 MHz, DMSO-d₆ @ 75 °C): δ ppm 9.91 (br s, 1H), 7.44-7.23 (m, 5H), 6.58 (br s, 1H), 5.52 (br s, 1H), 4.59-4.51 (m, 1H), 4.46 (br s, 1H), 1.52 (d, J = 7.0 Hz, 3H), 1.43 (d, J = 7.0 Hz, 3H).
	95 ----- 1 and 50	328 (M+H)⁺ ¹H NMR (400 MHz, DMSO-d₆ @ 75 °C): δ ppm 9.91 (br s, 1H), 7.44-7.23 (m, 5H), 6.58 (br s, 1H), 5.52 (br s, 1H), 4.59-4.51 (m, 1H), 4.46 (br s, 1H), 1.52 (d, J = 7.0 Hz, 3H), 1.43 (d, J = 7.0 Hz, 3H).
	99 ----- 1	342 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆ @ 50 °C): δ ppm 9.79 (br s, 1H), 7.46-7.23 (m, 5H), 6.51 (d, J = 6.7 Hz, 1H), 5.13 (br s, 1H), 4.50 (quin, J = 6.9 Hz, 1H), 4.37 (s, 1H), 3.15-3.01 (m, 1H), 2.60-2.50 (m, 1H), 1.40 (d, J = 6.7 Hz, 3H), 1.31 (d, J = 7.0 Hz, 3H).
	100 ----- 1 and 50	314 (M+H)⁺ ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 10.32 (br s, 1H), 7.40-7.34 (m, 4H), 7.29-7.25 (m, 1H), 6.81 (d, J = 6.6 Hz, 1H), 4.60-4.54 (m, 1H), 4.49-4.40 (m, 3H), 1.42 (d, J = 6.6 Hz, 3H).

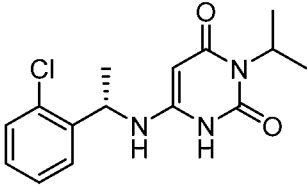
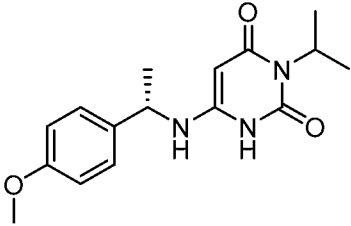
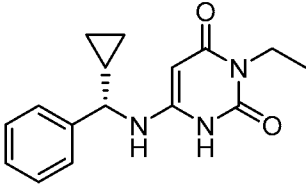
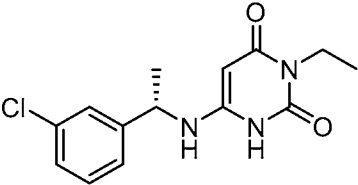
	101 ---- 1 and 50	288 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.50 (br s, 1H), 7.56-7.44 (m, 4H), 7.38-7.24 (m, 1H), 6.41 (d, J = 6.4 Hz, 1H), 4.45 (q, J = 6.8 Hz, 1H), 4.25 (s, 1H), 1.54 (s, 9H), 1.38 (d, J = 6.8 Hz, 3H).
	102 ---- 57	290 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 10.31 (br s, 1H), 7.35-7.23 (m, 5H), 5.72 (d, J = 4.7 Hz, 1H), 4.67 (s, 1H), 4.40 (quin, J = 6.6 Hz, 1H), 4.05 (t, J = 5.7 Hz, 2H), 3.56 (t, J = 5.7 Hz, 2H), 3.27 (s, 3H), 1.46 (dd, J = 6.7, 1.6 Hz, 3H).
	103 ---- 1 and 59	342 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆, @ 75 °C): δ ppm 9.91 (br s, 1H), 7.37-7.24 (m, 5H), 6.59 (br s, 1H), 5.51 (br s, 1H), 4.45 (br s, 1H), 4.31 (q, J = 6.9 Hz, 1H), 1.83-1.67 (m, 2H), 1.52 (d, J = 7.4 Hz, 3H), 0.86 (t, J = 7.4 Hz, 3H).
	104 ---- 1 and 58	300 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.80 (br s, 1H), 7.37-7.31 (m, 4H), 7.27-7.22 (m, 1H), 6.52 (br, 1H), 4.48 (q, J = 6.7 Hz, 1H), 4.32 (br s, 1H), 3.93 (br, 1H), 1.62 (br, 1H), 1.38 (d, J = 6.7 Hz, 3H), 1.33 (d, J = 7.0 Hz, 3H), 0.48-0.41 (m, 1H), 0.27-0.21 (m, 1H), 0.14 (dq, J = 9.4, 4.8 Hz, 1H), 0.02 (m, 1H).

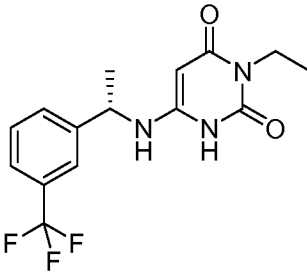
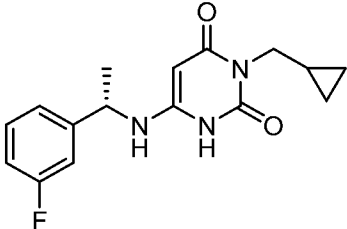
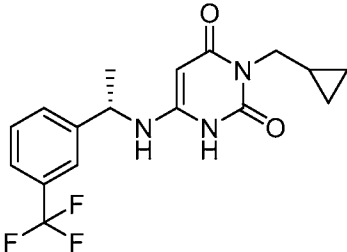
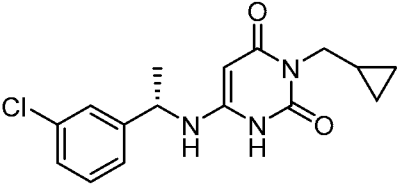
	105 ---- 1 and 58	300 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.81 (br s, 1H), 7.37-7.30 (m, 4H), 7.26-7.22 (m, 1H), 6.53 (d, J = 5.9 Hz, 1H), 4.48 (q, J = 6.8 Hz, 1H), 4.32 (d, J = 1.6 Hz, 1H), 3.85 (m, 1H), 1.61 (m, 1H), 1.38 (d, J = 7.0 Hz, 3H), 1.32 (d, J = 6.7 Hz, 3H), 0.49-0.42 (m, 1H), 0.28-0.22 (m, 1H), 0.17-0.12 (m, 1H), 0.01-(-)0.05, (m, 1H).
	106 ---- 8	300 (M+H)⁺ ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 9.96 (br s, 1H), 7.36-7.24 (m, 5H), 6.48 (d, J = 6.3 Hz, 1H), 4.40 (s, 1H), 4.36-4.27 (m, 1H), 3.63 (q, J = 6.6 Hz, 2H), 2.67-2.50 (partially obscured m, 1H) 2.02-1.95 (m, 1H), 1.90-1.78 (m, 4H), 1.66-1.57 (m, 1H), 0.98 (t, J = 6.6 Hz, 3H).
	107 ---- 67 and 59	318 (M+H)⁺ ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 9.76 (br s, 1H), 6.92 (d, J = 1.8 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 6.80 (dd, J = 6.0, 1.8 Hz, 1H), 6.44 (d, J = 7.2 Hz, 1H), 5.99 (s, 2H), 4.93-4.88 (m, 1H), 4.41-4.35 (m, 2H), 1.35 (d, J = 6.6 Hz, 3H) 1.28 (d, J = 1.2 Hz, 3H) 1.26 (d, J = 1.2 Hz, 3H).

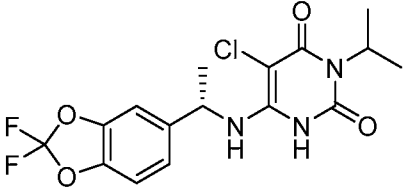
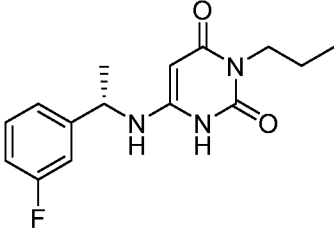
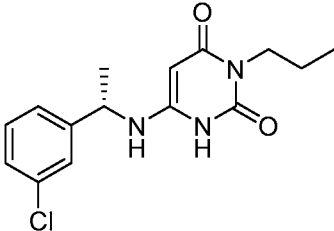
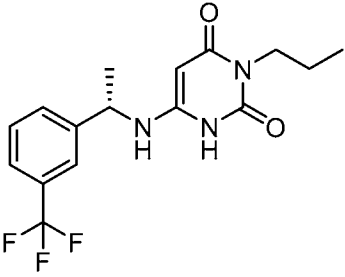
	108 ---- 67 and 59	304 (M+H)⁺ ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 9.93 (br s, 1H), 6.92 (d, J = 1.5 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 6.82-6.79 (m, 1H), 6.48 (d, J = 7.2 Hz, 1H), 5.99 (s, 2H), 4.45-4.39 (m, 2H), 3.65 (q, J = 6.6 Hz, 2H), 1.36 (d, J = 6.9 Hz, 3H) 0.99 (t, J = 6.9 Hz, 3H).
	109 ---- 1, 5 and 7	328 (M+H)⁺ ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 10.28 (br s, 1H), 7.39-7.24 (m, 5H), 6.81 (d, J = 6.6 Hz, 1H), 4.47-4.33 (m, 4H), 1.80-1.67 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H).
	110 ---- 1 and 50	286 (M+H)⁺ ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 10.01 (br s, 1H), 7.39-7.33 (m, 4H), 7.30-7.23 (m, 1H), 6.60 (d, J = 6.0 Hz, 1H), 4.52 (q, J = 6.6 Hz, 1H), 4.38 (s, 1H), 3.49 (d, J = 6.9 Hz, 2H), 1.40 (d, J = 6.9 Hz, 3H) 1.08-1.00 (m, 1H), 0.37-0.33 (m, 2H), 0.28-0.23 (m, 2H).
	111 ---- 7 and 59	340 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 10.29 (br s, 1H), 7.37-7.33 (m, 4H), 7.30-7.25 (m, 1H), 6.98 (d, J = 5.6 Hz, 1H), 4.42 (q, J = 9.2 Hz, 2H), 4.35 (d, J = 1.6 Hz, 1H), 3.89-3.85 (m, 1H), 1.24-1.15 (m, 1H) 0.61-0.56 (m, 1H), 0.50-0.33 (m, 3H).

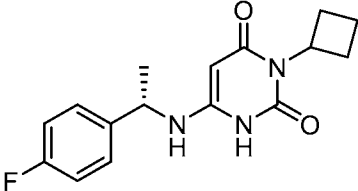
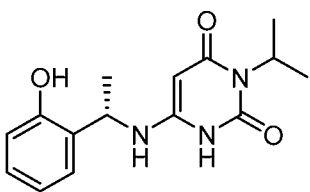
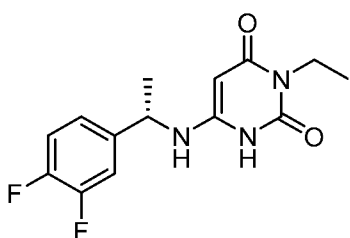
	112 ---- 8 and 59	354 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 10.27 (br s, 1H), 7.45-7.25 (m, 5H), 6.73 (br s, 1H), 4.46-4.35 (m, 4H), 2.67-2.50 (partially obscured m, 1H), 2.04-2.01 (m, 1H), 1.90-1.79 (m, 4H), 1.68-1.62 (m, 1H).
	113 ---- 15	306 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆ @ 90 °C): δ ppm 9.86 (br s, 1H), 7.39-7.31 (m, 4H), 7.29-7.25 (m, 1H), 6.48 (d, J = 6.7 Hz, 1H), 5.00-4.91 (m, 1H), 4.78 (m, 1H), 4.56-4.50 (m, 1H), 4.45-4.38 (m, 2H), 3.76-3.70 (m, 2H), 1.42 (d, J = 7.4 Hz, 3H).
	114 ---- 1 and 51	360 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆ @ 90 °C): δ ppm 9.86 (br s, 1H), 7.25 (dd, 8.4, 5.7 Hz, 2H), 7.10-7.04 (m, 2H), 5.94 (br s, 1H), 5.52 (br s, 1H), 4.62 (br s, 1H), 3.79-3.71 (m, 1H), 2.76 (d, J = 6.7 Hz, 2H), 1.55 (d, J = 7.0 Hz, 3H), 1.11 (d, J = 6.3 Hz, 3H).
	115 ---- 62	290 (M+H)⁺

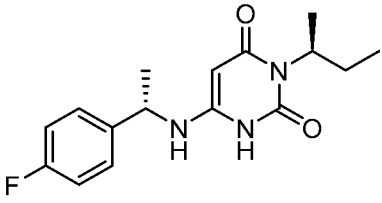
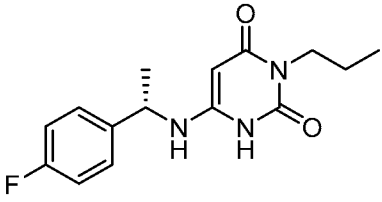
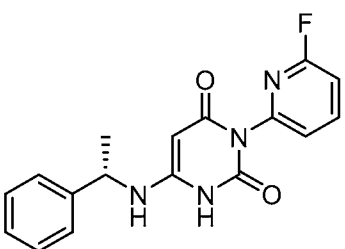
	116 ---- 62	290 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.83 (br s, 1H), 9.68 (br s, 1H), 7.14 (dd, J = 7.4, 1.6 Hz, 1H), 7.05 (td, J = 7.6, 1.6 Hz, 1H), 6.82-6.74 (m, 2H), 6.40 (d, J = 7.0 Hz, 1H), 4.92-4.85 (m, 1H), 4.60 (quin, J = 6.9 Hz, 1H), 4.30 (d, J = 2.4 Hz, 1H), 1.35 (d, J = 6.7 Hz, 3H), 1.27-1.22 (m, 6H).
	117 ---- 1 and 59	340 (M+H)⁺ ¹H-NMR (300 MHz, CDCl₃): δ ppm 10.40 (br s, 1H), 7.44-7.26 (m, 5H), 6.13 (br s, 1H), 4.80 (br s, 1H), 4.45 (m, 1H), 1.76-1.52 (m, 5H), 1.35-1.27 (m, 2H).
	118 ---- 1 and 51	376 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 10.27 (br s, 1H), 7.29-7.22 (m, 3H), 7.15-7.10 (m, 2H), 7.01 (dd, J = 8.2, 2.3 Hz, 2H), 6.12 (br s, 1H), 4.72 (d, J = 2.0 Hz, 1H), 3.79-3.71 (m, 1H), 2.76 (d, J = 6.7 Hz, 2H), 1.09 (d, J = 6.7 Hz, 3H).
	119 ---- 5 and 59	354 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.84 (br s, 1H), 7.43 (d, J = 1.2 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.21 (dd, J = 8.4, 1.2 Hz, 1H), 6.54 (d, J = 6.8 Hz, 1H), 4.90 (q, J = 6.8 Hz, 1H), 4.55-4.52 (m, 1H), 4.34 (d, J = 2.0 Hz, 1H), 1.39 (d, J = 6.8 Hz, 3H), 1.31-1.26 (m, 6H).

	120 ---- 5 and 59	308 (M+H)⁺ ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 9.87 (m, 1H), 7.48-7.28 (m, 4H), 6.66 (d, J = 6.6 Hz, 1H), 4.93-4.84 (m, 1H), 4.70 (quin, J = 6.6 Hz, 1H), 4.08 (s, 1H), 1.41 (d, J = 6.6 Hz, 3H), 1.28-1.24 (m, 6H).
	121 ---- 5	304 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.68 (m, 1H), 7.25-7.21 (m, 2H), 6.91-6.87 (m, 2H), 6.43 (m, 1H), 4.92-4.85 (m, 1H), 4.41 (quin, J = 6.7 Hz, 1H), 4.32 (s, 1H), 3.71 (s, 3H), 1.35 (d, J = 6.7 Hz, 3H), 1.27-1.23 (m, 6H).
	122 ---- 7 and 59	286 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 7.38-7.33 (m, 4H), 7.28-7.25 (m, 1H), 6.80 (br s, 1H), 4.24 (s, 1H), 3.82-3.78 (m, 1H), 3.63 (q, J = 6.8 Hz, 2H), 1.17-1.13 (m, 1H), 0.97 (t, J = 6.8 Hz, 3H), 0.59-0.54 (m, 1H), 0.47-0.32 (m, 3H).
	123 ---- 1 and 59	294 (M+H)⁺ ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 10.00 (br s, 1H), 7.44 (s, 1H), 7.42-7.30 (m, 3H), 6.61 (d, J = 6.6 Hz, 1H), 4.57-4.53 (m, 1H), 4.38 (d, J = 1.8 Hz, 1H), 3.65 (q, J = 6.9 Hz, 2H), 1.39 (d, J = 6.9 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H).

	124 --- 1 and 59	328 (M+H) ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 7.75 (s, 1H), 7.72-7.59 (m, 3H), 6.99 (br s, 1H), 4.68-4.62 (m, 1H), 4.38 (s, 1H), 3.65 (q, J = 6.6 Hz, 2H), 1.42 (d, J = 6.6 Hz, 3H), 1.01 (t, J = 4.5 Hz, 3H).
	125 --- 1 and 59	304 (M+H)+ ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 10.01 (br s, 1H), 7.42 (dd, J = 7.8, 6.0 Hz, 1H), 7.20 (d, J = 7.5 Hz, 2H), 7.12-7.06 (m, 1H), 6.62 (d, J = 7.2 Hz, 1H), 4.56 (quin, J = 6.9 Hz, 1H), 4.39 (s, 1H), 3.49 (d, J = 6.9 Hz, 2H), 1.40 (d, J = 6.6 Hz, 3H), 1.07-0.99 (m, 1H), 0.37-0.34 (m, 2H), 0.30-0.22 (m, 2H).
	126 --- 1 and 59	354 (M+H)+ ¹H-NMR (300 MHz, CD₃OD): δ ppm 7.73-7.50 (m, 4H), 4.63 (q, J = 6.9 Hz, 1H), 3.62 (d, J = 7.2 Hz, 2H), 1.50 (d, J = 6.9 Hz, 3H), 1.17-1.10 (m, 1H), 0.45-0.39 (m, 2H), 0.32-0.26 (m, 2H).
	127 --- 1 and 59	320 (M+H)+ ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 10.01 (br s, 1H), 7.45 (s, 1H), 7.42-7.30 (m, 3H), 6.64 (d, J = 6.9 Hz, 1H), 4.58-4.53 (m, 1H), 4.39 (s, 1H), 3.50 (d, J = 7.2 Hz, 2H), 1.40 (d, J = 6.6 Hz, 3H), 1.07-1.03 (m, 1H), 0.37-0.31 (m, 2H), 0.25-0.22 (m, 2H).

	128 ---- 3	388(M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.50 (br s, 1H), 7.52- 7.22 (m, 3H), 4.87-4.72 (m, 1H), 4.52-4.41 (m, 1H), 1.60-1.48 (m, 3H), 1.41-1.27 (m, 6H).
	129 ---- 1 and 59	292 (M+H)⁺ ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 10.00 (br s, 1H), 7.40 (dt, J = 7.8 Hz, 0.6 Hz, 1H), 7.26 (d, J = 7.8 Hz, 2H), 7.09-7.06 (m, 1H), 6.60 (d, J = 6.9 Hz, 1H), 4.46 (q, J = 6.6 Hz, 1H), 4.38 (s, 1H), 3.60-3.55 (m, 2H), 1.47-1.39 (m, 5H), 0.79 (t, J = 7.5 Hz, 3H).
	130 ---- 1 and 59	308 (M+H)⁺ ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 10.01 (br s, 1H), 7.44 (t, J = 0.9 Hz, 1H), 7.41-7.38 (m, 1H), 7.34-7.31 (m, 2H), 6.62 (d, J = 5.1 Hz, 1H), 4.55 (q, J = 6.7 Hz, 1H), 4.38 (s, 1H), 3.54 (dd, J = 6.0, 5.7 Hz, 2H), 1.47-1.39 (m, 5H), 0.84 (t, J = 7.5 Hz, 3H).
	131 ---- 1 and 59	342 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 10.05 (br s, 1H), 7.74 (s, 1H), 7.68-7.56 (m, 3H), 6.69 (d, J = 6.4 Hz, 1H), 4.70-4.63 (m, 1H), 4.40 (s, 1H), 3.59-3.54 (m, 2H), 1.49-1.40 (m, 5H), 0.86 (t, J = 6.0 Hz, 3H).

	132 --- 1	304 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.85 (br s, 1H), 7.37-7.33 (m, 2H), 7.18-7.13 (m, 2H), 6.52 (d, J = 7.4 Hz, 1H), 5.14-5.05 (m, 1H), 4.50 (quin, J = 6.8 Hz, 1H), 4.31 (s, 1H), 2.84-2.78 (m, 2H), 1.97-1.91 (m, 2H), 1.70-1.54 (m, 2H), 1.36 (t, J = 6.7 Hz, 3H).
	133 --- 1	290 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.83 (br s, 1H), 9.68 (br s, 1H), 7.14 (dd, J = 7.4, 1.6 Hz, 1H), 7.07-7.03 (m, 1H), 6.81-6.74 (m, 2H), 6.42 (d, J = 7.0 Hz, 1H), 4.92-4.85 (m, 1H), 4.60 (quin, J = 6.8 Hz, 1H), 4.31 (d, J = 2.3 Hz, 1H), 1.35 (d, J = 7.0 Hz, 3H), 1.27-1.22 (m, 6H).
	134 --- 1	296 (M+H)⁺ ¹H-NMR (300 MHz, DMSO-d₆): δ ppm 10.03 (br s, 1H), 7.48-7.39 (m, 2H), 7.23-7.20 (m, 1H), 6.60 (d, J = 5.1 Hz, 1H), 4.58-4.53 (m, 1H), 4.38 (s, 1H), 3.66 (q, J = 5.1 Hz, 2H), 1.39 (d, J = 5.1 Hz, 3H), 0.99 (t, J = 5.1 Hz, 3H).

	135 ---- 1	306 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.95 (br s, 1H), 7.36 (dd, J = 9.0, 5.5 Hz, 2H), 7.18-7.14 (m, 2H), 6.54 (d, J = 7.0 Hz, 1H) 4.66 (br s, 1H), 4.54-4.49 (m, 1H), 4.34 (s, 1H), 1.97-1.86 (m, 1H), 1.65-1.55 (m, 1H), 1.38 (d, J = 6.8 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H), 0.70 (t, J = 6.8 Hz, 3H).
	136 ---- 1	292 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 9.95 (br s, 1H), 7.36 (dd, J = 9.0, 5.5 Hz, 2H), 7.18-7.14 (m, 2H), 6.54 (d, J = 7.0 Hz, 1H) 4.56-4.49 (m, 1H), 4.35 (d, J = 2.3 Hz, 1H), 3.57-3.53 (m, 2H), 1.44-1.36 (m, 5H), 0.77 (t, J = 7.4 Hz, 3H).
	137 ---- 65	327 (M+H)⁺ ¹H-NMR (400 MHz, DMSO-d₆): δ ppm 10.36 (br s, 1H), 8.09 (q, J = 8.0 Hz, 1H), 7.39- 7.35 (m, 4H), 7.30-7.22 (m, 3H), 6.87 (m, 1H), 4.61 (quin, J = 6.8 Hz, 1H), 4.49 (s, 1H), 1.44 (d, J = 6.8 Hz, 3H).

Example 73. Myosin inhibition assay

[0199] Small molecule agents were assessed for their ability to inhibit the enzymatic activity of bovine cardiac myosin using a biochemical assay that couples the release of ADP (adenosine diphosphate) from cardiac myosin to an enzymatic coupling system consisting of pyruvate kinase and lactate dehydrogenase (PK/LDH) and monitoring the absorbance decrease of NADH (at 340 nm) as a function of time. PK converts ADP to ATP (adenosine triphosphate) by converting PEP (phosphoenolpyruvate) to pyruvate. Pyruvate is then converted to lactate by LDH by converting NADH (nicotinamide adenine dinucleotide) to

NAD (oxidized nicotinamide adenine dinucleotide). The source of cardiac myosin was from bovine heart in the form of skinned myofibrils. Prior to testing small molecule agents, the bovine myofibrils were assessed for their calcium responsiveness and the calcium concentration that achieves either a 50% (pCa_{50}) or 75% (pCa_{75}) activation of the myofibril system was chosen as the final condition for assessing the inhibitory activity of the small molecule agents. All enzymatic activity was measured in a buffered solution containing 12 mM PIPES (piperazine-N,N'-bis(2-ethanesulfonic acid), 2 mM magnesium chloride at pH 6.8 (PM12 buffer). Final assay conditions were 1 mg/mL of bovine cardiac myofibrils, 0.4 mM PK/LDH, 50 μ M ATP, 0.1 mg/mL BSA (bovine serum albumin), 10 ppm antifoam, 1 mM DTT, 0.5 mM NADH, 1.5 mM PEP at the desired free calcium concentration required to achieve either 50% or 75% activation of the myofibrils.

[0200] A dilution series of compound was created in DMSO such that the final desired concentration of compound would be achieved in a volume of 100 μ L with a fixed DMSO concentration of 2% (v/v). Typically 2 μ L of the dilution series were added to 96 well plate to achieve an 8 or 12 point dose response. Following the addition of 50 μ L of a solution containing bovine cardiac myofibrils, PK/LDH and a solution of calcium (that achieved the desired activation), the enzymatic reaction was started with the addition of 50 μ L of a solution containing ATP, PEP and NADH. The reaction progress was followed in a Molecular Devices M5e plate reader at ambient temperature using clear half area plates. The plate reader was configured to read absorbance at 340 nm in kinetics mode for 15 minutes. Data were recorded as the slope of the absorbance response to time. The slopes of the absorbance response as a function of time were normalized to slopes on the plate containing DMSO. This normalized rate was then plotted as a function of small molecule concentration and the data was fitted to a four-parameter fit using GraphPad Prism. The midpoint of this plot is the IC_{50} and is the concentration at which fifty percent of the total response is inhibited. Any agent that failed to achieve a fifty percent inhibition at the highest concentration tested was reported as an IC_{50} greater than the highest concentration tested (ie. $IC_{50} > 25 \mu$ M).

Table 2. Myosin Inhibition Activity of Selected Compounds^a

Compound No.	Biochemical Activity (pCa_{75})	Biochemical Activity (pCa_{50})
--------------	-------------------------------------	-------------------------------------

1	+++	+++
2	++	
3	+++	
4	+++	
5	+++	
6	+++	
7	+++	
8	+++	
9	+++	
10	+++	
11	++	
12	+++	
13	+++	
14	+++	
15	+++	
16	++	
17	+++	
21	+++	
22	++	
24	+++	
25	+	
26	+++	
27	+++	+++
28	+++	
29	+++	
30	+++	
31	+++	
32	+++	
33	+++	
34	+++	
35	+++	+++
36		++
37	++	
38	+++	+++
39	+++	
40	+++	
41	+++	
42	+++	
43	+++	
44	+++	
45	+++	+++
46	++	
47	++	
48	++	++

49	+++	+++
50	+++	
51	++	
52	+++	
53	++	
54	++	++
55	+++	
56	+	
57		++
58	+++	
59	+++	
61	++	
62		+++
63		+++
64		++
65		++
66		++
67		+++
68		+++
69	++	+++
70	++	
71		+++
72	++	
73	++	
74	++	
75	++	
76	++	
77	++	
78	+++	
79	++	
80	+++	
81	++	
82	+++	+++
83	+++	
84	+++	
85	+++	
86	++	
90	++	
91	++	
92	++	++
93	+++	++
94	+++	
95	+++	+++
99	+++	

100	++	
101		++
102		++
103		+++
104		+++
105		+++
106		+++
107		+++
108		+++
109		++
110		++
111		++
112		+++
113		++
114		+++
115		
116		+++
117		+++
118		+++
119		+++
120		+++
121		+++
122		++
123		+++
124		+++
125		+++
126		++
127		+++
128		++
129		++
130		+++
131		+++
132		+++
133		+++
134		+++
135		+++
136		+++
137		+++

^a +++ corresponds to IC50 values below 1 uM. ++ corresponds to IC50 values from 1 to 15 uM. + corresponds to IC50 values above 15 uM.

[0201] Selectivity against rabbit skeletal myofibrils was assessed as described above with the exception that the source of myosin was that of fast skeletal myosin from rabbit in the form of myofibrils. Dose responses against rabbit skeletal myofibrils were also determined as described above.

5

Example 74. Stereochemical preference for activity

[0202] Matched pairs of stereoisomers were tested for their ability to inhibit myosin activity as described above. The results are summarized in Table 3. In all cases, the (R) stereoisomer is significantly less active than the (S) stereoisomer.

10

Table 3. Relative activities of (S) and (R) stereoisomers^a

(S) Stereoisomer			(R) Stereoisomer		
Cmpd No.	IC50 (pCa ₇₅)	IC50 (pCa ₅₀)	Cmpd No.	IC50 (pCa ₇₅)	IC50 (pCa ₅₀)
1	0.67 μ M	0.56 μ M	19R	23.93 μ M	51.87 μ M
21	0.39 μ M		20R	19.64 μ M	
59	0.45 μ M		60R	>39.2 μ M	

^aassay conducted using 0.5 μ M myosin, therefore IC50 values below 1.0 μ M are approximate.

15

Example 75. Cardiomyocyte contractility assay

[0203] Contractility of adult rat ventricular myocytes is determined by edge detection with an IonOptix contractility system. Aliquots of myocytes in Tyrode buffer (137 mM NaCl, 3.7 mM KCL, 0.5 mM MgCl₂, 1.5 mM CaCl₂, 4 mM HEPES, 11 mM glucose) are placed in a perfusion chamber (Series 20 RC-27NE; Warner Instruments), allowed to adhere to the coverslip, and then perfused with 37°C Tyrode buffer. Myocytes are field stimulated at 1Hz and 10V. Only myocytes with clear striations, quiescent prior to pacing, with a cell length of 120-180 microns, a basal fractional shortening equal to 3-8% of the cell length, and a contraction velocity greater than 100 microns per second are used for contractility experiments. To determine the response to compounds, myocytes are first perfused for 60 seconds with Tyrodes buffer followed by 5 minutes of compound and a 140 second washout with Tyrodes buffer. Data is continuously recorded using IonOptix software. Contractility data is analyzed using Ionwizard software (IonOptix). For each cell, 10-20 contractility transients were averaged and compared under basal (no compound) and compound-treated

30

conditions. Compound activity is measured by effects on fractional shortening (FS), where fractional shortening is the ratio of the peak length of the cell at contraction divided by the basal cell length normalized to 100% for an untreated cell.

Table 4. Inhibition of Cardiomyocyte Contraction by Selected Compounds^a

ID	Activity at 0.3 uM	Activity at 1.0 uM
1	++	+++
2	++	+++
12	n.d.	++
19	n.d.	+
27	++	n.d.
67	n.d.	+++

^a + represents fractional shortening inhibition values less than 33%. ++ represents fractional shortening inhibition values from 33% to 66%. +++ represents fractional shortening inhibition values greater than 66%.

Example 76. Acute pharmacodynamic effect in rat.

[0204] Representative compounds were tested for their ability to modulate cardiac contractility in rat as a measure of *in vivo* target engagement. Fractional shortening, a measure of contractility, was determined by noting the change in the diameter of the left ventricle at the end of systole/contraction (LVESd) relative to diastole/relaxation (LVEDd) and expressing this change as the ratio $FS = (LVEDd - LVESd)/LVEDd$. Fed male Sprague-Dawley rats were lightly anesthetized with isoflurane and baseline fractional shortening was measured in the parasternal position using transthoracic echocardiography (TTE). Following this measurement, animals were recovered and received a single dose of compound (4 mg/kg) by oral gavage. At three hours post-dose, second and third echocardiograms were collected under light anesthesia to determine drug effects on contractility. Effects are represented in Table 5 as a percent reduction of baseline fractional shortening.

Table 5. Inhibition of Contractility in Rat by Selected Compounds^a

ID	% Reduction in Fractional Shortening 3h post-dose
1	+++

45	+
48	+++
49	+++
69	+
70	++
71	+++

^a+ represents a relative change in fractional shortening less than 15%. ++ represents a relative change in fractional shortening between 15-30%. +++ presents a relative change in fractional shortening greater than 30%.

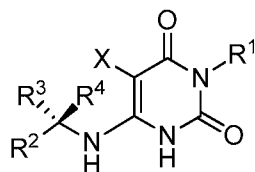
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[0205] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference. Where a conflict exists between the instant application and a reference provided herein, the instant application shall dominate

10

WHAT IS CLAIMED IS:

1. A compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein

R^1 is a member selected from the group consisting of C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkyl- C_1 - C_4 alkyl, 4- to 7-membered heterocycloalkyl, phenyl, phenyl- C_1 - C_4 alkyl, 5- to 6-membered heteroaryl and 5- to 6-membered heteroaryl- C_1 - C_4 alkyl, wherein each R^1 is optionally substituted with from 1-3 R^a ;

R^2 is a member selected from the group consisting of phenyl, phenyl- C_1 - C_4 alkyl, 5- to 6-membered heteroaryl and 5- to 6-membered heteroaryl- C_1 - C_4 alkyl, wherein each R^2 is optionally substituted with from 1-5 R^b ;

R^3 is a member selected from the group consisting of C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, and 4- to 7-membered heterocycloalkyl wherein each R^3 is optionally substituted with from 1-3 R^c ;

R^4 is H;

X is a member selected from the group consisting of H and F;

each R^a is independently selected from the group consisting of halo, CN, hydroxyl, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, phenyl, phenyl- C_1 - C_4 alkyl, phenyl- C_1 - C_4 alkoxy, phenoxy, $-\text{COR}^{a1}$, $-\text{CO}_2\text{R}^{a1}$, $-\text{SO}_2\text{R}^{a1}$, $-\text{SO}_2\text{NR}^{a1}\text{R}^{a2}$, and $-\text{CONR}^{a1}\text{R}^{a2}$, wherein each R^{a1} and R^{a2} is independently selected from the group consisting of H, C_1 - C_4 alkyl and phenyl, or optionally R^{a1} and R^{a2} when attached to a nitrogen atom are combined to form a 4- to 6- membered ring;

each R^b is independently selected from the group consisting of halo, CN, hydroxyl, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, phenoxy, phenyl- C_1 - C_4 alkoxy, methylenedioxy, difluoromethylenedioxy, $-\text{COR}^{b1}$, $-\text{CO}_2\text{R}^{b1}$, $-\text{SO}_2\text{R}^{b1}$, $-\text{SO}_2\text{NR}^{b1}\text{R}^{b2}$, $\text{CONR}^{b1}\text{R}^{b2}$, $\text{NR}^{b1}\text{R}^{b2}$, 5- to 6-membered heteroaryl, and 5- to 6-membered heterocyclyl optionally substituted with oxo, wherein each R^{b1} and R^{b2} is independently selected from the group consisting of H and C_1 - C_4 alkyl or optionally R^{b1} and R^{b2} when attached to a nitrogen atom are combined to form a 4- to 6- membered ring; and

29 each R^c is independently selected from the group consisting of halo, hydroxyl and C₁-C₂
30 alkoxy.

1 2. A compound of claim 1, or a pharmaceutically acceptable salt thereof,
2 wherein,

3 R¹ is a member selected from the group consisting of C₁-C₈ alkyl, C₃-C₈ cycloalkyl, 4- to 7-
4 membered heterocycloalkyl, phenyl, and 5- to 6-membered heteroaryl, wherein each
5 R¹ is optionally substituted with from 1-3 R^a;

6 R² is phenyl, which is optionally substituted with from 1-5 R^b;

7 R³ is a member selected from the group consisting of C₁-C₄ alkyl, C₃-C₄ cycloalkyl, and 4- to
8 7-membered heterocycloalkyl wherein each R³ is optionally substituted with from 1-2
9 R^c;

10 R⁴ is H;

11 X is a member selected from the group consisting of H and F;

12 each R^a is independently selected from the group consisting of halo, CN, C₁-C₄ alkyl, C₁-C₄
13 alkoxy, -COR^{a1}, -CO₂R^{a1}, -SO₂R^{a1}, -SO₂NR^{a1}R^{a2}, and -CONR^{a1}R^{a2}, wherein each
14 R^{a1} and R^{a2} is independently selected from the group consisting of H and C₁-C₄ alkyl
15 or optionally R^{a1} and R^{a2} when attached to a nitrogen atom are combined to form a 4-
16 to 6- membered ring;

17 each R^b is independently selected from the group consisting of halo, CN, C₁-C₄ alkyl, C₁-C₄
18 alkoxy, -COR^{b1}, -CO₂R^{b1}, -SO₂R^{b1}, -SO₂NR^{b1}R^{b2}, CONR^{b1}R^{b2}, NR^{b1}R^{b2}, 5- to 6-
19 membered heteroaryl, and 5- to 6-membered heterocyclyl optionally substituted with
20 oxo, wherein each R^{b1} and R^{b2} is independently selected from the group consisting of
21 H and C₁-C₄ alkyl or optionally R^{b1} and R^{b2} when attached to a nitrogen atom are
22 combined to form a 4- to 6- membered ring; and

23 each R^c is independently selected from the group consisting of halo and C₁-C₂ alkoxy.

1 3. A compound of claims 1 or 2, or a pharmaceutically acceptable salt
2 thereof, wherein X is H.

1 4. A compound of claims 1 or 2, or a pharmaceutically acceptable salt
2 thereof, wherein R¹ is selected from the group consisting of C₃-C₄ alkyl, C₃-C₅ cycloalkyl,
3 and 4- to 6-membered heterocycloalkyl, wherein each R¹ is optionally substituted with from
4 1-2 R^a.

1 **5.** A compound of claims **1** or **2**, or a pharmaceutically acceptable salt
2 thereof, wherein R¹ is selected from the group consisting of phenyl and 5- to 6-membered
3 heteroaryl, wherein each R¹ is optionally substituted with from 1-3 R^a.

1 **6.** A compound of claims **1** or **2**, or a pharmaceutically acceptable salt
2 thereof, wherein R¹ is selected from the group consisting of C₃-C₄ alkyl, C₃-C₅ cycloalkyl,
3 and 4- to 6-membered heterocycloalkyl.

1 **7.** A compound of claims **1** or **2**, or a pharmaceutically acceptable salt
2 thereof, wherein R¹ is 4- to 6-membered heterocycloalkyl, optionally substituted with from 1-
3 2 R^a selected from the group consisting of C₁-C₄ alkyl, C₁-C₄
4 alkoxy, -COR^{a1}, -CO₂R^{a1}, -SO₂R^{a1}, -SO₂NR^{a1}R^{a2}, and -CONR^{a1}R^{a2}, wherein each R^{a1} and
5 R^{a2} is independently selected from the group consisting of H and C₁-C₄ alkyl.

1 **8.** A compound of claims **1** or **2**, or a pharmaceutically acceptable salt
2 thereof, wherein R¹ is selected from the group consisting of cyclobutyl, isopropyl, isobutyl,
3 1-methoxypropan-2-yl, cyclopentyl, cyclohexyl, 4-tetrahydropyranyl, 1-
4 (methylsulfonyl)piperidin-4-yl, 1-(methoxycarbonyl)piperidin-4-yl, 4,4-difluorocyclohexyl,
5 phenyl, 2-pyridyl, 3-pyridyl, 3-isoxazolyl, 5-isoxazolyl, and 1-methyl-3-pyrazolyl.

1 **9.** A compound of claims **1** or **2**, or a pharmaceutically acceptable salt
2 thereof, wherein R² is optionally substituted with from 1-2 R^b.

1 **10.** A compound of claims **1** or **2**, or a pharmaceutically acceptable salt
2 thereof, wherein R² is selected from the group consisting of phenyl, 3-methylphenyl, 2-
3 fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,5-difluorophenyl, 3,5-difluorophenyl, 3-
4 chlorophenyl, 3-methoxyphenyl, 3-(3-oxazolidin-2-onyl)phenyl, 3-(2-methyl-1-
5 imidazolyl)phenyl, 3-(1-pyrazolyl)phenyl, and 3-(1,2,4-triazol-1-yl)phenyl.

1 **11.** A compound of claims **1** or **2**, or a pharmaceutically acceptable salt
2 thereof, wherein R³ is selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxyalkyl,
3 and C₃-C₄ cycloalkyl.

1 **12.** A compound of claims **1** or **2**, or a pharmaceutically acceptable salt
2 thereof, wherein R³ is selected from the group consisting of methyl, ethyl, propyl,
3 cyclopropyl, cyclobutyl and 2-methoxymethyl.

1 **13.** A compound of any of claims **1** to **10**, or a pharmaceutically acceptable
2 salt thereof, wherein R³ is methyl.

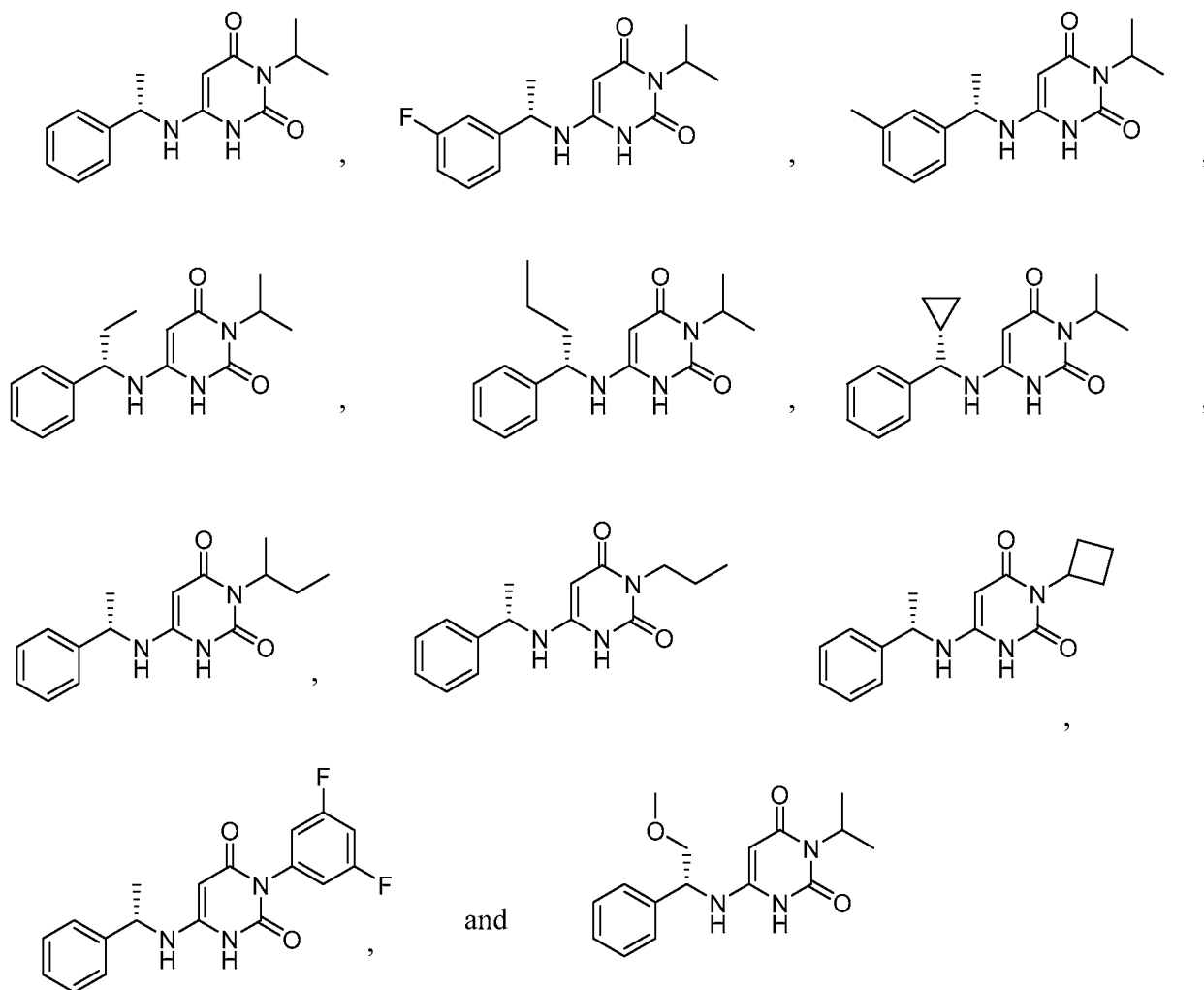
1 **14.** A compound of claims **1** or **2**, or a pharmaceutically acceptable salt
2 thereof, wherein R¹ is isopropyl; R² is optionally substituted with 1-2 R^b; and R³ is methyl.

1 **15.** A compound of claims **1** or **2**, or a pharmaceutically acceptable salt
2 thereof, wherein R¹ is 4- to 6-membered heterocycloalkyl, optionally substituted with from 1-
3 2 R^a selected from the group consisting of C₁-C₄ alkyl, C₁-C₄
4 alkoxy, -COR^{a1}, -CO₂R^{a1}, -SO₂R^{a1}, -SO₂NR^{a1}R^{a2}, and -CONR^{a1}R^{a2}, wherein each R^{a1} and
5 R^{a2} is independently selected from the group consisting of H and C₁-C₄ alkyl; R² is
6 optionally substituted with 1-2 R^b; and R³ is methyl.

1 **16.** A compound of claims **1** or **2**, or a pharmaceutically acceptable salt
2 thereof, wherein R¹ is selected from the group consisting of phenyl and 5- to 6-membered
3 heteroaryl, wherein each R¹ is optionally substituted with from 1-3 R^a; R² is optionally
4 substituted with from 1-2 R^b; and R³ is methyl.

1 **17.** A pharmaceutical composition comprising a compound of any of
2 claims **1-16**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable
3 excipient.

18. A compound of claim **1**, selected from the group consisting of:



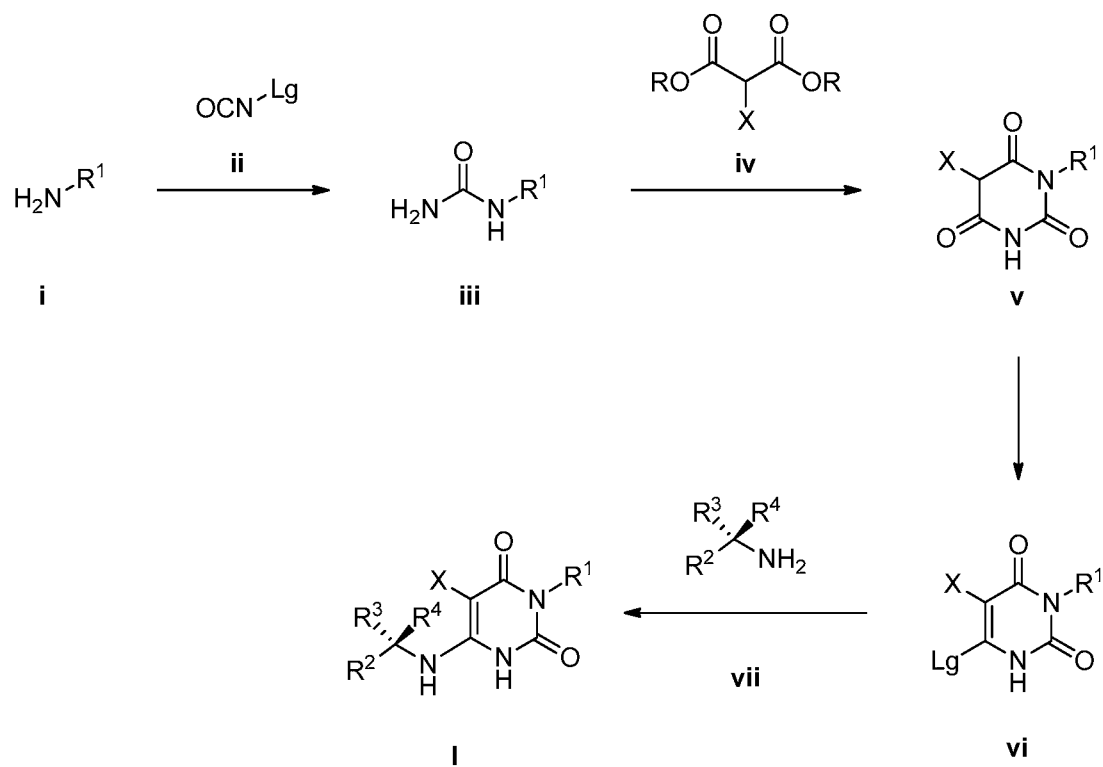
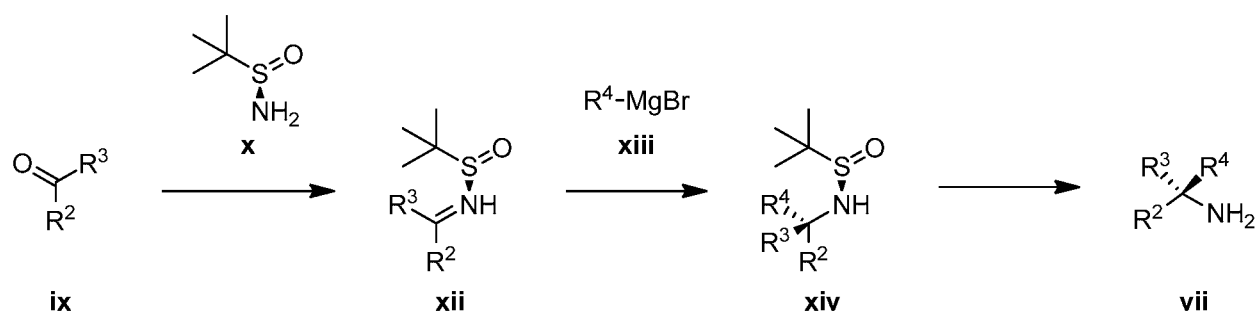
or a pharmaceutically acceptable salt thereof.

19. A method of treating hypertrophic cardiomyopathy (HCM), or a cardiac disorder having a pathophysiological feature associated with HCM, comprising administering to a subject in need thereof an effective amount of a compound of any of claims **1-16**, or **18** or a pharmaceutically acceptable salt thereof.

20. A method of treating a disease or disorder selected from the group consisting of diastolic heart failure with preserved ejection fraction, ischemic heart disease, angina pectoris, and restrictive cardiomyopathy, comprising administering to a subject in need thereof an effective amount of a compound of any of claims **1-16**, or **18** or a pharmaceutically acceptable salt thereof.

1 **21.** A method of treating a disease or disorder characterized by left
2 ventricular hypertrophy due to volume or pressure overload, said disease or disorder selected
3 from the group consisting of chronic mitral regurgitation, chronic aortic stenosis, and chronic
4 systemic hypertension; in conjunction with therapies aimed at correcting or alleviating the
5 primary cause of volume or pressure overload, including valve repair/replacement or
6 effective antihypertensive therapy, comprising administering to a subject in need thereof an
7 effective amount of a compound of any of claims **1-16**, or **18** or a pharmaceutically
8 acceptable salt thereof.

1 **22.** A method of treating hypertrophic cardiomyopathy (HCM), or a
2 cardiac disorder having a pathophysiological feature associated with HCM, comprising
3 administering to a subject in need thereof an effective amount of a compound of any of
4 claims **1-16**, or **18** or a pharmaceutically acceptable salt thereof combined with therapies that
5 retard the progression of heart failure by down-regulating neurohormonal stimulation of the
6 heart and attempt to prevent cardiac remodeling (*e.g.*, ACE inhibitors, angiotensin receptor
7 blockers (ARBs), β -blockers, aldosterone receptor antagonists, or neural endopeptidase
8 inhibitors); therapies that improve cardiac function by stimulating cardiac contractility (*e.g.*,
9 positive inotropic agents, such as the β -adrenergic agonist dobutamine or the
10 phosphodiesterase inhibitor milrinone); and therapies that reduce cardiac preload (*e.g.*,
11 diuretics, such as furosemide) or afterload (vasodilators of any class, including but not
12 limited to calcium channel blockers, phosphodiesterase inhibitors, endothelin receptor
13 antagonists, renin inhibitors, or smooth muscle myosin modulators).

Figure 1**A****B**

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 95604-909864	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2014/043192	International filing date (<i>day/month/year</i>) 19 June 2014 (19-06-2014)	(Earliest) Priority Date (<i>day/month/year</i>) 21 June 2013 (21-06-2013)
Applicant MYOKARDIA, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6**bis**(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,

- ☐ the text is approved as submitted by the applicant
☒ the text has been established by this Authority to read as follows:

PYRIMIDINEDIONE COMPOUNDS AGAINST CARDIAC CONDITIONS

5. With regard to the **abstract**,

- ☐ the text is approved as submitted by the applicant
☒ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☒ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/043192

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D403/12 A61K31/513 C07D401/04 C07D401/12 C07D403/04
C07D405/04 C07D405/12 C07D239/545 C07D239/553 C07D413/04
A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HERBERT GOLDNER ET AL: "Neue Reaktionen mit Nitrosouracilderivaten, II. Synthese von 8H-Xanthinen, 8H-Xanthin-7-N-oxiden und 3H-Pyrimido[5.4-c]-1.2.5-oxadiazinen", JUSTUS LIEBIGS ANNALEN DER CHEMIE, vol. 692, no. 1, 7 April 1966 (1966-04-07), pages 134-150, XP055134233, WEINHEIM; DE ISSN: 0075-4617, DOI: 10.1002/jlac.19666920117 page 144; table 1; compound 9th ----- -/--	1-4, 10-13



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

13 August 2014

Date of mailing of the international search report

04/09/2014

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Sotoca Usina, E

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/043192

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/014868 A2 (WARNER LAMBERT CO [US]; HICKS JAMES LESTER [US]; ROARK WILLIAM HOWARD) 19 February 2004 (2004-02-19) Pages 29-31 Embodiments 74, 75, 80, 81, 88, 89 Page 33 3rd Embodiment; claims 1-4, 8-9 -----	1-22
A	US 5 008 267 A (KATAKAMI TSUTOMU [JP] ET AL) 16 April 1991 (1991-04-16) the whole document -----	1-22
A	SAEKI T ET AL: "SELECTIVE BLOCK OF DELAYED RECTIFYING POTASSIUM CURRENT IN THE RABBIT SINOATRIAL NODE BY A NOVEL CLASS III ANTIARRHYTHMIC AGENT MS-551", HEART AND VESSELS, SPRINGER, BERLIN, DE, vol. 9, no. 2, 1 January 1994 (1994-01-01) , pages 87-95, XP002049602, ISSN: 0910-8327, DOI: 10.1007/BF01751942 the whole document -----	1-22
A	JP H06 128238 A (MITSUI TOATSU CHEMICALS) 10 May 1994 (1994-05-10) the whole document -----	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2014/043192

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004014868	A2	19-02-2004	AT 359791 T 15-05-2007
		AU 2003250471 A1 25-02-2004	
		BR 0313385 A 14-06-2005	
		CA 2497656 A1 19-02-2004	
		DE 60313350 T2 03-01-2008	
		EP 1553949 A2 20-07-2005	
		ES 2283851 T3 01-11-2007	
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		US 2004053952 A1 18-03-2004	
		WO 2004014868 A2 19-02-2004	

US 5008267	A	16-04-1991	AT 115952 T 15-01-1995
		AU 613805 B2 08-08-1991	
		AU 4386989 A 31-05-1990	
		DE 68920125 D1 02-02-1995	
		DE 68920125 T2 03-08-1995	
		DK 535789 A 30-04-1990	
		EP 0369627 A2 23-05-1990	
		ES 2066000 T3 01-03-1995	
		HU 210780 B 28-07-1995	
		NO 894299 A 30-04-1990	
		NZ 231165 A 25-02-1992	
		US 5008267 A 16-04-1991	

JP H06128238	A	10-05-1994	NONE

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t 925 472 5000 f 925 472 8895

direct dial 925 472 5015
direct fax 925 407 8331
wkezer@kilpatricktownsend.com

December 3, 2015

VIA ePCT

Authorized Officer
PCT Operations Division
The International Bureau of WIPO
32, chemin des Colombettes
1211 Geneva, 20
Switzerland

Re: International Application No. PCT/US2014/043192
Filed: 19 June 2014
Title: PYRIMIDINEDIONE COMPOUNDS AGAINST CARDIAC CONDITIONS
Applicant: MYOKARDIA, INC.
Agent File No.: 095604-0909864

Dear Colleagues,

Pursuant to PCT Rule 92*bis*, the Applicant respectfully requests to change the Applicant's address on the international application as follows:

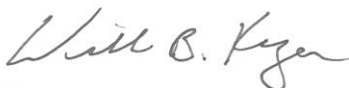
FROM:

MYOKARDIA, INC.
400 East Jamie Ct.
Suite 102
South San Francisco, California 94080
United States of America

TO:

MYOKARDIA, INC.
333 Allerton Avenue
South San Francisco, California 94080
United States of America

Respectfully submitted,



William B. Kezer, Ph.D.
Reg. No. 37,369
Kilpatrick Townsend and Stockton LLP

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December 3, 2015

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wkezer@kilpatricktownsend.com

VIA ePCT

Authorized Officer
PCT Operations Division
The International Bureau of WIPO
32, chemin des Colombettes
1211 Geneva, 20
Switzerland

Re: International Application No. PCT/US2014/043192
Filed: 19 June 2014
Title: PYRIMIDINEDIONE COMPOUNDS AGAINST CARDIAC CONDITIONS
Applicant: MYOKARDIA, INC.
Agent File No.: 095604-0909864

Dear Colleagues,

Pursuant to PCT Rule 92bis, the Applicant respectfully requests to change the Inventor's addresses on the international application as follows:

FROM:

OSLOB, Johan
400 East Jamie Ct.
Suite 102
South San Francisco, California 94080
United States of America

TO:

OSLOB, Johan
c/o MyoKardia, Inc.
333 Allerton Avenue
South San Francisco, California 94080
United States of America

FROM:

ANDERSON, Robert
400 East Jamie Ct.
Suite 102
South San Francisco, California 94080
United States of America

TO:

ANDERSON, Robert
c/o MyoKardia, Inc.
333 Allerton Avenue
South San Francisco, California 94080
United States of America

FROM:

AUBELE, Danielle
400 East Jamie Ct.
Suite 102
South San Francisco, California 94080
United States of America

TO:

AUBELE, Danielle
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333 Allerton Avenue
South San Francisco, California 94080
United States of America

FROM:

EVANCHIK, Marc
400 East Jamie Ct.
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United States of America

TO:

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c/o MyoKardia, Inc.
333 Allerton Avenue
South San Francisco, California 94080
United States of America

FROM:

FOX, Jonathan Charles
400 East Jamie Ct.
Suite 102
South San Francisco, California 94080
United States of America

TO:

FOX, Jonathan Charles
c/o MyoKardia, Inc.
333 Allerton Avenue
South San Francisco, California 94080
United States of America

FROM:

KANE, Brian
400 East Jamie Ct.
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South San Francisco, California 94080
United States of America

TO:

KANE, Brian
c/o MyoKardia, Inc.
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South San Francisco, California 94080
United States of America

FROM:

LU, Puping
400 East Jamie Ct.
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South San Francisco, California 94080
United States of America

TO:

LU, Puping
c/o MyoKardia, Inc.
333 Allerton Avenue
South San Francisco, California 94080
United States of America

FROM:

MCDOWELL, Robert
400 East Jamie Ct.
Suite 102
South San Francisco, California 94080
United States of America

TO:

MCDOWELL, Robert
c/o MyoKardia, Inc.
333 Allerton Avenue
South San Francisco, California 94080
United States of America

FROM:

RODRIGUEZ, Hector
400 East Jamie Ct.
Suite 102
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United States of America

TO:

RODRIGUEZ, Hector
c/o MyoKardia, Inc.
333 Allerton Avenue
South San Francisco, California 94080
United States of America

FROM:

SONG, Yonghong
400 East Jamie Ct.
Suite 102
South San Francisco, California 94080
United States of America

TO:

SONG, Yonghong
c/o MyoKardia, Inc.
333 Allerton Avenue
South San Francisco, California 94080
United States of America

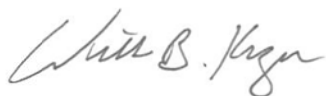
FROM:

SRAN, Arvinder
400 East Jamie Ct.
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South San Francisco, California 94080
United States of America

TO:

SRAN, Arvinder
c/o MyoKardia, Inc.
333 Allerton Avenue
South San Francisco, California 94080
United States of America

Respectfully submitted,

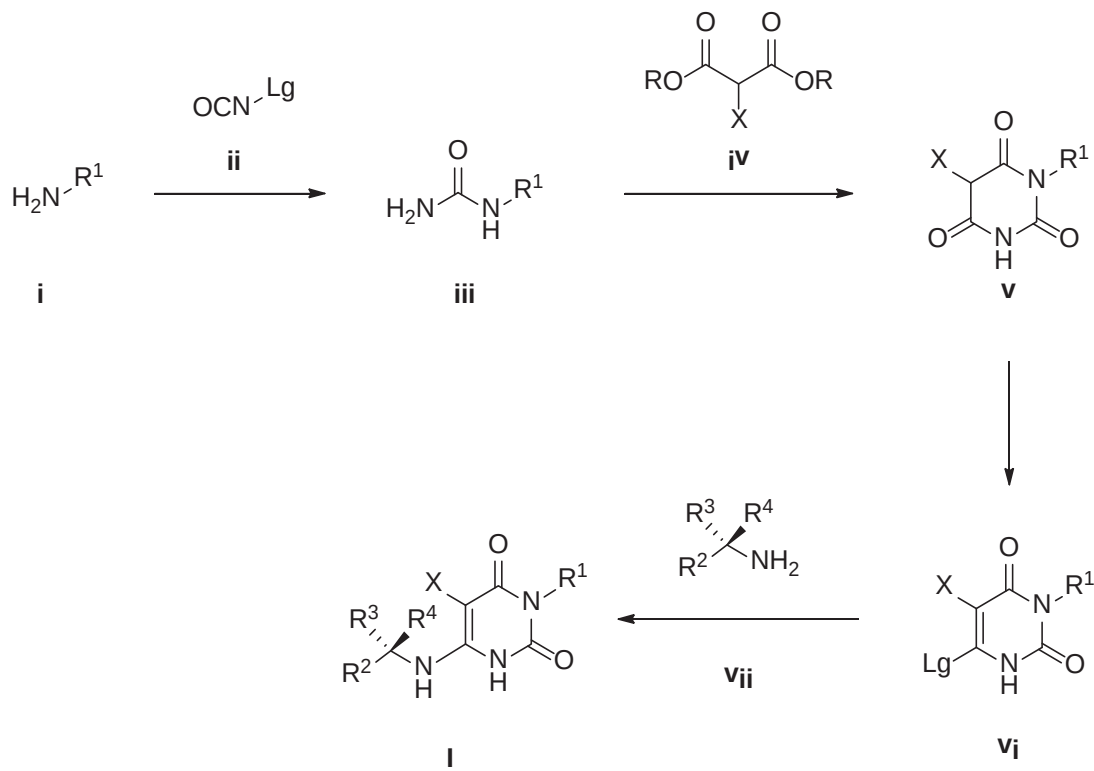


William B. Kezer, Ph.D.
Reg. No. 37,369
Kilpatrick Townsend and Stockton LLP

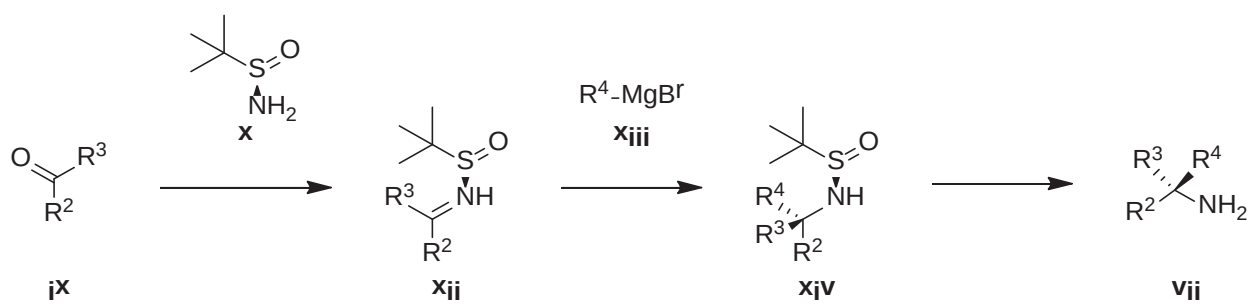
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Figura 1

A



B





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UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

JUNE 4, 2014

PTAS

WILLIAM B. KEZER, ESQ.
KILPATRICK TOWNSEND & STOCKTON LLP
TWO EMBARCADERO CENTER, 8TH FLOOR
SAN FRANCISCO, CA 94111-3823

502835042

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REEL/FRAME: 033017/0112
NUMBER OF PAGES: 4

BRIEF: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

DOCKET NUMBER: 95604-907011 (000102US)

ASSIGNOR:

OSLOB, JOHAN

DOC DATE: 04/21/2014

ASSIGNOR:

ANDERSON, ROBERT

DOC DATE: 04/21/2014

ASSIGNOR:

AUBELE, DANIELLE

DOC DATE: 04/21/2014

ASSIGNOR:

EVANCHIK, MARC

DOC DATE: 04/21/2014

ASSIGNOR:

LU, PUPING

DOC DATE: 04/29/2014

ASSIGNOR:

KANE, BRIAN

DOC DATE: 04/21/2014

ASSIGNOR:

MCDOWELL, ROBERT

DOC DATE: 04/21/2014

ASSIGNOR:
RODRIGUEZ, HECTOR

DOC DATE: 04/21/2014

ASSIGNOR:
SONG, YONGHONG

DOC DATE: 04/21/2014

ASSIGNOR:
SRAN, ARVINDER

DOC DATE: 04/21/2014

ASSIGNEE:
MYOKARDIA, INC.
400 EAST JAMIE CT.
SUITE 102
SOUTH SAN FRANCISCO, CALIFORNIA
94080

APPLICATION NUMBER: 61981366
PATENT NUMBER:
TITLE: PYRIMIDINEDIONE COMPOUNDS

FILING DATE: 04/18/2014
ISSUE DATE:

ASSIGNMENT RECORDATION BRANCH
PUBLIC RECORDS DIVISION

PATENT ASSIGNMENT COVER SHEET

Electronic Version v1.1
 Stylesheet Version v1.2

EPAS ID: PAT2881638

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
JOHAN OSLOB	04/21/2014
ROBERT ANDERSON	04/21/2014
DANIELLE AUBELE	04/21/2014
MARC EVANCHIK	04/21/2014
PUPING LU	04/29/2014
BRIAN KANE	04/21/2014
ROBERT MCDOWELL	04/21/2014
HECTOR RODRIGUEZ	04/21/2014
YONGHONG SONG	04/21/2014
ARVINDER SRAN	04/21/2014

RECEIVING PARTY DATA

Name:	MYOKARDIA, INC.
Street Address:	400 EAST JAMIE CT.
Internal Address:	SUITE 102
City:	SOUTH SAN FRANCISCO
State/Country:	CALIFORNIA
Postal Code:	94080

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	61981366

CORRESPONDENCE DATA

Fax Number: (415)576-0300

Correspondence will be sent to the e-mail address first; if that is unsuccessful, it will be sent using a fax number, if provided; if that is unsuccessful, it will be sent via US Mail.

Phone: (925) 472-5000

Email: kheldt@kilpatricktownsend.com

Correspondent Name: WILLIAM B. KEZER, ESQ.

Address Line 1: KILPATRICK TOWNSEND & STOCKTON LLP

Address Line 2: TWO EMBARCADERO CENTER, 8TH FLOOR

Address Line 4: SAN FRANCISCO, CALIFORNIA 94111-3823

ASSIGNMENT OF PATENT APPLICATION

For good and valuable consideration, the receipt of which is hereby acknowledged, Assignors,

1. Johan Oslob, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080;
2. Robert Anderson, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080;
3. Danielle Aubele, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080;
4. Marc Evanchik, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080;
5. Brian Kane, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080;
6. Puping Lu, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080;
7. Robert McDowell, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080;
8. Hector Rodriguez, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080;
9. Yonghong Song, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080; and
10. Arvinder Sran, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080

hereby sell, assign and transfer to Assignee, Myokardia, Inc., a corporation of the state of Delaware, located at 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080, and the successors, assigns and legal representatives of the Assignee all of its right, title and interest for the United States and its territorial possessions and in all foreign countries in and to, any and all improvements which are disclosed in the invention entitled:

PYRIMIDINEDIONE COMPOUNDS

- (a) U.S. Provisional Patent Application No. 61/981,366 filed on April 18, 2014

and any legal equivalent thereof in a foreign country, including the right to claim priority and, in and to, all Letters Patent to be obtained for said invention by the above application or any continuation, division, continuation-in-part, extension, conversion to 35 USC 111(a) or substitute thereof, and any reissue, reexamination or extension of said Letters Patent and all rights under all International Conventions for the Protection of Industrial Property;

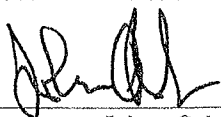
Assignors hereby covenant that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment;

Assignors further covenant that Assignee will, upon its request, be provided promptly with all pertinent facts and documents relating to said invention and said Letters Patent and legal equivalents as may be known and accessible to Assignor and will testify as to the same in any interference, litigation, or proceeding relating thereto and will promptly execute and deliver to Assignee or its legal representative any and all papers, instruments or affidavits required to apply for, obtain, maintain, issue or enforce said application, said invention and said Letters Patent and said equivalents thereof which may be necessary or desirable to carry out the purposes thereof.

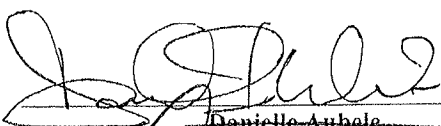
An attorney of record is authorized and requested by the execution of this assignment to insert into this assignment the filing date and serial number of said application(s) when officially known.

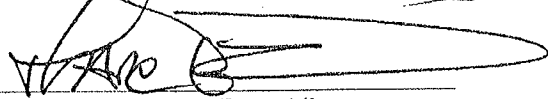
AND the Assignors request the Commissioner of Patents and Trademarks to issue said Letters Patent of the United States and any reissue or extension thereof to the Assignee, Myokardia, Inc.

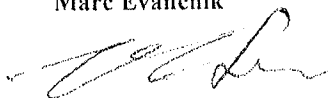
IN TESTIMONY WHEREOF, Assignors have signed their names on the dates indicated.

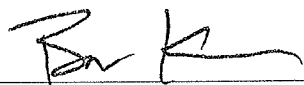
Signature:  Date: 4/21/2014
Johan Oslob

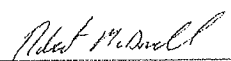
Signature:  Date: 4/21/2014
Robert Anderson

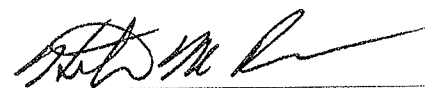
Signature:  Date: 4-21-14
Danielle Aubele

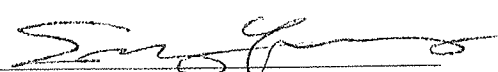
Signature:  Date: 4/21/2014
Marc Evanchik

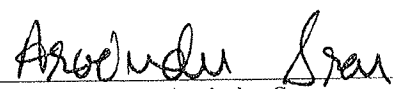
Signature:  Date: 4/29/2014
Puping Lu

Signature:  Date: 4/21/2014
Brian Kane

Signature:  Date: 4/21/2014
Robert McDowell

Signature:  Date: 4/21/2014
Hector Rodriguez

Signature:  Date: 4/21/2014
Yonghong Song

Signature:  Date: 4/21/2014
Arvinder Sran



UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

APRIL 3, 2014

PTAS

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DOC DATE: 02/20/2014

ASSIGNOR:
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DOC DATE: 02/19/2014

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AUBELE, DANIELLE

DOC DATE: 02/19/2014

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DOC DATE: 02/19/2014

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DOC DATE: 02/19/2014

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DOC DATE: 02/19/2014

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DOC DATE: 02/19/2014

ASSIGNOR:
SRAN, ARVINDER

DOC DATE: 02/19/2014

ASSIGNEE:
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SOUTH SAN FRANCISCO, CALIFORNIA
94080

APPLICATION NUMBER: 61838088
PATENT NUMBER:
TITLE: PYRIMIDINEDIONE COMPOUNDS

FILING DATE: 06/21/2013
ISSUE DATE:

APPLICATION NUMBER: 61939655
PATENT NUMBER:
TITLE: PYRIMIDINEDIONE COMPOUNDS

FILING DATE: 02/13/2014
ISSUE DATE:

ASSIGNMENT RECORDATION BRANCH
PUBLIC RECORDS DIVISION

PATENT ASSIGNMENT COVER SHEET

Electronic Version v1.1
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SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
JOHAN OSLOB	02/20/2014
ROBERT ANDERSON	02/19/2014
DANIELLE AUBELE	02/19/2014
MARC EVANCHIK	02/19/2014
PUPING LU	02/25/2014
BRIAN KANE	02/19/2014
ROBERT MCDOWELL	02/19/2014
HECTOR RODRIGUEZ	02/19/2014
YONGHONG SONG	02/19/2014
ARVINDER SRAN	02/19/2014

RECEIVING PARTY DATA

Name:	MYOKARDIA, INC.
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Internal Address:	SUITE 102
City:	SOUTH SAN FRANCISCO
State/Country:	CALIFORNIA
Postal Code:	94080

PROPERTY NUMBERS Total: 2

Property Type	Number
Application Number:	61838088
Application Number:	61939655

CORRESPONDENCE DATA

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Address Line 4: SAN FRANCISCO, CALIFORNIA 94111-3834

ASSIGNMENT OF PATENT APPLICATION

For good and valuable consideration, the receipt of which is hereby acknowledged, Assignors,

1. Johan Oslob, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080;
2. Robert Anderson, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080;
3. Danielle Aubele, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080;
4. Marc Evanchik, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080;
5. Brian Kane, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080;
6. Puping Lu, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080;
7. Robert McDowell, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080;
8. Hector Rodriguez, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080;
9. Yonghong Song, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080; and
10. Arvinder Sran, c/o 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080

hereby sell, assign and transfer to Assignee, Myokardia, Inc., a corporation of the state of Delaware, located at 400 East Jamie Ct., Suite 102, South San Francisco, CA 94080, and the successors, assigns and legal representatives of the Assignee all of its right, title and interest for the United States and its territorial possessions and in all foreign countries in and to, any and all improvements which are disclosed in the invention entitled:

PYRIMIDINEDIONE COMPOUNDS

- (a) U.S. Provisional Patent Application No. 61/838,088 filed on June 21, 2013; and
- (b) U.S. Provisional Patent Application No. 61/939,655 filed February 13, 2014

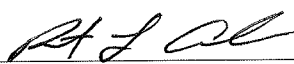
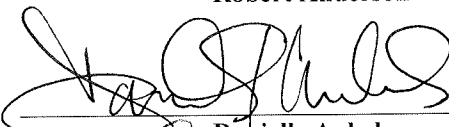
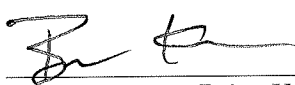
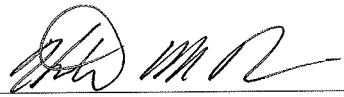
and any legal equivalent thereof in a foreign country, including the right to claim priority and, in and to, all Letters Patent to be obtained for said invention by the above application or any continuation, division, continuation-in-part, extension, conversion to 35 USC 111(a) or substitute thereof, and any reissue, reexamination or extension of said Letters Patent and all rights under all International Conventions for the Protection of Industrial Property;

Assignors hereby covenant that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment;

Assignors further covenant that Assignee will, upon its request, be provided promptly with all pertinent facts and documents relating to said invention and said Letters Patent and legal equivalents as may be known and accessible to Assignor and will testify as to the same in any interference, litigation, or proceeding relating thereto and will promptly execute and deliver to Assignee or its legal representative any and all papers, instruments or affidavits required to apply for, obtain, maintain, issue or enforce said application, said invention and said Letters Patent and said equivalents thereof which may be necessary or desirable to carry out the purposes thereof.

An attorney of record is authorized and requested by the execution of this assignment to insert into this assignment the filing date and serial number of said application(s) when officially known.
AND the Assignors request the Commissioner of Patents and Trademarks to issue said Letters Patent of the United States and any reissue or extension thereof to the Assignee, Myokardia, Inc.

IN TESTIMONY WHEREOF, Assignors have signed their names on the dates indicated.

Signature: 	Date: <u>2/20/2014</u>
Johan Oslob	
Signature: 	Date: <u>2/19/2014</u>
Robert Anderson	
Signature: 	Date: <u>2-19-2014</u>
Danielle Aubele	
Signature: 	Date: <u>02/19/2014</u>
Marc Evanchik	
Signature: 	Date: <u>02/25/2014</u>
Puping Lu	
Signature: 	Date: <u>2/19/2014</u>
Brian Kane	
Signature: 	Date: <u>2/19/2014</u>
Robert McDowell	
Signature: 	Date: <u>2/19/2014</u>
Hector Rodriguez	
Signature: 	Date: <u>2/19/2014</u>
Yonghong Song	
Signature: 	Date: <u>2/19/2014</u>
Arvinder Sran	

RESUMEN

Se proporcionan nuevos compuestos de pirimidinodiona y sales farmacéuticamente aceptables de los mismos, que son útiles para el tratamiento de la miocardiopatía hipertrófica (MCH) y condiciones asociadas con hipertrofia ventricular izquierda o disfunción diastólica.

- 5 Se describe la síntesis y caracterización de los compuestos y sales farmacéuticamente aceptables de los mismos, así como los métodos para el tratamiento de HCM y otras formas de enfermedades del corazón.